IDENTIFYING ADOLESCENTS AT RISK OF DEVELOPING NEGATIVE OUTCOMES AFTER RECEIVING OPIOID ANALGESICS FOR CHRONIC NON-CANCER PAIN MANAGEMENT USING MACHINE LEARNING ALGORITHMS

by

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Abstract

Canada's prescription opioid dispensing rates have increased since the early 21st century and this has contributed to an increase in opioid-related morbidity and mortality. Adolescents are one of the most vulnerable age groups when it comes to experiencing morbidity and mortality related to opioids. Adolescents who consume prescription opioids are also more susceptible to developing substance use disorder in later years. This thesis has two goals. The first goal is to study the epidemiology of prescription opioid dispensation among adolescents aged 12 to 17 years residing in Alberta between April 1st, 2010, and March 31st, 2015 who were treated for non-cancer pain. Its second goal is to create a supervised machine learning model that could predict the occurrence of negative outcomes following the dispensation of prescription opioids for chronic non-cancer pain management among the above-mentioned study population.

This study relied on the administrative data gathered by Alberta Health, particularly the use of the community pharmacies dataset. In order to achieve the goals of this research it was necessary to construct episodes of opioid consumption for study subjects. All incidences of opioid dispensations to study subjects were found and supply day quantities plus a 60-day washout were added to them to determine the predicted end date of each dispensation. The occurrence of a successive opioid dispensation that happened before the predicted end date of the last dispensation would constitute a new event in that episode.

In total 78805 opioid prescriptions were filled by study subjects during this study period of which %82.17 were incidence cases. The incidence proportion of opioid-containing dispensations among the study population had an increasing trend over the study period. Furthermore, male subjects and rural residents had a higher ratio of opioids dispensed overall dispensations for adolescent males and rural residents compared to the same ratios for females and urban residents. Based on the left-skewed age histogram of opioid dispensations older adolescents were dispensed more opioids than younger ones.

An advantage of supervised machine learning algorithms is their ability to make predictions about unseen data by generalizing from observed pieces of evidence. To achieve the second goal of this research, prescription opioid dispensation episodes lasting 90 days or longer were extracted in order to remove episodes that were acute pain related. Overall 699 eligible episodes were deemed eligible as chronic non-cancer pain therapies of which 71 episodes had resulted in negative outcomes up to one year after the end of the episode. Among all the features that were considered in this study, duration and number of dispensations in an episode, subject's age at baseline, and having a mental disease diagnosis at the baseline were significantly different among those with and without negative outcomes. A random forest model with accuracy= 0.71, AUC= 0.85, recall= 0.86, precision= 0.61, and f-score= 0.72 was superior to other models. This algorithm was particularly interesting as it used only three features for its predictions; episode length, number of dispensations in the episode, and mental disorder diagnoses at baseline.

While opioid dispensation to most age groups in Canada has had decreasing trends in recent years, the incidence proportion of prescription opioid dispensation for non-cancer pain to adolescents 12 to 17 years of age in Alberta had an increasing trend from 2010 to 2015. However, it is possible to create a simple machine learning algorithm with very few features that can predict, with good sensitivity, which episodes of opioid dispensation for chronic con-cancer pain among individuals aged 12 to 17 will result in experiencing negative outcomes. These are concerning and promising results for prescribers and policy-makers.

Preface

This thesis is a previously unpublished original work by Helia Koosha. It is presented in the paper-format, which means that each chapter is presented with its own introduction, methods, results, discussion, conclusion and list of references.

Chapters 2 and 3 are written with the intention that they might be submitted for publication in the future.

To Masoud, Avina, and Nika

You fill my heart with joy and strength

Acknowledgments

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CHAPTER 1

INTRODUCTION

1.1 Introduction

The International Association for the Study of Pain (2020) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". Individuals learn the concept of pain via their life experiences and experience of pain is affected by psychological, biological, and social factors (International Association for the Study of Pain, 2020). When it comes to pain assessment, without any objective biological pain markers and tools for measuring its intensity, self-reporting of pain plays a major role (International Association for the Study of Pain, 2020; Mazur, Radziewicz Winnicki, & Szczepański, 2013). This makes identification and management of pain among pediatric population particularly difficult. While the exact prevalence of pain among pediatric population is unknown, it is estimated that between 15-25% of children and adolescents suffer from recurrent or chronic pain (Mazur, Radziewicz Winnicki, & Szczepański, 2013). Pain among children and adolescents has been called a public health problem (Cooper et al., 2017; Groenewald, Wright, & Palemo, 2015; Hogan, Taddio, Katz, Shah, & Krahn, 2016; Mazur, Radziewicz Winnicki, & Szczepański, 2013; Vega et al., 2018).

When it comes to pharmacologic measures to address pain, opioid analgesics are commonly used as critical medication of choice (Boudreau et al., 2009; Busse et al., 2017; Canadian Institute for Health Information, 2018; Donroe, Socias, & Marshall, 2018; Fischer, Jones, & Rehm, 2014; Murphy, Goldner, & Fischer, 2015). Opioids are frequently prescribed to children and adolescents to treat their moderate to severe pain (Mazur, Radziewicz Winnicki, &

Szczepański, 2013; Rieder & Jong, 2021; Cooper et al., 2017; World Health Organization, 2020). However, the effectiveness and side-effects of long-term use of opioids for pain management among pediatric population remains controversial (Mazur, Radziewicz Winnicki, & Szczepański, 2013; Vega et al., 2018; Jones, Kaoser, & Fischer, 2021).

As a result of the rampant increase in the availability and use of POs to address pain, North America experienced a morbidity and mortality crisis, called the "Opioid Epidemic", in the second decade of this century (US Department of Health and Human Services, 2021; Canadian Institute for Health Information, 2019; Canadian Institute for Health Information, 2018; Jones, Kaoser, & Fischer, 2021; Fischer, Rehm, & Tyndall, 2016; IQVIA, 2021). Adolescents and young adults have been, unfortunately, at the center of this epidemic. In the USA, a 91% increase in fatality resulting from drug overdose among 15 to 19 year-olds was observed from 2000 to 2009 (Allen et al., 2017). Moreover, it is estimated that in the US, for every young adult overdose death, there are119 emergency room visits and 22 treatment admissions (Substance Abuse and Mental Health Services Administration, 2020). In Canada, from 2013 to 2017, youth 15 to 24 years of age experienced the second fastest growing opioid-poisoning rate in the country, an increase of 53% (Canadian Institute for Health Information, 2018). The rise in the availability and dispensation of PO analgesics for CNCP therapy for adolescent makes it crucial to study epidemiology of PO use among them and the negative outcomes associated with PO use makes it important to attempt to identify individuals who are at higher risk for such outcomes.

1.2 Importance of Chronic Non-Cancer Pain Therapy

Chronic non-cancer pain (CNCP) is commonly defined as pain unrelated to malignancy that is present for most of days in a span longer than three months (Busse et al., 2017; World Health Organization, 2020). Surveys done by various sources including the World Health

Organization (WHO) estimate that around %20 of adults worldwide suffer from CNCP (Busse et al., 2017; Els et al., 2017; Noble et al., 2010). A survey of chronic pain performed in Europe reported that on average patients struggled with pain for seven years with some reporting pain that had lasted over 20 years (Noble et al., 2010).

CNCP is a significant burden on any society; it imposes a huge healthcare cost on the society while decreasing daily life activities and quality of life of those suffering from it (Busse et al., 2017; Els et al., 2017; Hogan, Taddio, Katz, Shah, & Krahn, 2016). Studies performed in Canada suggest that CNCP is the main cause of healthcare resource utilization and disability among working age adults with its direct and indirect managing cost estimates reaching about $43 billion per year (Busse et al., 2017; Hogan, Taddio, Katz, Shah, & Krahn, 2016).

Although prevalence of CNCP increases with age, CNCP is also a source of major concern in pediatric population to the point that it has been called "a modern public health disaster" (Cooper et al., 2017; Groenewald, Wright, & Palemo, 2015; Hogan, Taddio, Katz, Shah, & Krahn, 2016; Mazur, Radziewicz Winnicki, & Szczepański, 2013; Vega et al., 2018; Gold, Mahrer, Yee, & Palermo, 2009; World Health Organization, 2020). CNCP in children and adolescents can have three sources; tissue inflammation or damage (somatic), internal organ injury or inflammation (visceral), or central or peripheral nervous system inflammation, damage, or malfunction (neuropathic) (Mazur, Radziewicz Winnicki, & Szczepański, 2013). The most common sources of CNCP-related complaints among children and adolescents are headaches, abdominal pains, and musculoskeletal pains (Gold, Mahrer, Yee, & Palermo, 2009; Vega et al., 2018).

In the United States, pain-related conditions in children in 2007 to 2008 were associated with an incremental healthcare cost of $ 1339 per capita (Groenewald, Wright, & Palemo, 2015).

The annual economic burden of chronic pain in adolescents in the US is estimated to be around $19.5 billion USD annually (World Health Organization, 2020).

Aside from a substantial healthcare cost, CNCP in children and adolescents has considerable long-term and short-term consequences (World Health Organization, 2020). Some of the negative consequences of CNCP in pediatric population are missing school and lower academic performance, missing out on social life and feeling socially excluded, and withdrawing from physical activities with consequently lower fitness levels (Vega et al., 2018; Gold, Mahrer, Yee, & Palermo, 2009; Hunfeld et al., 2001; World Health Organization, 2020). In their paper Vega et al. (2018) also state that CNCP in adolescents and children can lead to chronic insomnia which can exacerbate the negative side-effects of CNCP. Adolescents suffering chronic pain have a lower self-reported quality of life compared to their healthy peers (Gold, Mahrer, Yee, & Palermo, 2009; Hunfeld et al., 2001; World Health Organization, 2020). The negative effects of CNCP do not only impact the young patients but also their families and friends (Vega et al., 2018; World Health Organization, 2020). Most notably, parents of these patients experience significant stress and loss of productivity that in turn damages the family life and the well-being of their other offspring (Vega et al., 2018; Hunfeld et al., 2001).

1.3 Interaction of Opioids with the Human Body

Opioids are a class of centrally acting analgesics that act by binding the mu, delta, and kappa opioids-receptors that are widely distributed throughout human central and peripheral nervous system (Els et al., 2017; Noble et al., 2010). Through complicated changes at cellular and molecular levels, opioids reduce the perception of pain and increase a recipient's tolerance to painful stimuli (Els et al., 2017). The opioid family of drugs can be divided to three groups;

synthetic compounds, semi-synthetic compounds, and plant-based naturally-occurring compounds that are also called opiates (Noble et al., 2010).

Mu, kappa and delta receptors all function within the pain pathways in the human body (Els et al., 2017; Vanderah, 2010). When opioid agonists bind with these receptors they activate the pain inhibitory pathways in the central nervous system effectively hindering the transmission of pain signal by the cells (Vanderah, 2010). However, in their publications Vanderah (2010) and Al-Hasani and Bruchas (2011) indicate that majority of the opioid analgesics currently available in the market act on mu receptors and there are very few or no pharmacologic opioids available that would target kappa or delta opioid-receptors in humans.

Mu opioid-receptors are located on many periphery sites such as lungs, heart, kidneys, liver, and enteric neurons of the gastrointestinal (GI) system as well as in high density in the brain and spinal cord (Streicher & Bilsky, 2018). This diverse distribution of the mu opioid receptors across the body is the reason behind various side-effects of opioid analgesics such as constipation, urinary retention, hives, nausea, drowsiness, respiratory depression, and cough suppression (Streicher & Bilsky, 2018; Al-Hasani & Bruchas, 2011). Euphoria and mood enhancement are other unwanted side-effects of opioids that result from activation of the central dopamine reward pathways in users (Al-Hasani & Bruchas, 2011).

1.4 Using Opioid Analgesics for CNCP Management

While many studies and trials suggest that opioids are effective in short-term treatment of moderate to severe acute pain and cancer pain, their effectiveness in chronic pain management and improving of daily function when used for long period is a subject of debate (Canadian Institute for Health Information, 2017; Franklin, 2014; Hegmann et al., 2014). For instance, in their

publication Hegmann et al. (2014), indicated that they were unable to find any quality trials that demonstrated superiority of opioids when compared with nonsteroidal anti-inflammatory and other medications for treatment of CNCP.

Use of opioids to treat CNCP is associated with substantial risks and various adverse side-effects (Al-Hasani & Bruchas, 2011; Busse et al., 2017; Canadian Institute for Health Information, 2018; Canadian Institute for Health Information, 2017; Els et al., 2017; Franklin, 2014; Noble et al., 2010; World Health Organization, 2020). Respiratory depression, endocrine dysregulation, hives, nausea, euphoria, sedation, and insomnia are stated as some of the short-term side-effects of opioids (Al-Hasani & Bruchas, 2011; Els et al., 2017; Franklin, 2014). Concerns have also been raised about developing physiological dependence on opioids and opioid abuse after the initiation of PO use (Boscarino et al., 2010; Busse et al., 2017; Canadian Institute for Health Information, 2017; Els et al., 2017; Kolodny et al., 2015; World Health Organization, 2020).

When it comes to CNCP management among pediatric population, physicians are cautious regarding prescribing opioid analgesics as it is hard to minimize the risk of treatment while maximizing the pain relief (Cooper et al., 2017; Wilton et al., 2021). Multiple studies and reports in both Canada and US have indicated that adolescents who use PO analgesics have some of the highest risks when it comes to experiencing negative outcomes such as overdose poisoning fatalities, ED visits, and hospitalization (Allen et al., 2017; Canadian Institute for Health Information, 2018; Connock et al., 2007; Miech, Johnston, O'Malley, Keyes, & Heard, 2015; Voepel-Lewis et al., 2018). Moreover, among adolescent patients use of opioid analgesics could be associated with misuse initiation and developing substance use disorder in later years (Allen et al., 2017; Miech, Johnston, O'Malley, Keyes, & Heard, 2015; Wilton et al., 2021; Vowles et al., 2015; World Health Organization, 2020).

1.5 Study Rationale

In regards to prescribing opioids for CNCP and identifying individuals with a higher risk of showing adverse outcomes after initiation, there is very little guideline available for physicians, and as a result their prescribing practices varies widely (Allen et al., 2017; Busse et al., 2017; Franklin, 2014; Gomes, Mamdani, Paterson, Dhalla, & Juurlink, 2014; Hegmann et al., 2014). Furthermore, as opioids can cause opioid-induced hyperalgesia in recipients, prescribing higher doses of opioid overtime have become common practice worldwide (Canadian Institute for Health Information, 2017; Franklin, 2014). Unfortunately, strong associations have been found between opioid dispensing levels and both opioid-related morbidity and mortality by many researchers (Busse et al., 2017; Canadian Institute for Health Information, 2017; Centers for Disease Control and Prevention, 2016; Dunn et al., 2010; Fischer, Jones, & Rehm, 2014; Gomes, Mamdani, Paterson, Dhalla, & Juurlink, 2014).

Statistics published by Canadian Institute for Health Information (2017) indicate that between 2012 and 2016 young Canadians age 15 to 24 were prescribed opioids less frequently (88 persons per 1,000 population) than other age groups. However, a report published by IQVIA (2021) showed that in Canada between 2015 and 2020 among all age groups the only age group that saw an increasing trend in their prevalence of opioid dispensation was the 0 to 18 year age group. Even though administration of opioid analgesics to adolescent CNCP sufferers appears to be less frequent than that of adults, still many researchers have pointed to a large void in research pertaining to this subject (Allen et al., 2017; Cooper et al., 2017; World Health Organization, 2020). For example, Cooper et al. (2017) searched several databases for clinical trials where opioids were used to treat chronic pain in children from birth to 17 years of age and found no

studies that met the requirements for their review. They ranked the quality of evidence they had found as very low (Cooper et al., 2017).

Faced with this void of research and considering the importance of it because of possible adverse effects of opioid analgesic in the treatment of CNCP in adolescents, an investigation into epidemiology of opioid dispensation to adolescents and of ways to identify those at risk of negative outcomes after long-term PO use in the province of Alberta is necessary. The research objectives of this thesis are: 1) to investigate the epidemiology of PO dispensation among adolescents aged 12 to 17 years and suffering from non-cancer chronic pain in Alberta; 2) to propose and evaluate a machine learning model that can identify adolescents who are more likely to experience a negative outcome after initiating PO use for CNCP management.

1.6 Use of Administrative Health Data for Research

Administrative health data is typically generated in healthcare systems by healthcare workers as they interact with patients and are collected for administrative purposes such as billing, planning, record-keeping, and monitoring (Smith et al., 2018; Yu et al., 2016). Although administrative health data is not collected for research purposes, many characteristics of these databases have made them attractive data sources for researchers. Administrative data capture a large representative portion of the population with diverse sociodemographic characteristics often including years of follow-up data and is a cost-sensitive and time-sensitive alternative to collecting research data (Mazzali & Duca, 2015; Yu et al., 2016). However, the use of administrative health data for research has its drawbacks. For example, the quality of data that is not explicitly gathered for research might not be high enough and the absence of qualitative medical data that are usually

present in medical records are some of the limitations of using administrative health data for research (Mazzali & Duca, 2015; Smith et al., 2018; Yu et al., 2016).

Data quality is defined as the fitness of data for use in a specific context to investigate a particular phenomenon (Rothbard, 2015; Smith et al., 2018). According to Rothbard (2015) and Yu et al. (2016) accuracy, validity, and reliability of data are key aspects of data quality, and the most common issues in these areas arise from input entering and coding errors. Organizations that produce administrative health data are best suited to address these errors (Rothbard, 2015; Yu et al., 2016).

The data for this research was generated and maintained exclusively by Alberta Health. The Government of Canada mandates healthcare systems in the country to report hospitalization and ambulatory care administrative data to the Canadian Institute for Health Information (CIHI) where it will become a part of a national repository called the Discharge Abstract Database (DAD) (Canadian Institute for Health Information, 2012; Yu et al., 2016). The DAD data are rigorously reviewed and controlled by CIHI using strict processes and frameworks (Canadian Institute for Health Information, 2012). CIHI shares the results of these reviews with data providers, such as Alberta Health, to assist with the improvement of their data entry and coding processes and enhance the administrative data quality of the healthcare systems in Canada (Canadian Institute for Health Information, 2012).

Another feature that greatly impacts the utilization of administrative health data for research is its linkability (Smith et al., 2018; Yu et al., 2016). To use administrative datasets for research it is crucial to link the datasets properly. This is generally done with the use of unique identifiers for each subject. If the datasets are from different organizations then chances are that

these unique identifiers would not match (Yu et al., 2016). This research benefitted from using administrative health data provided by Alberta Health. Data linkage in this study was facilitated by unique identifiers generated by Alberta Health. Consequently, no errors were encountered during the linking of datasets.

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CHAPTER 2

EPIDEMIOLOGY OF OPIOID DISPENSATION FOR NON-CANCER PAIN AMONG ALBERTA ADOLESCENTS AGED 12 TO 17 AND DIAGNOSIS DETERMINATION

2.1 Introduction

The beginning of the 21st century has been marked with a significant increase in the utilization of prescription opioid (PO) analgesics for pain management in North America (Smolina, Gladstone, & Morgan, 2016; Kolodny et al., 2015; Boudreau et al., 2009; Donroe, Socias, & Marshall, 2018). In the first decade of the millennium PO sales in the United States nearly quadrupled and Canada's consumption of POs doubled (Donroe, Socias, & Marshall, 2018) In Canada, defined daily doses (DDDs) of PO increased from 20.3 DDD per 1000 population per day to 23.0 DDD per 1000 population per day between 2005 and 2010, which then declined in 2016 to 19.6 DDD per 1000 population per day (Fischer, Jones, Krahn, & Rehm, 2011; Fischer, Jones, Vojtila, & Kurdyak, 2018). While there are some promising reports about decreasing trends, Canada still ranks second in the world for PO consumption per capita after the US (Canadian Institute for Health Information, 2019; Murphy, Goldner, & Fischer, 2015; Donroe, Socias, & Marshall, 2018).

Inter-provincial comparisons show that rates of PO consumption and expenditures vary considerably across different provinces in Canada (Fischer & Argento, 2012; Fischer, Jones, & Rehm, 2014; Fischer, Jones, Krahn, & Rehm, 2011; Donroe, Socias, & Marshall, 2018). From 2005 through 2012, dispensing data from the retail pharmacies in Canada showed that Alberta had the highest annual PO dispensation rate in Canada, more than three times the rate of Quebec, which

had the lowest (Fischer, Jones, & Rehm, 2014; Donroe, Socias, & Marshall, 2018). Similarly, the data from a representative sample of retail pharmacies from 2010 to 2013 across Canada showed that PO expenditures in Alberta and Ontario (the country's highest) were almost twice that of Quebec (the country's lowest) (Murphy, Goldner, & Fischer, 2015). Alberta reached its peak PO dispensation in 2011-2012. Following this peak, the province reported a decline in its PO dispensation level that eventually reached lower than its pre-peak levels in 2020 (Fischer, Jones, & Rehm, 2014; Jones, Kaoser, & Fischer, 2021).

Opioids are commonly used worldwide for pain management (Murphy, Goldner, & Fischer, 2015; Fischer, Jones, & Rehm, 2014; Canadian Institute for Health Information, 2018; Donroe, Socias, & Marshall, 2018; Boudreau et al., 2009; Busse et al., 2017). However, use of opioids to treat chronic pain is associated with substantial risks and various adverse side-effects (Busse et al., 2017; Fischer, Keates, Bühringer, Reimer, & Rehm, 2014; Murphy, Goldner, & Fischer, 2015; Canadian Institute for Health Information, 2018; Canadian Institute for Health Information, 2019; Boudreau et al., 2009). Among adolescent patients use of opioid analgesics is associated with poisoning, misuse initiation, and developing substance use disorder in later years (Miech, Johnston, O'Malley, Keyes, & Heard, 2015; Voepel-Lewis et al., 2018). In the USA, fatal poisoning that was mainly due to PO overdose soared about 91% among 15 to 19 year-olds from 2000 to 2009 (Allen et al., 2017). A study by Miech et al. (2015) has concluded that the risk of future opioid misuse increases by 33% for individuals who have had exposure to legitimate PO before high school graduation. Another article by Allen et al. (2017) indicates that among new heroin users about 80% have previously used opioid analgesics. A report by Canadian Institute for Health information (2018) states that from 2013 to 2017 youth aged 15 to 24 experienced a 53% increase in their opioid poisoning rate, which was the second fastest-growing in Canada. The same

report also adds that for the same period Alberta youth aged 15 to 24 and younger adults aged 25 to 44 had the highest rates of emergency department visits due to opioid poisoning.

A study of trends of non-cancer related PO dispensing among Alberta adolescents aged 12 to 17 based on data supplied by the Alberta Ministry of Health is presented in this chapter. Diagnoses for which individuals were prescribed POs are also investigated.

2.2 Methods

Six electronic administrative health datasets maintained by Alberta Ministry of Health, Alberta Health, were used for this population-based, retrospective study. Table 2.1 provides relevant information about these datasets.

Alberta Health assigns a Unique Lifetime Identifier (ULI) to all residents of Alberta who are registered with the Alberta Health Care Insurance Plan (AHCIP). Datasets maintained by Alberta Health are linked using these ULIs. To maintain confidentiality, an algorithm that produces a fictional identifier is used to preserve the link across datasets before data is released to researchers (Alberta Health, 2017).

Opioid medications included in this study were codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, butorphanol, dextropropoxyphene, meperidine, oxycodone, oxymorphone, morphine, nalbuphine, opium, tapentadol, tramadol, and pentazocine. Patients consuming methadone or buprenorphine were excluded from this cohort as these medications are regularly used for opioid dependence treatment (Alford, Compton, & Samet, 2006; Connock et al., 2007).

The Pharmaceutical Information Network (PIN) dataset was primarily used for obtaining data about general and PO dispensations from all community pharmacies in AB. It is estimated

that while some POs are dispensed in places such as hospitals or hospice and palliative care centers, about 80% of POs dispensed in Canada are dispensed by community pharmacies (Fischer, Jones, Krahn, & Rehm, 2011). In this study, an eligible PO dispensation was one that was dispensed to a patient 12 to 17 years of age not treated for cancer pain between April 1st, 2010 and March 31st, 2015. As part of the data release agreement for this research, individuals treated for cancer pain were excluded from this data by Alberta Health prior to its release using the related ICD-10-CA codes in the Inpatient and Ambulatory care datasets and ICD-9 codes in the Claims dataset (ICD-9 codes, 2022; ICD-10-CA codes, 2022). Once all the cases of PO dispensations of interest were extracted they were compared with all pharmacy dispensations to patients 12 to 17 years of age not treated for cancer between April 1st, 2010 and March 31st. Ratios of opioid prescriptions to all other prescriptions were calculated comparing males and females as well as urban and rural residents for each year in the study period.

In order to capture incident cases of PO dispensation, episodes of opioid dispensation were constructed based on the data in the PIN dataset. The first PO dispensation to a member of the population of interest was considered the first event in that episode. To determine the end date of the event supply day quantities were used. A wash-out period of 60 days was added to the predicted end-date. The prescriptions were combined if a new prescription was received within the 60-day wash-out period. If an individual had multiple PO dispensations in one day, the one with the longer supply period was used for the episode tabulation. Incident cases were the first events in the constructed episodes occurring between April 1st, 2010 to March 31st, 2015. Finally, incidence cases were divided based on the date they occurred between years 2010 and 2015 (each year starting on April 1st and ending on March 31st of the next year). An individual was counted more than once if they had multiple distinct episodes of PO dispensations. The incidence proportions

were calculated by dividing the number of incident cases by the population of 12 to 17-year-old adolescents in Alberta (Statistics Canada, 2022).

Once the incidence cases of PO dispensation were identified they were used to determine the diagnosis for which PO analgesic was prescribed. The claims and Inpatient datasets were searched for the closest records that had occurred on the day of the dispensation up to three months before that date. If a diagnosis was not found for the subject in this period a 'Missing' diagnosis was assigned to that record. The "Most Responsible Health Diagnosis" field in the Claims (ICD-9 codes) and Inpatient datasets (ICD-10-CA codes) were used and the *International Classification of Diseases, 9th Revision*, and *International Classification of Diseases, 10th Revision, (Canadian Modification)* were employed to extract diagnoses information for records of interest (ICD-9 codes, 2022; ICD-10-CA codes, 2022).

SAS v9.4 (SAS Institute Inc., Cary, NC, 2017) software was used to perform all analyses in this chapter.

Table 2. 1 Relevant description of Alberta Health datasets

Dataset	Covered Period	Notable Components*
Ambulatory Care	April 1, 2005 to March 31, 2016	Emergency Department visits and Day Procedures; admission date, transfer information, provider information, coded diagnoses (ICD-10-CA), and intervention information
Inpatient	April 1, 2005 to March 31, 2016	Hospital morbidity and discharge abstracts; admission/discharge/transfer dates, provider information, coded diagnoses (ICD-10-CA), and intervention information
Pharmaceutical Information Network (PIN)	April 1, 2008 to March 31, 2016	Quantity dispensed, dispensation date, dispensed day supply quantity, Drug Identification Number (DIN), and Anatomic Therapeutic Classification (ATC) code
Population Registry	April 1, 2005 to March 31, 2016	Basic demographic and geographic information such as date of birth, gender, and first three digits of postal code
Practitioner Claims	April 1, 2005 to March 31, 2016	Fee-for-service practitioner claims; date of service, up to three diagnostic codes (ICD-9), and provider and facility information
Vital Statistics – Deaths	April 1, 2008 to December 31, 2015	Date of death, hospital identifier, cause of death, and demographic information including age, gender, and first three digits of postal code

* Data in this column is obtained from "Overview of Administrative Health Datasets" by Alberta Health (2017)

2.3 Results

Based on the PIN dataset, a total of 142,893,114 prescriptions were filled in pharmacies across Alberta for people not treated for cancer pain from April 1st, 2010 to March 31st, 2015 of which 1,991,783 were filled for 12 to 17 year-old adolescents. The number of opioid containing prescriptions filled for all age groups from April 1st, 2010 to March 31st, 2015 were 10,195,560. The number of PO dispensed to 12 to 17 year-old adolescents for the same period were 78,805.

Table 2.2 provides more details about pharmacy-dispensations to Albertan adolescents during the study period.

Table 2. 2 Annual numbers of related pharmacy dispensations and opioid dispensations to adolescents 12 to 17 years of age treated for non-cancer pain in Alberta by sex and residence from April 1st, 2010 to March 31st, 2015

Dispensation Type	Characteristic	Year*, n (%)					
		2010-2011	2011-2012	2012-2013	2013-2014	2014-2015	Total
All	**Sex**						
	Females	250731 (58.75)	251829 (58.66)	242270 (58.80)	222625 (59.20)	204504 (58.83)	1171959 (58.84)
	Males	176057 (41.25)	177479 (41.34)	169735 (41.20)	153444 (40.80)	143109 (41.17)	819824 (41.16)
	Residence						
	Rural	87095 (20.41)	85104 (19.82)	78971 (19.17)	70602 (18.77)	61747 (17.76)	383519 (19.26)
	Urban	339693 (79.59)	344204 (80.18)	333034 (80.83)	305467 (81.23)	285866 (82.24)	1608264 (80.74)
Opioid Analgesic	**Sex**						
	Females	8017 (54.46)	8521 (54.78)	8753 (53.69)	8749 (54.77)	8691 (53.48)	42731 (54.22)
	Males	6705 (45.54)	7034 (45.22)	7549 (46.31)	7226 (45.23)	7560 (46.52)	36074 (45.78)
	Residence						
	Rural	3545 (24.08)	3619 (23.27)	3873 (23.76)	3788 (23.71)	3544 (21.81)	18369 (23.31)
	Urban	11177 (75.92)	11936 (76.73)	12429 (76.24)	12187 (76.29)	12707 (78.19)	60436 (76.69)

* Each year in this table expands from April 1st to March 31st of the next year

The mean dispensation age for PO analgesics in this study was 16.34 ± 1.4 years. A histogram of this age distribution is provided for visualization (Figure 2.1).

Figure 2. 1 Age histogram of opioid dispensation to adolescents 12 to 17 years of age treated for non-cancer pain in Alberta from April 1st, 2010 to March 31st, 2015
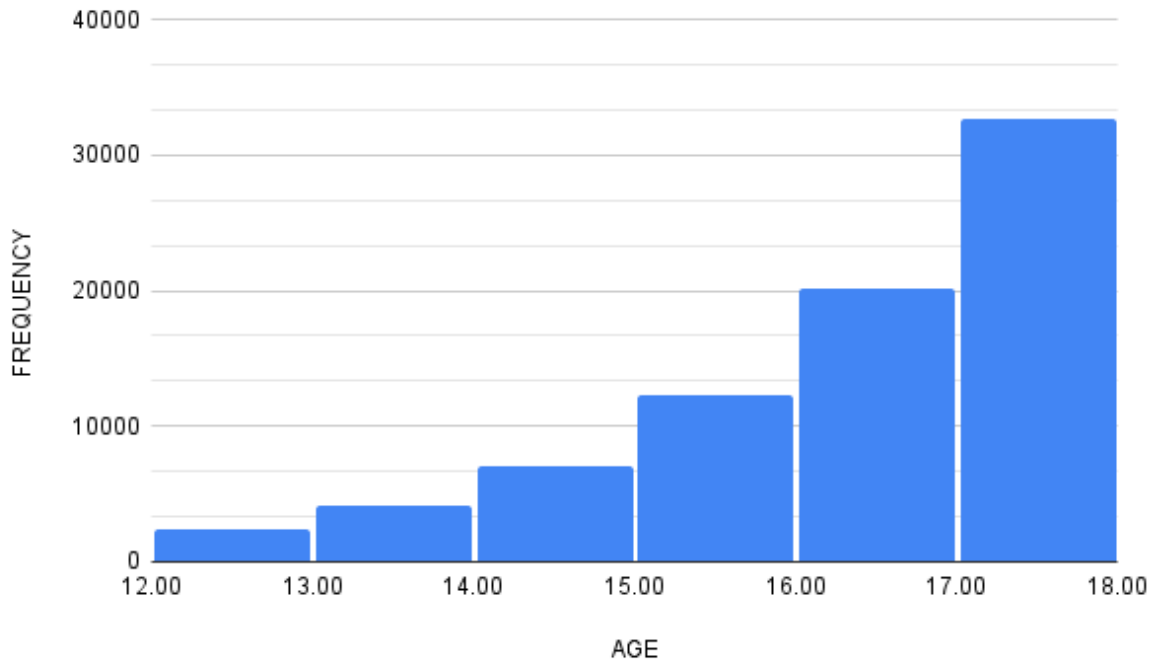

PO dispensation trends by gender and residence among the population of interest during this study period are shown in Figures 2.2 and 2.3. Among this population while the crude numbers of opioid analgesic dispensed to the males are smaller than that of females each year, but the ratio of POs dispensed to adolescent males over all prescriptions dispensed to adolescent males compared to similar ratios for adolescent females shows that male Albertans aged 12 to 17 treated for non-cancer pain are actually being dispensed more opioid analgesics than females. The same is correct for rural residents versus urban residents of Alberta among the population under study. Furthermore, Alberta has an increasing trend of opioid dispensation to adolescents 12 to 17 years of age who are not treated for cancer over this study period.

Figure 2. 2 Annual ratios of POs dispensed over all prescriptions dispensed to Albertans aged 12 to 17 treated for non-cancer pain by gender (per 1000) from April 1st, 2010 to March 31st, 2015
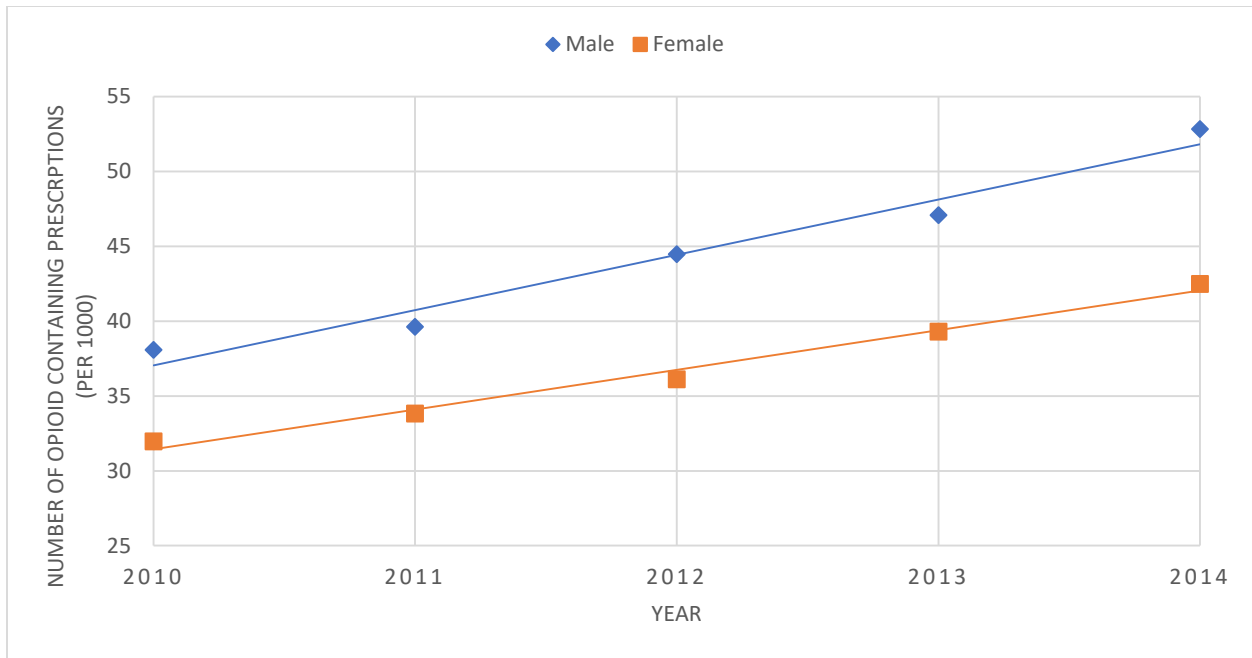
Figure 2. 3 Annual ratios of POs dispensed over all prescriptions dispensed to Albertans aged 12 to 17 treated for non-cancer pain by residence (per 1000) from April 1st, 2010 to March 31st, 2015
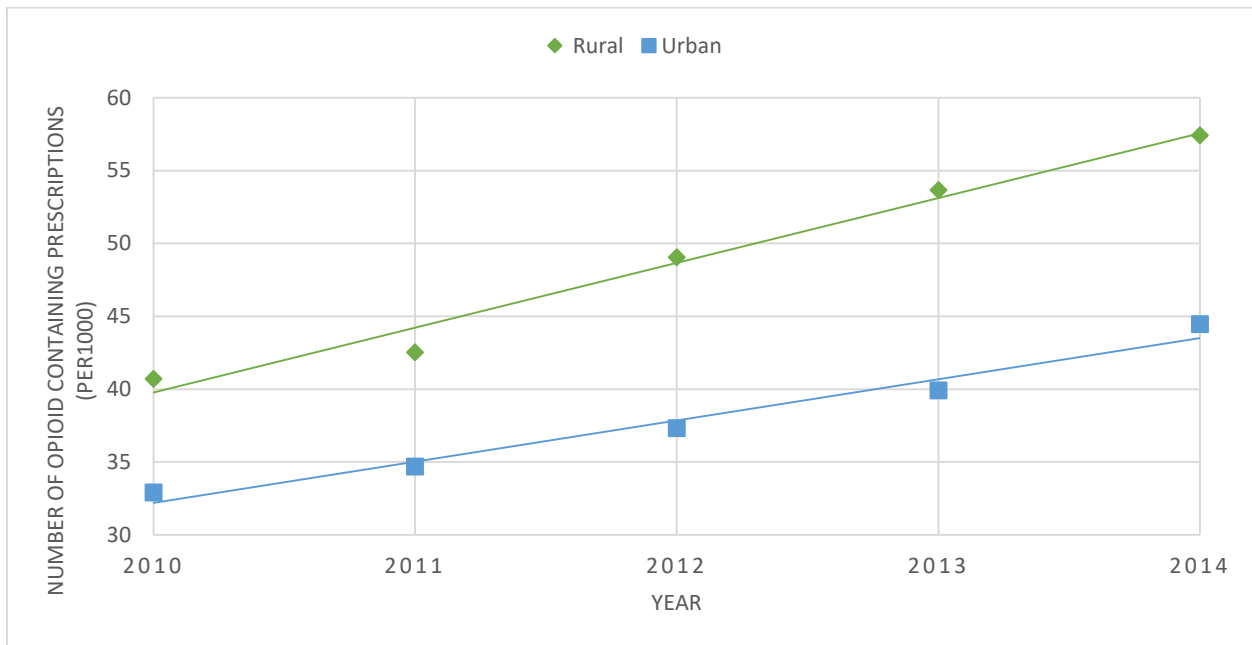
The majority of PO dispensed each year were incident cases. These cases averaged at 82.17% of all opioid dispensations in the population of interest over the span of five years. The most frequently used opioid formulation (86.21% of the cases) was "codeine and paracetamol" followed by "tramadol and paracetamol" (6.79% of the cases) (WHO Collaborating Centre for Drug Statistics Methodology, 2021).

Figure 2. 4 Incidence proportion of opioid-containing dispensations among Albertans 12 to 17 years of age treated for non-cancer pain (per 1000) from April 1st, 2010 to March 31st, 2015
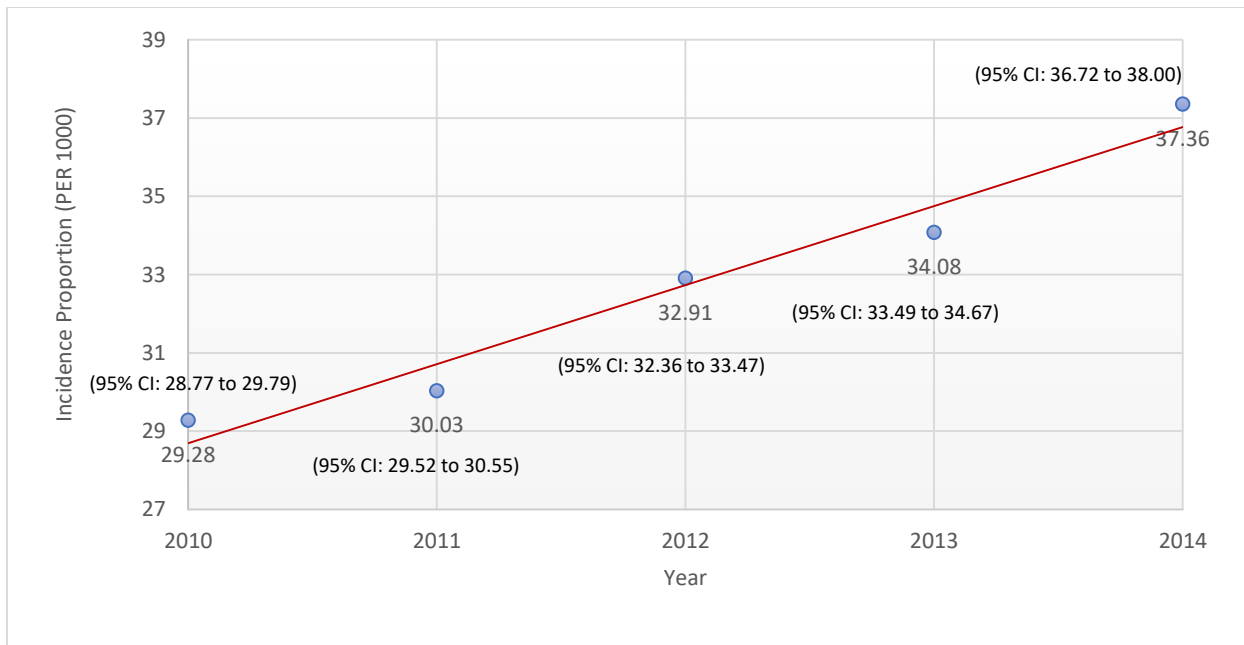
The main diagnoses for which the incident cases of PO dispensation occurred throughout the study period for the population of interest was "injury and poisoning" (19.98%) followed by "symptoms, signs, and ill-defined conditions" (11.68%), and "diseases of the respiratory system" (11.45%). These diagnoses correspond to chapters 17, 16, and 8 of the ICD-9 respectively (ICD-9 codes, 2022). In addition, 7.63% of diagnoses for which incidence of opioid analgesic was

dispensed were missing in this study. The histogram in Figure 2.5 provides a visualization of these diagnoses by gender.

Figure 2. 5 Diagnoses for which incident cases of opioid-containing prescription occurred for Albertans aged 12 to 17 treated for non-cancer pain between April 1st, 2010 and March 31st, 2015 by gender (-1: missing diagnosis)
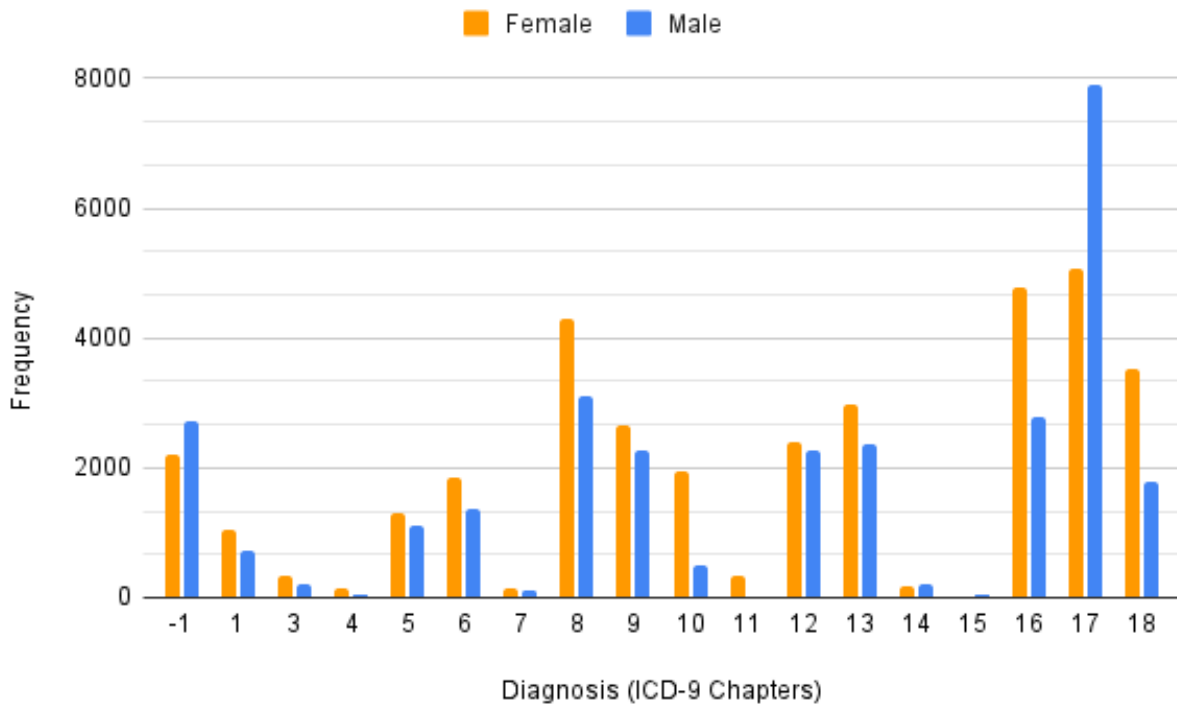
2.4 Discussion

In Canada the pediatric population has some of the lowest rates of PO consumption compared to older age groups. The Alberta Triplicate Prescription Program (TPP) Atlas (2013) reported that between 2001 and 2012 individuals aged 0 to 17 had the lowest number of PO dispensation per 1000 population in the province while individuals aged 50 to 64 had the highest rates. A publication by Canadian Institute for Health information (CIHI) (2019) also states that in Canada from 2013 to 2018 long-term (more than 90-days) PO consumption was most common among seniors and least common among individuals less than 25 years of age. Moreover, a report by

IQVIA (2021) estimated that in 2015 opioid dispensation prevalence in Canada among individuals 18 or younger was 0.5%. During the period covered in this study, while 1.39% of total prescriptions dispensed in Alberta were filled for adolescents 12 to 17 years of age not treated for cancer, only 0.77% of PO dispensations unrelated to cancer went to 12 to 17 year-old adolescents. Similar to Canada-wide results for pediatric PO dispensation, opioid analgesic dispensation rates from 2010 to 2015 for Albertan adolescents not treated for cancer pain was low.

The age distribution plot of the study population is left-skewed with average age being 16.34 ± 1.4 years (Figure 2.1). This is consistent with many other researches who have found consumption of PO analgesics (and all analgesics in general) increases with age. For example, the Alberta TPP Atlas (2016) reported that in 2015 of all PO patients in AB, children 0 to 9 years of age made up the smallest age-group at 0.4%. This percentage climbed to only 4.7% for Albertans 10 to 19 years of age and continued a steady increase until it reached the maximum of 20% for individuals 50 to 59 years of age. Moreover, from 2013 to 2018 the proportion of people starting opioid therapy in Ontario, Saskatchewan, and British Columbia was lowest among children under 15 and consistently increased with age. In all years seniors 65 and older had the highest proportions of starting opioid therapy (Canadian Institute for Health Information, 2019). The reason for such trends and observations is that age is one of the main factors associated with development of pain; older people experience a higher prevalence of pain caused by multi-morbidity resulting from advanced age (Schopflocher, Taenzer, & Jovey, 2011; Mills, Nicolson, & Smith, 2019). Even among children and adolescent prevalence of pain increases with age (King et al., 2011; Gobina et al., 2019).

Between 2010 and 2015, the annual ratios of POs dispensed over all prescriptions dispensed to Albertans 12 to 17 years of age for non-cancer treatments shows a steady increase. Moreover,

an increasing trend can be observed in the annual incidence proportion of opioid dispensations among 12 to 17 year-old Albertans not treated for cancer pain. This is a concerning result since Fischer et al. (2014) reported that in Alberta while annual PO dispensations increased from 2005 to 2011 the province saw a decreasing trend starting at 2012. A comparison between 2015 and 2020 prevalence of opioid dispensation in Canada by age group published by IQVIA (2021) shows that the only age group that saw an increase instead of a decrease was the 0 to 18-year age group. This could mean that while prescribers have become more conservative in prescribing opioids to adults, they have not followed the same conservative opioid prescribing patterns when it comes to adolescents.

During the study period the ratios of POs dispensed over all prescriptions dispensed for non-cancer treatment by gender and by residence to Albertans 12 to 17 years of age for non-cancer-treatment shows that boys and rural residents actually have received more POs per 1000 prescriptions than girls and urban residents (Figures 2.2 and 2.3). As observed in Table 2.2 from 2010 to 2015 males made up 41.16% and rural residents made up 19.26% of all prescription recipients. These percentages went up to 45.48% and 23.31% respectively when it came to males and rural residents receiving opioid analgesics. This is an interesting result because women generally experience and report more pain than men and are more likely to seek solutions to alleviate their pain (Mills, Nicolson, & Smith, 2019). Even among the pediatric population girls were more likely to experience and complain about pain (King et al., 2011; Gobina et al., 2019).

The main reason that adolescents in this study population sought pain relief across Alberta was for pain caused by injuries. Figure 2.5 shows that injuries were much more common among boys compared to girls. In addition, 7.63% of diagnoses for which incidence of PO dispensation occurred were determined as "missing". In Alberta some medical procedures, such as dental

procedures, are not covered by AHCIP. Hence, the administrative data regarding these procedures and their providers are not gathered by Alberta Health. However, the PIN dataset does contain the dispensation records of prescriptions filled in community pharmacies that relate to these procedures. In their study conducted between 2011 and 2017 in Nova Scotia, Matthews et al. (2019) found that the main portion of opioid prescriptions to individuals less than 18 were prescribed by dentists and dental specialists. Similarly, in 2009 dentists were identified as the main prescribers of POs to individuals between 10 and 19, accounting for about 31% of opioid prescribed to them in the US. Hence, it is possible that a large majority of these missing diagnoses cases were in fact prescribed for dental procedures.

This study examined Claims and Inpatient datasets for the closest diagnostic records from the dates of the incidences of PO dispensations to three months before those dates in order to determine the diagnoses for which opioid analgesics were dispensed. As is explained in the previous paragraph, some medical procedures in Alberta are not recorded in Inpatient and Claims datasets. These two factors might have introduced misclassifications into the diagnoses compiled for this study, and some of the diagnoses attributed to the incidences of PO dispensations may not have been accurate.

This study benefited from using pre-existing administrative data that made it effective both in terms of time and cost and provided a large population-based sample. On the other hand, the data used in this study was not collected for research purposes. Hence, the quality and accuracy of the data might not be of the highest standards. Moreover, although community pharmacies account for a large majority of PO dispensed in Canada, they do not account for all of it. Most importantly, dispensation amounts and data do not necessarily equate to consumption data but they are a close indirect measure of opioid analgesic consumption in a region.

2.5 Conclusions

Abuse and misuse of opioid analgesics fueled by liberal PO dispensations in Canada has become a public health crisis in recent years (Fischer, Jones, Vojtila, & Kurdyak, 2018; Fischer & Argento, 2012; Donroe, Socias, & Marshall, 2018; Canadian Institute for Health Information, 2018; Kolodny et al., 2015). This study investigates PO consumption in 12 to 17 year-old adolescents; an under-studied yet critical and vulnerable age group. The results of this study suggests that although for adults the trends of prescribing opioid analgesics have become decreasing as a result of reports and guidelines published in recent years, the PO dispensation trend was still increasing among adolescents in Alberta during this study period (Canadian Institute for Health Information, 2019; Canadian Institute for Health Information, 2018; Fischer, Jones, Vojtila, & Kurdyak, 2018). More notably, this increasing trend was more pronounced among certain demographics such as males and rural residents. It is important for healthcare providers to address pain and try to ease as it is a major problem and a debilitating issue in the lives of many people (Mills, Nicolson, & Smith, 2019). But policy makers and healthcare providers should closely monitor trends of PO analgesics particularly in the vulnerable populations as their side-effects can be devastating to people and society.

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CHAPTER 3

IDENTIFYING ADOLESCENTS AT RISK OF DEVELOPING NEGATIVE OUTCOMES FOLLOWING PRESCRIPTION OF OPIOID ANALGESICS FOR CHRONIC NON-CANCER PAIN USING A MACHINE LEARNING ALGORITHM

3.1 Introduction

Chronic non-cancer pain (CNCP) is commonly defined as pain not due to cancer that is present for most days in a span longer than three months (Busse et al., 2017). A shift in the chronic pain management culture calling it the neglected "fifth vital sign" combined with changes in attitudes towards using opioid analgesics to manage CNCP resulted in substantial increases in the use of prescription opioids (PO) in the North America (Donroe, Socias, & Marshall, 2018; Jones, Kaoser, & Fischer, 2021; Allen et al., 2017). This excessive rise in prescribing opioid analgesics resulted in growing numbers of opioid-related morbidity and mortality that devastated North America and is befittingly named the "Opioid Epidemic" (US Department of Health and Human Services, 2021; Canadian Institute for Health Information, 2019; Canadian Institute for Health Information, 2018; Jones, Kaoser, & Fischer, 2021; Fischer, Rehm, & Tyndall, 2016; IQVIA, 2021). The resulting mortality and morbidity have mainly manifested themselves as death or hospitalization due to opioid poisoning, opioid-use disorders, and adverse drug reactions (Fischer, Rehm, & Tyndall, 2016; Canadian Institute for Health Information, 2018; Fischer & Argento, 2012; US Department of Health and Human Services, 2021; Fischer, Jones, Vojtila, & Kurdyak, 2018; Pal, 2014).

Fischer et al. (2011) and Pal (2014) state that in the US the number of opioid-related deaths have more than tripled from 4000 deaths in 1999 to 13800 deaths in 2006. In 2016 and 2019 this grim figure further increased to 37273 and 70630 drug overdose deaths, respectively (Fischer,

Jones, Varatharajan, Malta, & Kurdyak, 2018; US Department of Health and Human Services, 2021). Sadly, the high opioid-related mortality, which has even adversely affected the life expectancy among select sub-populations in the US, is just the tip of the iceberg (Fischer, Jones, Varatharajan, Malta, & Kurdyak, 2018). In his publication Pal (2014) states that in 2013 for every overdose death in the US there were 825 nonmedical users, 130 PO abusers or dependents, and 32 emergency department visits due to drug misuse or abuse. Centers for Disease Control and Prevention (CDC) estimates that in 2017 the economic burden of opioid epidemic in the US had reached $1.02 trillion (2021).

The statistics of opioid-related morbidity and mortality in Canada is just as concerning as those of the United States. While opioid-related mortality statistics at national level are not available in Canada prior to 2016, analysis of provincial databases show a drastic rise in opioid-related deaths from 2005 to 2015 in all provinces (Donroe, Socias, & Marshall, 2018). For instance, Ontario's number of opioid-related deaths increased five folds from 1991 to 2014 (Fischer, Rehm, & Tyndall, 2016). Statistics Canada (2019) reported that in 2017 in Canada the number of accidental deaths due to poisoning, of which 94% were due to drug overdoses, had surpassed the number of accidental deaths due to transport accidents. These deaths that are mainly occurring among male adults aged 30 to 39 are mostly affecting British Columbia, Alberta, and Ontario. A report by Canadian Institute for Health Information (CIHI) (2018) Indicates that hospitalization and emergency department (ED) visits due to opioid poisoning have also risen in Canada from 2013 to 2017 with northern and western regions being the worst hit. The report also adds that Alberta alone experienced a 20% increase in ED visits due to opioid poisoning from 2017 to 2018 with Alberta youth aged 15 to 24 consistently having one of the highest rates from 2013 to 2017.

Since adolescents and young adults who receive PO analgesics for pain management are at high risk of being adversely affected, the objective of this study is to explore the possibility of creating a well-performing machine learning algorithm that can predict which individuals are more likely to suffer a negative outcome after receiving PO for treatment of CNCP. The results of this study may enable prescribers and policy-makers to identify adolescents who are likely to experience a negative outcome after starting PO therapy, and perhaps develop interventions to reduce or avoid the adverse effects in this age group.

3.2 Methods

Six electronic datasets that were maintained by Alberta Health were used to gather the necessary data for this research. Table 2.1 contains a description of these datasets. Residents of Alberta (AB) who are registered with the Alberta Health Care Insurance Plan (AHCIP) are all issued Unique Lifetime Identifiers (ULIs) which are used to link Alberta Health maintained datasets. For confidentiality purposes, these identifiers are scrambled by Alberta Health before the release of the data to a third party through employing a scrambling algorithms that still maintains the ability to link across datasets (Alberta Health, 2017).

Codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, butorphanol, dextropropoxyphene, meperidine, oxycodone, oxymorphone, morphine, nalbuphine, opium, tapentadol, tramadol, and pentazocine are the opioids that are included in this research. Methadone and buprenorphine are not included as they are generally used for the treatment of opioid dependence (Alford, Compton, & Samet, 2006; Connock et al., 2007).

Fischer et al. (2011) estimates that a large majority of PO used in Canada is dispensed in community pharmacies. Hence, for this study the Pharmaceutical Information Network (PIN) dataset was the main source used for obtaining data about PO dispensations in AB.

To perform analyses in this chapter SAS v9.4 (SAS Institute Inc., Cary, NC, 2017) software was used. Machine learning algorithms in this chapter were constructed and evaluated using Weka v3.8.5 (The University of Waikato, 2020) and Python v3.9 (Van Rossum & Drake, 2009).

3.2.1 Eligible CNCP Episodes

Since CNCP is defined as non-cancer pain that persists for more than three months, it was necessary to build episodes of PO consumption for individuals included in this cohort (Busse et al., 2017). Before data was released for this research, Alberta Health excluded patients treated for cancer pain based on the relevant ICD-9 codes in Claims dataset and ICD-10-CA codes in Inpatient and Ambulatory care datasets (ICD-9 codes, 2022; ICD-10-CA codes, 2022). For the purpose of this study, only episodes that had lasted for 90 days or longer, started between April 1st, 2010 and March 31st, 2015, and occurred to an individual aged 12 to 17 not suffering cancer were considered. Selecting a minimum of 90 days for a CNCP episode is consistent with the work of Edlund et al. (2014) who have concluded that this threshold can effectively exclude patients with acute pain. An eligible episode could have started and concluded in a single calendar year or lasted over the span of more than one calendar year. An individual could have more than one eligible episode in the span of this study.

An episode started when an initial event of opioid analgesic dispensation to an individual aged 12 to 17 occurred with no opioid dispensation in the prior 60 days. Supply day quantity plus

a 60-day washout were used to predict the end-date of each prescription. The washout period of 60-days was selected via data explorations that were similar to the work done by Katz et al. (2009). In the event that multiple POs were dispensed to an individual on the same day, each dispensation was counted independently in this episode. Additionally, the one with the longer supply period was used in constructing the episode. A new event in an episode would be a successive PO dispensation that occurred before the predicted end-date of the previous dispensation. An episode's end-date was the date of the last PO dispensation plus the days' supply of the last dispensing.

3.2.2 Outcomes

In this study a negative outcome is defined as subsequent death, hospitalization or requiring emergency care due to self-harm, drug/alcohol related issues, or poisoning that had occurred from the beginning of an eligible episode up to one year after its end-date. A positive outcome was when an episode and its consequent one-year follow-up period ended without a negative outcome.

The one-year follow-up period after the end date of an eligible episode is consistent with the work Oliva et al. (2020). In their publication investigating associations between overdose and suicide deaths among US Veterans after stopping POs and the length of PO use Oliva et al. (2020) have concluded that patients who have been treated for longer periods with POs before stopping were at greater risk of experiencing adverse outcomes. They have suggested that patients should be closely monitored for up to a year after receiving long-term PO therapies (Oliva et al., 2020). Since, the goal of this research is to produce a predictive ML model that results in the best health outcome for adolescents who are the subjects of this study, a one-year period after the end date of an eligible episode is used as a conservative timeframe.

To identify morbidities that were considered the negative outcomes of PO use for CNCP management for the purpose of this study, the main diagnoses fields of the Inpatient and Ambulatory Care datasets were used. The works by Dunn et al. (2010), Lo-Ciganic et al. (2019) and *ICD-10-CM Injury Surveillance Toolkit* published by Council of State and Territorial Epidemiologists (2021) were used as a guide to extract relevant ICD-10 injury codes associated with harms resulting from PO use. Finally, negative outcomes of interest were identified from the two datasets indicated above using the relevant ICD-10 codes.

To identify mortalities, the cause of death fields from the Vital Statistics – Deaths dataset were used. The CDC's *ICD Framework: External Cause of Injury Mortality Matrix (2015)* was used to identify all deaths caused by external injuries among the study subjects. Suicides, unintentional, and undetermined deaths which have occurred to study subjects during their PO use episode up to one year after its end were selected as mortalities of interest for further investigation.

3.2.3 Opioid Strength and Dosage

The association between PO dosage and experiencing negative outcomes in adult population has been widely studied. This association has resulted in guidelines such as "Guideline for Prescribing Opioids for Chronic Pain" by CDC (2016) and "The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain" (Busse et al., 2017) to recommend safe daily doses for POs and suggest that prescribers should avoid prescribing higher daily doses to their patients. Receiving higher PO dosage can be associated with experiencing adverse outcomes among adolescents with CNCP. In their publication, Chua et al. (2019) suggest that compared to adolescents that do not use POs, the risk of experiencing an overdose increases with each increase in the daily dose of POs among adolescents who have consumed POs for non-cancer pain. In its "Guideline for Prescribing Opioids for Chronic Pain" (2016) CDC warns against prescribing POs to pediatric population for

CNCP therapy particularly in high daily doses due to lack of sufficeint evidence about benefits and potnetial increased risk of harms of such treatment and the likelihood of experiencing future negative outcomes after using POs among this population. Hence, it is critical to study the total dosage and daily dosage of POs dispensed to this study population.

To determine the daily dose of each PO dispensation first the total number of medication dispensed was divided by the supply day quantity to determine the unit number of medications dispensed for each day. This number was then multiplied by the strength of that opioid medications in milligrams. The total PO dose for dispensation was simply calculated by multiplying the supply quantity of the drug by the strength of that medication in milligrams.

The potencies of opioid formulas can be converted to a standard unit called the morphine milligram equivalent (MME). For each opioid formula, an established conversion factor is multiplied by the daily dose of the dispensed PO (Maryland Department of Health, 2020). MME enables comparison of the strength of PO dispensations among study subjects. Furthermore, if multiple opioid medications are prescribed to one subject on the same day, it is possible to add prescription dosages using this standard unit. A standard equianalgesic conversion table was used to achieve the MME conversion based on relevant Drug Identification Numbers (DIN). For the purpose of this study, it was assumed that patients took the maximum dose prescribed to them as they were instructed.

3.2.4 Data Features

Many researchers have pointed to a paucity of literature in regard to risk factors that lead to experiencing opioid and drug related adverse outcomes among youths and adolescents. For example, in their systematic review of risk factors for drug overdose among young people by

Lyons et al. (2019), from the 9607 publications that they found in their original search only 12 articles were finally included in their review. The literature is even more sparse when it comes to using administrative data to find risk factors associated with adverse effects of PO use among adolescents. The majority of research done in this field suggest combinations of psychological, environmental, sociodemographic, and even genetic factors could be associated with experiencing negative outcomes among adolescents who use opioids. Various combinations of factors such as being treated for psychiatric comorbidity or experiencing perceived stress, childhood trauma, unstable housing, having family members who use POs and witnessing an OD in a family member or a friend, being from a minority race, being male, and rural residence are indicated by numerous researchers as factors associated with increased risk of opioid misuse and overdose among youths and adolescents (Groenewald , Law, Fisher, Beals-Erickson, & Palermo, 2019; Lyons , Yule, Schiff , Bagley, & Wilens, 2019; Miech, Johnston, O'Malley, Keyes, & Heard, 2015; Monnat & Rigg, 2016; Nguyen, Glanz, Narwaney, & Binswanger, 2020; Pielech, Lunde , Becker, Vowles, & Sieberg, 2020; Silva, Schrager, Kecojevic, & Lankenau, 2013; Tabar et al., 2020). While some of these risk factors, such as psychiatric comorbidities, sex, and residence can be extracted from administrative data used for this research, many of these risk factors are not available. Considering the sparsity of literature that have used risk factors associated with negative outcomes related to opioid use among adolescent solely from administrative data, adult-related literature in this field were also used to find features that could be useful for this research.

To determine the subject's baseline sociodemographic characteristics, the first PO dispensation event in each episode was used. Gender was directly extracted from the population registry dataset. Age was calculated based on subject's date of birth at the baseline. Being a male, a rural resident, and an older adolescent are indicated as risk factors for opioid misuse and overdose

among adolescents (Groenewald , Law, Fisher, Beals-Erickson, & Palermo, 2019; Monnat & Rigg, 2016; Pielech, Lunde , Becker, Vowles, & Sieberg, 2020). The first three digits of each subject's postal code, the Forward Sortation Area (FSA), was used to determine their residence as rural or urban. The Census year 2016 data downloaded from the Canadian Census Analyzer provided by the University of Toronto (2014) was used to determine the median community household income for each subject based on their FSA.

After finding the first dispensation in each episode of interest, the date of the dispensation and up to three months prior to that date were searched in the Claims and Inpatient datasets in order to identify the closest record. In case a diagnosis was not found in that period a 'Missing' diagnosis was assigned to that record and the episode was removed from the eligible episodes. To establish the diagnoses that made prescribing PO analgesics necessary as the baseline cause of disease, the primary diagnosis fields in the Claims and Inpatient datasets and the *International Classification of Diseases, 9th Revision* [ICD-9] (2022) and *International Classification of Diseases, 10th Revision, (Canadian Modification)* [ICD-10-CM] (2022) codes were used.

Duration of PO use and multiple PO prescriptions have also been suggested as risk factors for misuse and overdose among both adolescents and adults (Edlund et al., 2014; Pielech, Lunde , Becker, Vowles, & Sieberg, 2020). Hence, based on each constructed episode, total number of dispensations in the episode and episode duration for each subject were calculated. The total MME for each episode was calculated by adding up MMEs for all days in that episode. This number was then divided by the total number of days in the episode to calculate an average MME for that episode. *The 2017 Canadian guideline for opioids for chronic non-cancer pain* (2017) and CDC's *Guideline for Prescribing Opioids for Chronic Pain* guideline (2016) advise levels lower than 90

MME as safe PO dosage for patients with CNCP. For each episode of interest, the number of days the subject had received MME $\geq$ 90 was also calculated.

3.2.5 Feature Selection and Statistical Analysis

The final dataset contained 699 episodes (observations) and 25 main features plus one binary dependent variable (class variable or label). The original 25 features were later expanded to 39 features that were better suited for creating ML algorithms using feature engineering techniques such as one-hot encoding, binning, and scaling (Rençberoğlu, 2019).

To select the best and most efficient subset of features for creating ML algorithms in this study, both filter and wrapper methods were used. Filter methods use statistical methods to find the correlation between one or subsets of feature and the class while wrapper methods use specific ML algorithms to evaluate various combinations of subsets of features to find the best feature subset (Verma, 2020). The wrapper subset evaluation, the information gain attribute evaluation, and the CFS subset evaluation options in conjunction with best first and ranker search methods in Weka were used to perform feature selection for this study. Using these feature evaluation methods, several feature subsets were then selected, and numerous ML algorithms were trained and evaluated with these subsets to find the best combinations of features and algorithms for the purpose at hand.

Baseline characteristics were compared between study subjects with or without a negative outcome. Comparisons were done using Student's t-test, $\chi 2$, or Fisher's exact test with a two-tailed $p<0.05$ being considered significant.

3.2.6 Model Selection and Evaluation

Challenges that were addressed in this research were working with a class-imbalanced dataset that has rather limited number of observations, particularly in regard to the negative outcome or the minority class. A class-imbalanced dataset is a dataset in which one class outcome is far less frequent than the other class outcomes (Khalilia, Chakraborty, & Popescu, 2011; Wadekar, 2019; Ramezankhani et al., 2016; Mienye & Sun, 2021). From the 699 episodes that made up the dataset for this study, 71 episodes, 10.16% of all episodes, had a negative outcome. Since in this dataset the positive outcome, or the majority class, contains almost nine times more observations than the negative outcome, or the minority class, this dataset is said to be class-imbalanced. A class-imbalance between positive and negative outcomes makes developing ML algorithms very challenging as most classifiers assume that the distribution of the class variable is uniform. Otherwise, they simply favor the class outcome that is in majority (Khalilia, Chakraborty, & Popescu, 2011; Brownlee, 2020; Ramezankhani et al., 2016). To overcome this challenge random undersampling was performed to extract a class-balanced dataset from the original dataset (Brownlee, Random Oversampling and Undersampling for Imbalanced Classification, 2020).

As mentioned earlier, another challenge that was faced in this research was having a limited number of observations in this study (a total of 699 observations of which only 71 were negative outcomes). Two evaluation procedures are mainly used in machine learning; dataset splitting and k-fold cross-validation (Gunasegaran & Cheah, 2017; Brownlee, 2018; Bronshtein, 2017). For a class-imbalanced dataset with limited number of observations both Brownlee (2018) and Gunasegaran and Cheah (2017) recommend using a 10-fold cross-validation procedure as it minimizes biases and reduces the chance of overfitting the model, thus improving the predictive accuracy of the algorithm.

Several commonly used ML classifiers were developed, adjusted, and evaluated using sets of features that were deemed to be most efficient for them. These classifiers were selected based on available literature and included decision tree (DT), random forest (RF), gradient boosting machine (GBM), logistic regression (LR), naïve Bayesian network (NB), and adaptive boosting (adaBoost) (Lo-Ciganic et al., 2019; Amirabadizadeh, Nazemi, Vaughn, Nakhaee, & Mehrpour, 2018; Tabar et al., 2020; Ramezankhani et al., 2016; Mienye & Sun, 2021).

Selecting the evaluation metrics for this study was perplexing, as well. Not only the dataset was class-imbalanced but also it was important to correctly identify individuals with a negative outcome (those in the minority class). In other words, the cost of missing an episode that ends with a negative outcome was higher than incorrectly classifying someone who did not suffer a negative outcome. Hence, it was critical to use cost-sensitive evaluation measures and one could not just rely on measures such as model accuracy. Several evaluation measures, namely, accuracy, area under the receiver operating curve (AUC), recall (or sensitivity), precision (or positive predictive value), and F-score were used to evaluate these algorithms to select the best one (Lo-Ciganic et al., 2019; Tabar et al., 2020; Ramezankhani et al., 2016; Bekkar, Djemaa, & Alitouche, 2013). However, the most important evaluation measure was recall. Recall in ML is the equivalent of sensitivity or true positive rate (TPR) in epidemiology (Ramezankhani et al., 2016; Ghoneim, 2019; Bekkar, Djemaa, & Alitouche, 2013):

$$Recall = Sensitivity = \frac{True\ positive}{True\ positive + False\ negative}$$

The F-score and the AUC curve were also important evaluation measures for these models. F-score is the harmonic mean of recall and precision (Bekkar, Djemaa, & Alitouche, 2013; Ghoneim, 2019):

$$F - score = \frac{2 \times Recall \times Precision}{Recall + Precision}$$

F-score is suitable for datasets with an uneven class distribution since an algorithm that performs better on the minority class achieves a higher F-score (Bekkar, Djemaa, & Alitouche, 2013; Ghoneim, 2019). Finally, the area under the ROC curve, which represents the relationship between true-positive rate (sensitivity) versus false-positive rate (1-specificity) for all possible threshold, was selected as another critical evaluation measure in this study (Joy, penhoet, & petitti, 2005; Bekkar, Djemaa, & Alitouche, 2013). This measure is preferred over accuracy for class-imbalanced datasets (Bekkar, Djemaa, & Alitouche, 2013).

3.3 Results

A total of 699 eligible episodes were constructed for this study. Out of these 699 episodes 607 of them were the first episodes and the rest were subsequent episodes (74 individuals had experienced two or more episodes). Six deaths had occurred among the study subjects that were caused by external injuries and had occurred during their PO use episodes or up to one year after the episodes' end dates. From these deaths two were caused by poisoning of undetermined intent, three were suicides, and one was the result of a transportation accident. Hence, the first five mortalities were included in this study as negative outcomes of interest. Characteristic distribution of the episodes included in this study are presented in Table 3.1.

Table 3. 1 Characteristic distribution of eligible episodes overall and by outcomes

Features	Total Episodes (n=699) mean±SD/n (median)	No Negative Outcome (n=628) mean±SD/n (median)	Negative Outcome (n=71) mean±SD/n (median)	P-Value
Age (years)	16.53±1.33 (17.01)	16.48±1.35 (16.95)	16.97±0.98 (17.40)	0.002
Sex				
Females	444	400	44	0.7750
Males	255	228	27	
Residence				
Rural	242	216	26	0.7088
Urban	457	412	45	
Median Community Household Income (CAD$)	103532.1±20958.4 (99607)	103896.6±21113.6 (99654)	100307.9±19372.6 (97235)	0.17
At Least One High-Dose Day (≥90 MME)	52	44	8	0.1946
Total Dose MME	2411.29±6846.31 (816)	2255.22±6911.97 (795)	3791.71±6107.27 (1494)	0.073
Average Daily Dose MME	11.18±27.18 (5.23)	10.87±27.78 (5.13)	13.92±21.2 (6.67)	0.2703
Episode Duration (days)	191.42±140.14 (141)	182.73±134.2 (138)	268.3±166.92 (239)	<0.0001
Number of Dispensations	9.36±26.81 (5)	8.21±23.52 (5)	19.45±45.78 (9)	0.0451
Cause of Disease*				
Ch. 1	18	16	2	0.7034
Ch. 3	16	13	3	0.2160
Ch. 4	4	4	0	1.0000
Ch. 5	96	80	16	0.0230
Ch. 6	46	43	3	0.6117
Ch. 7	3	3	0	1.0000
Ch. 8	113	107	6	0.0625
Ch. 9	33	30	3	1.0000
Ch. 10	30	25	5	0.2170
Ch. 11	5	5	0	1.0000
Ch. 12	31	29	2	0.7602
Ch. 13	92	83	9	0.8984
Ch. 14	5	4	1	0.4156
Ch. 16	16	16	0	0.3927
Ch. 17	126	113	13	0.9476
Ch. 18	65	57	8	0.5468

* Diagnoses are based on ICD-9 chapters

A feature importance plot showing these main 25 features and Weka's information gain attribute evaluation technique to demonstrate their importance is provided here for visualization (Figure 3.1).

Figure 3. 1 Feature importance plot
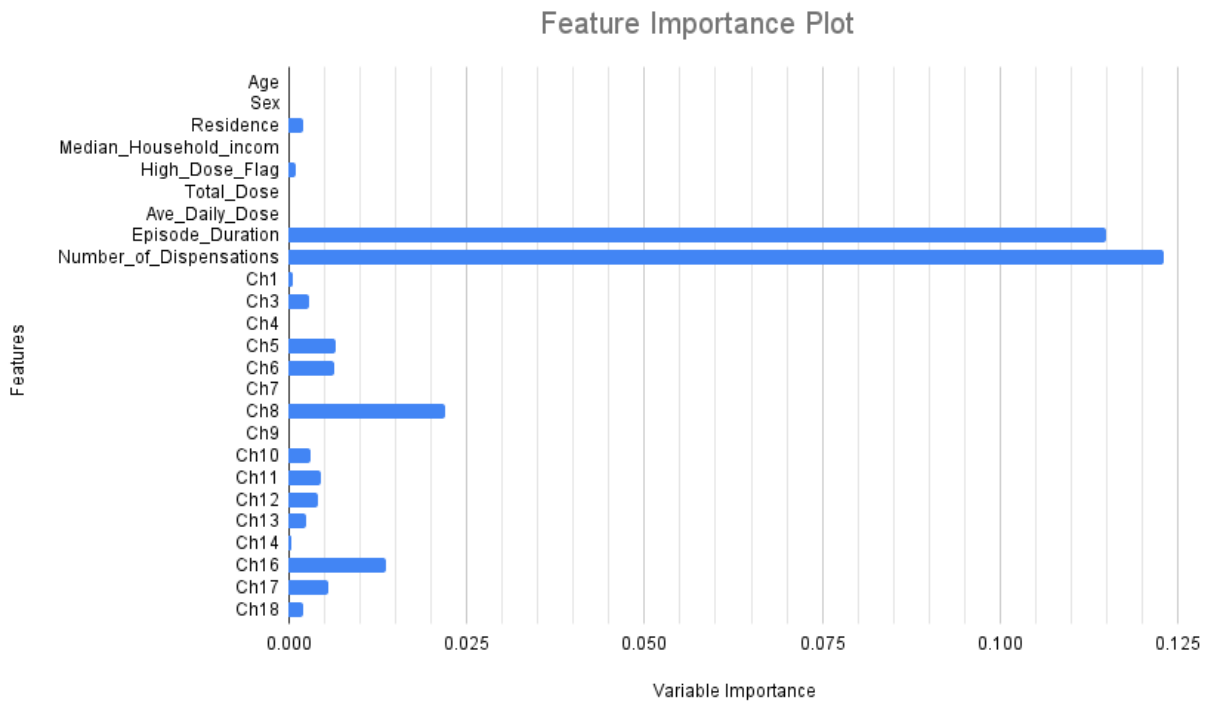
* Diagnoses are based on ICD-9 chapters

The average age was higher among subjects who experienced a negative outcome, and the difference was significant. The age distribution for both outcome groups were left-skewed. No significant differences were observed among the study subjects in each of the two outcome groups in terms of their genders, places of residence, or median community household incomes. In terms of qualities of each episode, those who had longer episodes were more likely to experience negative outcomes. Distributions of episode durations and number of prescriptions in the episodes for both outcome classes were right-skewed. The median duration of episode for those with a negative outcome was about 100 days longer than those without a negative outcome. Moreover,

subjects who had gone through more dispensations during their PO use episodes were more likely to experience negative outcomes. However, the differences between the average daily dose MME or the average of total PO dose MME were not significant between the subjects in the two outcome groups. In addition, no association at the 0.05 significance level was observed between receiving at least one high-dose day of PO that was larger than or equal to 90 MME and having a negative outcome among the study subjects. In regard to the baseline cause of disease, there was only an association between having a mental disorder diagnoses at the baseline (Chapter 5, ICD-9 codes) and having a negative outcome at the 0.05 significance level.

Episode duration and number of dispensations in the episode were the most important features appearing in all the feature groups selected by feature-selection methods used in this study. Other features that were instrumental in enhancing the performance of some algorithms were diagnoses of mental disorder at the baseline and having baseline age above average 16.53 years. The best performing algorithms was RF classifier.

Table 3. 2 Performance of ML algorithms in predicting the negative outcome of PO prescription for CNCP management in Adolescents 12 to 17

Algorithm	Accuracy	AUC	Recall	Precision	F-Score
RF	0.71	0.85	0.86	0.61	0.72
AdaBoost	0.73	0.74	0.73	0.66	0.70
GBM	0.63	0.77	0.73	0.55	0.63
DT	0.70	0.69	0.66	0.65	0.64
LR	0.67	0.69	0.37	0.72	0.47
NB	0.65	0.68	0.24	0.62	0.34

3.4 Discussion

In a report by CIHI (2018) it is claimed that in Alberta the two age groups that have experienced the highest rates of opioid poisoning ED visits between 2013 to 2017 are the 15 to 24

year-old youths and 25 to 44 year-old adults. Same report also states that after young adults aged 25 to 44, youths aged 15 to 24 have had the second fastest-growing rate of opioid-poisoning in Canada from 2013 to 2017. In an study done on individuals less than 20 years of age by Allen et al. (2017) it is reported that teenagers had higher odds of being admitted to hospitals for serious negative outcomes after PO exposure compared to younger children. This is consistent with the finding of this study that the average age for individuals having episodes that ended in negative outcome was 16.97±0.98 years and significantly higher than the average age of those in the other group. While the average age difference between the two outcome groups was statistically significant, the age of the participant was not one of the main factors that emerged from feature selection methods used in this study. The reason could have been because the age category for this study was a small period of only six years (12 to 17 years).

Among adult populations, males were found to be more at risk of experiencing negative outcomes such as opioid misuse, initiating other hard drugs, hospitalization due to PO poisoning, and overdose death (Ives et al., 2006; Canadian Institute for Health Information, 2018; Wilton et al., 2021; Hall et al., 2008). In Canada in 2017 men of all ages suffered more deaths due to accidental drug overdoses than their female counterparts (Statistics Canada, 2019). The statistics published in a report on CDC's website show that between 1999 to 2015 male adolescents aged 15 to19 had consistently higher death rate due to drug overdose than their female counterparts in the US (Curtin, Tejada-Vera, & Warner, 2017). The results from this study suggest that among 12- to 17-year-old adolescents having opioid dispensation episodes of 90 days or longer for CNCP treatment gender was not statistically associated with having a negative outcome. This inconsistency might be related to another variable: social support. In their systematic review of opioid-related overdose and socioeconomic marginalization Van Draanen et al. (2020) have

included many publications that have found strong negative association between measures of social support, such as marital status and living arrangements, and experiencing an overdose. Male 12- to 17-year-old adolescents, who are subjects of this study, are unlikely to live alone and without a parent or a guardian. On the other hand, adult males are more likely to live either alone or with their partners. This difference in living arrangement and social support can be associated with a higher risk of negative opioid-related outcome among male adults. In addition, the individual's place of residence (rural or urban) was not associated with having a negative outcome, either. This is consistent with a report published by CIHI (2018) that indicates that in Canada rates of opioid poisoning ED visits varies more by census subdivisions rather than living in urban areas or small cities.

One of the risk factors for overdose and opioid-use disorder that is frequently mentioned in the relevant literature is having a mental or psychiatric disorder (Webster, 2017; Fischer & Argento, 2012; Allen et al., 2017; Wilton et al., 2021). As can be seen in Table 3.1 having a mental disorder (Chapter 5, ICD-9 codes) was the only baseline cause of disease that showed significant association when it came to having a negative outcome. Although having mental health issues at the baseline and having a negative outcome were associated, it was not a very influential feature in developing ML algorithms for this study. This feature was employed in the developing of the RF model. But, it provided small enhancements to the performance of this model. This could be because only a small number of those who had negative outcome were diagnosed with mental issues at the baseline (16 cases). For reference, that is not much larger than the 13 cases diagnosed with injury and poisoning (Chapter 17, ICD-9 codes) who developed a negative outcome while having an injury or poisoning diagnoses at the baseline was not associated with having a negative outcome.

Many guidelines and literatures suggest links between receiving high doses of PO and increased risk of having a negative outcome (Centers for Disease Control and Prevention, 2016; Canadian Institute for Health Information, 2019; Dunn et al., 2010; Fischer, Rehm, & Tyndall, 2016). However, this study did not find the association between receiving high daily dose of above 90 MME and experiencing a negative outcome to be significant. Furthermore, the differences between the two outcome groups for averages of total dose MME and the averages of daily MME dose were not statistically different. This could be because the majority of studies that assessed the risk factors for having negative outcomes as a result of using PO were done among adult population. Among adolescents and youths, some researchers have listed chronic pain itself as a risk factor for opioid misuse. As explained by Pielech et al. (2020) and Groenewald et al. (2019) when pain is not properly treated in some adolescents they could resort to self-prescribing opioids to alleviate their pain. Pielech et al. (2020) state that a frequently mentioned driver for opioid self-medication and misuse among adolescents is, in fact, pain relief. It appears that prescribing low total and daily doses of POs to treat CNCP for adolescents could act as a double-edged sword that results in further negative outcomes for some who may not be satisfied with their pain treatment.

Duration of the episode was one of the main features that were best predictive of the negative outcome of each episode. The average duration of episodes that had ended in a negative outcome were longer than those that did not and the difference was significant. This is consistent with the work of Edlund et al. (2014) who had concluded that risk of opioid use disorder was primarily influenced by the duration of opioid treatment rather than by the dose given each day. In addition, Webster (2017) and Boscarino et al. (2010) have suggested that the duration of pain can also be a risk factor for experiencing negative outcomes such as self-harm, suicide, or drug-

dependence among those using PO analgesics for chronic pain. The duration of therapy in this study could be an indirect indicator of duration of pain for the study subjects.

Number of dispensations in the episode was also a major predictive feature in this study. Individuals who on average had more dispensations throughout their PO use episode were more likely to experience a negative outcome. In their publication White et al. (2009) have concluded that 4 prescription or more when measured over a period of 3 months and 12 prescriptions or more when measured over a period of one year are risk factors for opioid abuse. Furthermore, in their article Pielech et al. (2020) have mentioned that the risk of experiencing negative outcomes increases drastically among older adolescents who have received multiple outpatient opioid prescriptions.

Tree-based ML algorithms are very popular in healthcare and medical sciences (Amirabadizadeh, Nazemi, Vaughn, Nakhaee, & Mehrpour, 2018; Banerjee, Reynolds, Andersson, & Nallamothu, 2019; Ramezankhani et al., 2016). These algorithms are hierarchical predictors that are easy to construct, have good accuracy, and are intuitive to interpret. A random forest is an ensemble of many simple DTs. Basically, instead of optimizing a complex tree on the training data, which could increase the chance of overfitting and reduce stability of the tree, in a random forest many simple DTs are produced and the output class would be a vote between all trees (Banerjee, Reynolds, Andersson, & Nallamothu, 2019; Khalilia, Chakraborty, & Popescu, 2011). In this study RF was selected as the best model for identifying episodes that resulted in a negative outcome. The three features that this classifier used were duration of the episodes, number of dispensations in the episode, and having a mental disorder diagnoses at the baseline. Among the classifiers listed in Table 3.2, RF has demonstrated the best recall, AUC, and F-score. As was mentioned in Section 3.2.6 of this chapter a high recall or sensitivity is critical for this study since

it is important to not miss individuals that might have a negative outcome after going through an episode of PO use for CNCP therapy. The recall for the RF classifier developed for this research shows that 86% of episodes that resulted in negative outcomes were correctly identified by the classifier. The precision for the RF model is not very high. However, it should be remembered that there is generally a trade-off between precision and recall. The formula for precision is (Ghoneim, 2019; Bekkar, Djemaa, & Alitouche, 2013):

$$Precision = \frac{True\ positive}{True\ positive + False\ Positive}$$

The precision of 0.61 for this classifier indicates that of all the episodes who were labeled by this classifier as likely to have a negative outcome, 61% did have negative outcomes. When dealing with a cost-sensitive scenario, like the one at hand here, tuning the algorithm to maximize identifying those with negative outcomes inevitably results in an increase in mislabeling of those who did not have negative outcomes. In the RF model developed for this study, improving recall has resulted in an adverse effect on precision.

The accuracy for the selected RF model is not the highest either. However, the AUC for the model is higher than all other models. According to Bekkar et al. (2013) AUC is a better evaluation measure for datasets that are class-imbalanced and have dissimilar misclassification costs when compared with accuracy.

This study has many strengths including using a large population-based sample to construct the episodes of interest and using pre-existing administrative data that made it time and cost effective. The ML classifier developed for this study can be generalized to be used among adolescents in Alberta who are between 12 and 17 and are prescribed opioid analgesics for CNCP

therapy to predict adverse outcomes. Moreover, the classifier uses only three features to identify majority of episodes that are likely to end in negative outcomes which makes the classifier simple, fast, and stable.

This study has several limitations due to using administrative data. First, the study suffers from immortal time bias; participants should have gone through episodes of at least 90 days of PO use before they were eligible to be considered for this study. This is a limitation of using administrative data for this study. The way to address this bias would have been doing surveys from prescribers or patients to identify individuals who were prescribed PO for CNCP therapy but discontinued the use in less than 90 days due to experiencing negative outcomes. Moreover, many assumptions were made in constructing the episodes. For example, it was assumed that patients took their opioid medications according to directions that the drugs were prescribed to them. That might not be the case for some of the participants. Furthermore, many useful characteristics were not available in the administrative data used in this research, such as previous history of drug or alcohol misuse, identifiers to uniquely identify prescribers or pharmacies that patients used for PO use needs, an indicator describing pain as chronic or acute, or indication of severity of the pain.

3.5 Conclusion

This study shows that it is possible to create an ML classifier that could identify adolescents that are in risk of developing negative outcomes after receiving opioid analgesics for chronic non-cancer pain management. The random forest classifier developed in this study demonstrated a good recall, AUC and F-score. Of all episodes that ended in negative outcomes, this classifier was capable of correctly labeling 86% of them. Considering the importance of capturing episodes that result in a negative outcome after using PO for CNCP therapy this algorithm shows significant potentials to be used by policy-makers and prescribers.

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CHAPTER 4

OVERVIEW AND FUTURE DIRECTIONS

4.1 Overview

In this chapter a quick review of the previous chapters and the main contributions of this thesis are presented. Next, some research directions that might interest future researchers are proposed.

4.2 Summary and Contributions

In chapter one a brief historical context and review of previous research on prescription opioids (PO) was presented. Chronic non-cancer pain (CNCP) in adolescents, its personal and social burden and hence, the importance of treating CNCP in adolescents were briefly reviewed. Next, the role of opioids in the treatment of CNCP, its mechanism of action on human body, and the short-term and long-term side effects of using opioids among adolescents were shortly discussed. Finally, the importance of research into epidemiology and identification of those who are likely to experience negative outcomes after long-term PO use among adolescents were discussed.

The second chapter was dedicated to the epidemiology of opioid dispensation among adolescents aged 12 to 17 years treated for non-cancer pain and residing in Alberta from April 1st, 2010 to March 31st, 2015 and diagnosis for which they were prescribed opioid analgesics. The results of this study showed that the PO dispensation rates for the study population was smaller than the general public in Alberta. Moreover, the left-skewed age distribution suggest that the older adolescents received more PO dispensation compared to younger adolescents. The annual incidence proportion of PO dispensations among adolescents not treated for cancer pain in Alberta

had an increasing trend from 2010 to 2015. An increasing trend was also observed in the annual ratios of opioid analgesics dispensed over all prescriptions dispensed to the study population. Males and rural residents both had higher ratios of PO dispensed over all prescriptions dispensed annually compared to their female and urban resident counterparts. This was a concerning trend since other age groups in Canada had gone through decreasing PO dispensation trends (Canadian Institute for Health Information, 2019; Fischer, Jones, & Rehm, 2014; IQVIA, 2021). The main reason for seeking pain therapy among this study population was for injuries and males were more likely to require PO for injury-related pain management than females.

Since CNCP is defined as nonmalignant pain persisting for 3 months or longer (Busse et al., 2017), in the third chapter individuals who had gone through episodes of 90 days or more of consecutive PO dispensation were identified. Next, episodes that resulted in a negative outcome, such as hospitalization or requiring emergency care due to self-harm, drug/alcohol related issues, or poisoning or death that had occurred from the beginning of an eligible episode up to one year after its end date were labelled. These labels were used in creating and evaluating a random forest algorithm that could predict which episodes were likely to result in a negative outcome with high sensitivity (recall), F-score, and AUC. The features used to create this random forest model were the number of dispensations in an episode, length of the episode, and mental disorder as the cause of starting PO analgesics.

This research contributes to the PO analgesics body of knowledge by proposing a simple machine learning algorithm with very good evaluation metrics for predicting PO dispensation episodes of 90 consecutive days or longer that might result in a negative outcome among 12 to 17 years of age adolescents not treated for cancer-pain. Predicting which adolescents might experience a negative outcome after using PO analgesics for CNCP management is crucial since

adolescents have some of the highest risks when it comes to suffering outcomes such as overdose mortalities and morbidities such as ED visits and hospitalization (Allen et al., 2017; Canadian Institute for Health Information, 2018; Connock et al., 2007; Miech, Johnston, O'Malley, Keyes, & Heard, 2015; Voepel-Lewis et al., 2018). Many studies have used statistical modeling methods to identify risk factors for experiencing negative outcomes after initiating PO use among CNCP sufferers (Boscarino et al., 2010; Dunn et al., 2010; Edlund et al., 2014; Hall et al., 2008; Ives et al., 2006; White, Birnbaum, Schiller, Tang, & Katz, 2009; Wilton et al., 2021; Yang et al., 2015). But very few have focused on predicting which episodes are likely to have a negative outcome. This research helps to move beyond the identification of risk factors and into using the sophisticated associations between them to actually predict who is likely to develop a negative outcome.

4.3 Future Directions

Rather than being collected for research purposes, the data used in Chapters 2 and 3 was collected for administrative purposes. While use of administrative data in research is cost and time effective, it affects the quality of the research. Many useful features such as the family dynamics of study subjects, their education status, previous issues with alcohol or drugs, or their proximity to other drug abusers at home or school were not included in this data. These features might have been very critical in predicting who was more likely to suffer a negative outcome after initiating long-term PO use. In order to produce even better machine learning algorithms that are easier to understand and have better predictive abilities, it is necessary to collect data that is meant to be used for this purpose.

There are also other features that could be extracted from the data at hand to be used in future research such as:

- It has been suggested that some drug interactions, particularly that between PO and *Benzodiazepines*, increase the risk of experiencing negative outomes among PO users (Edlund et al., 2014; Lo-Ciganic et al., 2019). Cases of co-prescription of PO and *Benzodiazepines*, or other medications that might negatively interact with POs, can be found and included as a feature for future studies.

- White et al. (2009) have suggested that early PO refills and escalating dosages are two other risk factors associated with experiencing negative outcomes after long-term PO consumption. It is possible to make assumptions to establish the dosage trend and early refilling of the opioid prescriptions among study subjects based on the administrative data used in this study. These features can also be included in the future studies.

A very important assumption made in this study is that all the PO analgesics that are dispensed were consumed in full and as per prescribers' directions by the study subjects. This is a critical assumption that is most likely not true for some of the study subjects. This assumption may affect both the epidemiologic and analytic parts of this research in chapters 2 and 3. Future research could greatly benefit if true PO use habits of their study subjects could be quantified instead of making such assumption.

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