10-18-2024

Marijuana Legalization and Opioid Use Disorder in Ontario, Canada, From 2015 to 2021

LUKE OME AGADA
Walden University

Walden University

College of Health Sciences and Public Policy

This is to certify that the doctoral dissertation by

Luke Ome Agada

has been found to be complete and satisfactory in all respects,
and that any and all revisions required by
the review committee have been made.

Review Committee
Dr. James Rohrer, Committee Chairperson, Public Health Faculty
Dr. Howell Sasser, Committee Member, Public Health Faculty

Chief Academic Officer and Provost
Sue Subocz, Ph.D.

Walden University
2024

Abstract

Marijuana Legalization and Opioid Use Disorder in Ontario, Canada, From 2015 to 2021

by

Luke Ome Agada

MPH, Walden University, 2013

MSc, University of Benin, 1999

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Epidemiology

Walden University

October, 2024

Abstract

This study examined the trends in opioid-related hospitalizations and deaths in Ontario, Canada, from 2015, to 2021, with a particular focus on the periods before and after cannabis legalization. The social problem addressed was the ongoing opioid crisis, exacerbated by rising opioid-related health issues. Grounded in the harm reduction theory, this research explored whether cannabis legalization could serve as a substitute to mitigate opioid use disorder. Data were extracted from the Discharge Abstract Database, Emergency Department Database, National Ambulatory Care Reporting System, and Hospital Morbidity Database. Analysis using the generalized estimation equation (GEE) method revealed a significant increase in opioid-related hospitalizations, which rose from a mean of 405.56 (SD = 38.67) in 2015 to 1486.33 (SD = 49.803) in 2021, representing 366% increase. The hospitalization rate notably increased twofold in 2020 and threefold in 2021 compared to 2015. A one-way ANOVA demonstrated a statistically significant effect of time on both hospitalizations, $F(6,65) = 37.67$, $p < 0.001$, and deaths, $F(6,65) = 8.67$, $p < 0.001$. The GEE analysis indicated a significant rise in monthly hospitalizations from the illegal to the legal cannabis period ($B = 61.99$, $SE = 6.37$, $p < 0.001$), along with significant yearly increases in opioid-related deaths from 2015 to 2021. These findings suggest that opioid-related health issues intensified during the cannabis legalization era, though the specific impact of the COVID-19 pandemic on these trends remains unclear. The study's implications for social change include insights into the potential role of cannabis legalization as a harm reduction strategy, which could inform policies aimed at addressing the opioid crisis.

Marijuana Legalization and Opioid Use Disorder in Ontario, Canada, From 2015 to 2021

by

Luke Ome Agada

MPH, Walden University, 2013

MSc, University of Benin, 1999

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Epidemiology

Walden University

October 2024

Dedication

This dissertation is dedicated to my father, Peter Agada Okoh, and my mother, Theresa Uweh Agada, whose encouragement inspired me to pursue higher education. To my wife, Dr. Abieyuwa Agada, for her unwavering support, and to my children, Glory, Praise, and Peace Agada, who patiently endured my years of study and writing.

Acknowledgments

I extend my deepest gratitude to my chair, Dr. James Rohrer, for his invaluable guidance and unwavering support throughout the dissertation process. Your insightful feedback has been instrumental in shaping me as a scholar. I would also like to express my sincere thanks to my committee member, Dr. Howell Sasser, for his invaluable feedback, which greatly enhanced the quality of my quantitative research. Your wealth of knowledge has been a tremendous resource. Finally, I would like to acknowledge the Canadian Institute for Health Information (CIHI) for providing access to the secondary data used in this study.

Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction to the Study

Background

The United States and Canada continue to grapple with the consequences of the opioid overdose crisis. Despite numerous intervention programs designed to counter the problem, the opioid crisis continues to grow worse. In 2019, over 10 million people misused opioids, with an estimated 48,000 deaths within 12 months, and a total of 1.6 million people had an opioid use disorder (OUD) in the United States (Olfson et al., 2020).

The Centers for Disease Control and Prevention reported an opioid-related death (ORD) of 115 people per day in the United States in 2018 (Centers for Disease Control and Prevention, 2020). Between October and December 2020, there were 6,214 apparent opioid toxicity deaths and 1,716 between July and September 2020 in Canada. The COVID-19 pandemic appears to be worsening the opioid crisis; there is an 89% (5,148 apparent opioid deaths) increase in opioid-related-death since the onset of the COVID-19 pandemic (April to December 2020), compared to 2,722 apparent opioid deaths in the same period in 2019 (Public Health Agency of Canada, 2021). The opioid epidemic is a global crisis, with an estimated 26–36 million people with OUD around the world (Olfson et al., 2020).

As with the trend of ORD, the hospitalization rate from opioid overdose is significantly higher in the United States and Canada compared to the previous decade. About 24,670 opioid-related overdose hospitalizations occurred in Canada from January 2016 to December 2020 (Olfson et al., 2020). Preliminary data have indicated that 1,406

opioid poisoning hospitalizations occurred between October and December 2020 in Canada; this value represents a 40% increase in hospitalization compared to the period from July to September 2020 but a 40% increase compared to October to December 2019 (Public Health Agency of Canada, 2021). In addition to the rise in hospitalization, death, and poor quality of life, OUD significantly contributes to the overall cost of health care. The United States spends $78.5 billion on the opioid crisis per annum, while Canada spends $3.5 billion annually (Cheung, 2020).

Despite the several public health intervention programs implemented to prevent or reduce OUD over the past 2 decades, there has yet to be an effective intervention that addresses the problems of OUD (Blanco et al., 2020). Many scholars have recommended the need for a broader intervention program to alleviate the impact of OUD. A growing body of research suggests that increasing access to medical and recreational Cannabis may play a role in mitigating the opioid crisis (Centers for Disease Control and Prevention, 2020; Weiner et al., 2020; Wiese & Wilson-Poe, 2018). Observational and epidemiological studies have found an association between medical Cannabis use and opioid morbidity and mortality (Weiner et al., 2020; Wiese & Wilson-Poe, 2018). This dissertation study sought to verify if such an association exists between recreational Cannabis use and OUD. Canada legalized the use of recreational marijuana on June 18, 2018 (Government of Canada, 2021). A positive finding from this study further supports the claims that nationwide access to cannabis could provide the urgently needed solution to the current opioid crisis in North America.

Problem Statement

There have been several claims suggesting that increasing access to cannabis through marijuana decriminalization can reduce opioid-related hospitalizations (ORHs) and deaths from overdose (Bachhuber et al., 2014; Bradford et al., 2018; Li & Chihuri, 2020; Shi et al., 2019; Livingston et al., 2017; Vyas et al., 2018). In the United States, Bachhuber et al. (2014) reported a 24.8% annual reduction in opioid overdose mortality rate in states with medical cannabis laws compared to states with a total prohibition of cannabis use from 1999 to 2010. Shi et al. (2019) also reported a 29.6% reduction in the number of opioid prescriptions, a 29.9% reduction in opioid dosage, and a 28.8% reduction in opioid-related Medicaid spending in states with medical cannabis legalization compared with states without such law.

Contrary to the claim that enhancing access to marijuana use has the potential to reduce opioid-related harms, Shover et al. (2019) reported that states with medical cannabis laws experienced a 22.7% increase in opioid overdose deaths, a complete reversal of the earlier reports by Bachhuber et al. (2014). Shover et al.'s finding accords with the theory that marijuana is a companion drug rather than a substitution drug and that its use may be contributing to the opioid crisis (Finn, 2018). Several other researchers demonstrated that marijuana use increases rather than reduces OUD (DiBenedetto et al., 2018; Olfson et al., 2018). With such diverse opinions and mixed reports from various researchers on the potential role of marijuana in the fight against the opioid epidemic, the question remains: Would marijuana reduce the opioid-related adverse outcomes if patients substitute cannabis for opioids? Can the same study produce

similar results in Canada? Canada has a unique difference from the United States by enacting nationwide decriminalization of recreational marijuana in October 2018; therefore, Canada expected to have a more substantial effect of marijuana, if any, in reducing the opioid crisis compared to the values reported by the United States.

Over the past 2 decades, there has been a significant rise in ORHs and deaths worldwide, especially in North America (Gomes et al., 2018; Jette, 2018; Schuchat et al., 2017). The trend of opioid-associated fatalities and hospitalizations has increased steeply over the years in the United States and Canada (Gomes et al., 2017; Rudd et al., 2016).

Purpose of Study

Some scientists believe that increased access to cannabis through marijuana decriminalization may be a solution to the opioid epidemic; however, the role of marijuana in OUD remains unclear. The purpose of this study was to verify the plausibility of the claim that increased access to marijuana may be a game-changer in the fight against the opioid crisis. This study aimed to confirm whether ORDs and hospitalization rates changed in Ontario due to the nationwide decriminalization of marijuana in Canada in 2018.

Research Questions and Hypotheses

Research question (RQ)1: Is there a correlation between decriminalization of marijuana and ORDs per month in Ontario, Canada?

$H_0$1: There is no correlation between the decriminalization of marijuana and ORDs per month in Ontario, Canada.

H_a1*:* There is a correlation between the decriminalization of marijuana and ORDs per month in Ontario, Canada

RQ2: Is there a correlation between decriminalization of marijuana and ORHs per month in Ontario, Canada?

H_02: There is no correlation between the decriminalization of marijuana and ORHs per month in Ontario, Canada.

H_a2: There is a correlation between the decriminalization of marijuana and ORHs per month in Ontario, Canada.

Theoretical Framework

This study on marijuana-based interventions in ORDs and hospitalizations hinged on the theoretical framework of the harm reduction theory (see Wiese & Wilson-Poe, 2018). Two competing forces can drive opioid use behavior when the recreational marijuana law comes into effect. First, marijuana may be used as a substitute drug for opioids, thereby decreasing the use of opioids by people with OUDs. Secondly, physicians may prescribe cannabis for pain management in place of opioids, thereby limiting the risk of exposing patients to opioids and their associated consequences (Lucas, 2017). These two outcomes align with the theory of harm reduction.

The harm reduction principle is a proven, people-centered approach to reducing the health and social harms associated with substance abuse without necessarily requiring people to abstain from using these substances (Thomas, 2005). It represents a set of practical strategies and ideas to reduce adverse consequences of substance use. Harm reduction recognizes that some people struggling with problematic substance use may not

have the ability or willpower to remain abstinent from their substance of choice (Ng et al., 2017).

Therefore, the principle of harm reduction allows the individuals to continue their use of drugs or substances but provides an additional therapy or substitute substance or program that minimizes the harm associated with the principal substance abused. Medication-assisted treatment (MAT) modalities are a typical example of program intervention based on harm reduction theory. It includes methadone or buprenorphine (medications) to treat individuals living with opioid addiction and who are not in a position to abstain from their opioid use (Marlatt, 2001). Methadone and buprenorphine reduce craving and withdrawal symptoms and reduce associated opioid overdose deaths and hospitalizations because they are administered in supervised locations and possess safer pharmacological properties (Whelan & Remski, 2012).

Methadone and buprenorphine (MAT) therapy for OUD is a substitution therapy where methadone or buprenorphine are used safely in place of the opioid molecule abused. Methadone or buprenorphine has safer pharmacological properties than most short-acting opioids used by people living with OUD. Methadone or buprenorphine are long-acting opioids with a lower potential for addiction and minimal withdrawal adverse effects (Whelan & Remski, 2012). Other examples of the application of harm reduction theory in public health programs include the needle exchange program for injection drug users (Platt et al., 2018), safe injection sites for injection drug users (Marshall et al., 2011; Ng et al., 2017), the community naloxone kit program (Chimbar & Moleta, 2018; McDonald & Strang, 2016).

Based on the theory of harm reduction, the currently proposed decriminalization of marijuana as a public health tool to reduce the harm associated with OUD placed cannabis as the substituting drug for opioids. The reduced harm would be the potential decrease in deaths and hospitalizations due to opioid overdose (Lucas, 2017). Several peer-reviewed journals have reported the medicinal use and safety of cannabis in clinical practice (Amin & Ali, 2019; Bridgeman & Abazia, 2017; Freeman et al., 2019; Tapley & Kellett, 2019).

Nature of the Study

This study utilized a time series analysis with time as an independent variable. The number of deaths and hospitalizations among hospital patients per month in Ontario were the dependent variables, and the study's unit of analysis was the month. I extracted data on ORDs and hospitalizations in the Province of Ontario, Canada, from March 2015 to March 2021 from the Canadian Institute for Health Information (CIHI). I analyzed the data using the generalized estimation equation (GEE) to determine the effect of legalization of marijuana (medical and recreational) on ORDs and hospitalizations. Known risk factors for opioid and other substance use disorders are gender, age, race, marital status, and season (Dasgupta et al., 2018; Manubay et al., 2015; Salas et al., 2016).

The study exposure period was 36 months of marijuana decriminalization in Canada (2018 to 2021). ORD and hospitalization data for the 36 months of the exposure period (period of recreational marijuana legalization) were compared with 36 months of

data before marijuana use legalization to examine whether cannabis decriminalization affected the rate of opioid-related adverse effects.

Definitions

Decriminalization: The act of removing criminal sanctions against an act, article, or behavior.

Decriminalization of cannabis: This means that Cannabis would remain illegal, but the legal system would not prosecute a person for possession under a specified amount.

Legalization: The process of removing a legal prohibition against something not legal.

Legalization of cannabis: The process of removing all legal prohibitions against it.

Opioid-related death (ORD): A death caused by intoxication/toxicity (poisoning) resulting from substance use, where one or more of the substances is an opioid, regardless of how it was obtained (e.g., illegally or through personal prescription). Other substances may also be involved.

Opioid-related poisoning hospitalization (ORH): Acute care hospitalizations that recorded a significant diagnosis for opioid-related poisoning.

Assumptions

The fundamental assumption underlying this study was that all cases of opioid overdose in Ontario between 2015 and 2021 were reported to the hospital and included in the Hospital Discharge Abstract Database (DAD).

Another assumption was that all cases labeled as ORDs were considered deaths for which opioids were responsible, and the possible contribution of other drugs or substances was considered negligible. This study covered the period of the COVID-19 pandemic, and I assumed that a change in ORDs and hospitalization was not affected by the COVID-19 pandemic.

The statistical assumption fundamental to the study was that the variables were typically distributed among the population. The sample was randomized, cases represented the population, and the scores on variables were independent of other scores on the same variables; this assumption implied that the *F*-test for GEE analysis would yield inaccurate *p* values if this independent statistical assumption were violated, and there must have been a linear relationship between the outcome variable and the independent variables. The number of cases needed for the analysis was 55, as computed by G*Power. The total number of cases I analyzed for this study was 72 (36 months of exposure and 36 months of unexposed period).

Limitations

A limited exposure period was a significant limitation of this study. An exposure period of 3 to 5 years or more would have improved the reliability of the study outcome by providing more annual data for analysis; however, analyzing the data by months provided multiple variables for statistical analysis. Data on ORH and death accumulated in large numbers in a very short period due to the nature of the epidemics; therefore, monthly data were expected to be enough to reveal the impact of marijuana on hospitalizations and deaths due to opioids, if any.

Significance

The problematic opioid use in Canada is a significant cause of death and hospitalizations, especially among young adults (Belzak & Halverson, 2018). There were over 11,500 apparent ORDs in Canada between January 2016 and December 2018 (Government of Canada, 2021). In 2017, approximately 11 ORDs occurred each day, with an average of 32 ORHs per 100,000 people (Government of Canada, 2021). The high number of ORDs makes the opioid crisis a leading public health and safety concern in Canada (Belzak & Halverson, 2018). Several opioid-related harm reduction and intervention programs have been in use in Canada over the past 2 decades, but they have shown little success (Saloner et al., 2018). Some of these interventions include harm reduction, treatment expansion, improved data collection, safer prescribing, stigma reduction, criminal justice reform, and regulatory changes (Belzak & Halverson, 2018; D'Onofrio et al., 2015; Hawk et al., 2015; McGinty et al., 2015).

Finding an effective intervention program that will prevent ORDs and hospitalizations remains a current and significant public challenge in Canada; therefore, it would be a massive success if marijuana possesses the claimed ability to reduce the opioid crisis. Additionally, marijuana is a psychoactive substance and has the potential for abuse and behavior changes. Therefore, it is crucial to be very sure of its importance before recommending its use in the fight against the opioid epidemic. Like opioids, marijuana has been clinically used for pain management for decades and is a widely abused substance; however, unlike opioids, there are no associations between marijuana use and overdose injuries or death (Phillips et al., 2017).

Summary

Chapter 1 asserts that the opioid crisis has been continuing unabated with statistics on opioid use, overdose, and death shocking in the United States and Canada. Many intervention programs have been implemented to solve this issue, but the situation has deteriorated and has been intensively provoked by COVID-19. The chapter describes the context in which cannabis may be used on the backdrop of the growing legalization of the substance across the world, specifically in Canada where its use became legal in 2018 in relation to the management of opioid related harms. It presents mixed research data on the impact that cannabis has on OUD and hospitalization trends and whether it may act either as a drug that is replacing opioids or a drug that is potentially increasing the use of opioids. The scope of the research will be to follow the Cannabis Decriminalization Policy in relation to opioid fatalities and hospital admissions in Ontario while using the Harm Reduction theoretical perspective. In addition, potential limitations of the research and its implications for adequate solutions to the important problem of opioid usage in the general population are highlighted.

Chapter 2: Literature Review

Introduction

Opioid analgesic therapy is the mainstay approach for treating cancer and noncancer pain and has been used over several decades to effectively treat various types of pain (Pergolizzi et al., 2008). However, there has been a tremendous rise in ORH and death in the United States and Canada (Gomes et al., 2018; Jette, 2018; Schuchat et al., 2017). OUD and its consequences are among the most significant challenges to North America's public health (Centers for Disease Control and Prevention, 2020).

Pharmaceutical companies' influence on prescriber behaviors is one of the most impactful factors for OUD (Webster, 2017). Increased opioid advertisement by pharmaceutical companies was associated with physicians' rise in opioid prescriptions (Hollander et al., 2019; Ruder et al., 2017; Zee, 2009). Increased prescription of opioids is associated with an increase in OUD, and 2015, over 91 million (37.8%) adults in the United States used prescription opioids. Of this number, about 12 million misused prescription opioids, and 2 million had OUD (Han et al., 2015).

The economic burden for OUD in Canada from 2016 to 2020 is $5.71 billion in present terms, and the annual lost productivity is $358 million (Cheung et al., 2020). Webster (2017) examined the risk factors for OUD and provided several biological, psychiatric, and social risk factors associated with the disorder. A finding that increased access to cannabis could reduce ORH and death could provide the needed evidence for public health policymakers and healthcare professionals to develop a cannabis-based intervention for OUD.

Literature Search Strategy

This chapter includes a review of the results of a literature search focusing on OUD, ORD and hospitalization, current and past public health intervention for OUD, and the potential of medical cannabis use in reducing the opioid crisis. The literature review strategy used in this study included electronic searches and evidence-based research articles. For my literature search, I used the following databases: Health Indicators e-Publication, Google Scholar, Pro Quest Health and Medical Complete, SAGE Journals, EBSCOhost, Science Direct, and CIHI Access.

Key terms used to identify relevant articles were *opioid use disorder, opioid-related death, opioid-related hospitalization, opiates and pain management, the opioid crisis and interventions in the United States, the effectiveness of opioid harm reduction intervention, medical cannabis, recreational cannabis, cannabis*, and *the opioid crisis, pharmaceutical opiates, opioid crisis and interventions in the United States*. The search revealed 27 research studies that examined the impact and risk factors of an OUD, the effectiveness of past and current opioid-related public health interventions, and evidence for and against the potential role of medical cannabis in determining problematic opioid use. The harm reduction model (see Thomas, 2005) was the theoretical model used to examine the hypothesis that increasing access to cannabis through nationwide legalization will reduce ORDs and hospitalizations.

Theoretical Foundation

The theoretical framework for this study was the harm reduction theory. The harm reduction theory is a proven, people-centered approach to reducing the health and social

harms associated with substance abuse without requiring those who abstain from using these substances (Thomas, 2005). The contemporary harm reduction principle was birthed during the late 1980s in Canada alongside Australia and some Western European countries in response to the increasing rates of HIV infection among people who inject drugs (Riley et al., 2012). It represents a set of practical strategies and ideas to reduce adverse consequences of substance use. Harm reduction recognizes that some people struggling with problematic substance use may not have the ability or determination to remain abstinent from their substance of choice (Ng et al., 2017).

Two competing forces can drive opioid use behavior when the recreational marijuana law comes into effect. First, marijuana may be used as a substitute drug for opioids, thereby decreasing the use of opioids by people with OUDs. Secondly, physicians may prescribe cannabis for pain management in place of opioids, thereby limiting the risk of exposing patients to opioids and their associated consequences (Lucas, 2017). These two outcomes align with the theory of harm reduction. Therefore, the principle of harm reduction allows the individual to continue their use of drugs or substances but provides an additional therapy or substitute substance or program that minimizes the harm associated with the principal substance abused.

MAT modalities are a typical example of program intervention based on harm reduction theory. It includes methadone or buprenorphine (medications) to treat individuals living with opioid addiction and who are not in a position to abstain from their opioid use (Marlatt, 2001). Methadone and buprenorphine reduce withdrawal and other symptoms associated with opioid overdose deaths and hospitalizations because

treatment occurs in supervised locations. They also possess safer pharmacological properties than most opioids usually abused (Whelan & Remski, 2012).

Critical principles of harm reduction are pragmatism, humane values, focus on harms, balancing costs, and priority of immediate goals. The concept of pragmatism presupposes that some level of drug use in society is to be expected. Minimizing associated harm may be more realistic than eliminating drug use. Humane values refer to the idea that there should be no moralistic judgment about an individual's decision to use substances. The focus on harm considers the risk of harm associated with substance use rather than the extent of substance use. Balancing costs and benefits principal attempt to quantify the benefit of harm reduction intervention and compare it with other interventions or the complete absence of intervention

Methadone and buprenorphine (MAT) therapy is a widely used harm reduction approach to minimize OUD harms. It involves the substitution of the abused opioid with methadone and buprenorphine. Methadone and buprenorphine have safer pharmacological properties, a lower potential for addiction, and minimal withdrawal adverse effects than most short-acting opioids used by people living with OUD (Whelan & Remski, 2012).

Other examples of the application of harm reduction theory in public health programs include the needle exchange program for injection drug users (Platt et al., 2018), safe injection sites for injection drug users (Marshall et al., 2011; Ng et al., 2017), the community naloxone kit program (Chimbar & Moleta, 2018; McDonald & Strang, 2016). Other effectively practiced harm reduction intervention programs include needle

exchange programs (Kral et al., 2004; Wood & Cooney, 2004) and supervised injection sites (Hedrick, 2004; Kerr et al., 2005; Wood et al., 2007).

Based on the theory of harm reduction, the currently proposed decriminalization of marijuana as a public health tool to reduce the harm associated with OUD placed cannabis as the substituting drug for opioids. The reduced harm could be the potential decrease in deaths and hospitalizations due to opioid overdose (Lucas, 2017). Several peer-reviewed journals report the medicinal use and safety of cannabis in clinical practice (Amin & Ali, 2019; Bridgeman & Abazia, 2017; Freeman et al., 2019;Tapley & Kellett, 2019).

Literature Review Related to Key Variables and Concepts

A Historical Overview of Opioid Use in the United States and Canada

Opioids and their derivatives have been used for over a century with proven effectiveness in treating pain (; Inturrisi, 2002; Snyder & Pasternak, 2012). The discovery of opioids is credited to the Sumerians, the earliest immigrants to Mesopotamia, around 3400 BC. They were the first to identify and cultivate Papaver somniferum (opium poppy), and they called it Hul Gil, the joy plant. (Krikorian, 1975). The Sumerians consumed opium for medicinal purposes, to increase stamina for work, for religious purposes, and just for enjoyment.

The cultivation and use of poppy spread to Egypt in 1100 BC, Persia and India in 330 BC, and China in AD 400. By the early 19th century, opium consumption had spread worldwide (Latimer et al., 1981). In the late 18th century, opium and its derivative gained popularity in the United States, and the untoward effects of its use became noticeable. In

1902, several medical journals reported the side effects of opium and its derivatives, and a significant number of patients suffered from withdrawal symptoms.

Heroin addiction reached an alarming rate in 1903. The U.S. Congress banned the use of opium in 1905; in 1914, the U.S. Congress enacted the Harrison Narcotic Control Act of 1914 to control opioid abuse. The impact of the Harrison Narcotic Control Act on physicians and patients was significant, such that physicians and patients shun the use of opioids (Jones et al., 2018). Opioids remained underutilized for pain management until the latter half of the 20th century.

The significant rise in opioids in medicine in the latter half of the 20th century resulted from a few factors. First, there was poor management of chronic pain, probably due to the underutilization of opioids and undertreatment of pain. The result was an aggressive search for effective pain management in clinical settings. (Morgan, 1985; Zenz & Willweber-Strumpf, 1993). The position statement made by the World Health Organization in 1986 to resolve the under-treatment of post-operative and cancer pain further sparked the motivation for effective pain management in the hospital setting.

Furthermore, a faulty publication and claims by Max (1990) that opiate analgesics rarely result in addiction provided a scientific basis for many physicians to liberally use opioids for cancer and post-operative pain management with little concern for addiction. Max's study lacked validity because of the poorly designed retrospective study. To make matters worse, in 2000, the Joint Commission on Pain Management announced a protocol for pain management, requiring practitioners and organizations to perform

comprehensive quantitative assessments of pain based on the Institute of Medicine guidelines (Baker, 2017) to ensure adequate pain treatment.

In response to this, the Drug Enforcement Agency (DEA) and state medical boards agreed to ease regulatory investigations over physicians who prescribe opioids for pain, thereby encouraging physicians to prescribe opioids for pain (Joranson et al., 2002). Prescribers were required to provide adequate pain treatment by the joint commission recommendations; the consequence of this was a massive reliance on opioids and their derivatives in hospital settings. Most hospitals strove to attain and maintain The Joint Commission (TJC) pain management recommendation, mainly because maintaining the standards of TJC was a criterion for receiving federal health funding from hospitals. Therefore, hospital administration invested more in opioids and encouraged physicians to use opioids (Jones et al., 2018).

The pharmaceutical companies soon took advantage of these situations and manufactured and pushed opioids into the market. Pharmaceutical companies became another source of pressure and influence on physicians to prescribe opioids for pain management (Tucker, 2004). The result of these was the birth of the widespread use of opioids in therapy and its attendant consequences.

The Evolving Legal and Medical Landscape of Marijuana Use

Marijuana, also known as cannabis, is a flowering plant that has been in use for nonmedicinal purposes for over 5,000 years in Romania (Bennett, 2010); the earliest use of marijuana for medicinal purposes was in AD 400 (Zias et al., 1993). The United States Pharmacopeia described the therapeutic value of cannabis first in 1850. Following a

series of ethical and legal issues due to the concern of potential abuse and health implications of the use of marijuana, marijuana was delisted from United States Pharmacopeia in 1942. Subsequently, it became a crime to possess and use cannabis. The lack of access to cannabis limited research studies on its potential in medicine (Cameron & Dillinger, 2011; Piomelli et al., 2019).

In the United States, California was the first to allow physicians to supervise cannabis for medicinal purposes in 1996 (Cerdá et al., 2012). Currently, 47 states in the United States have physician-supervised access to medical marijuana (Bridgeman & Abazia, 2017). Eleven states allow recreational marijuana through state-wide legalization (Bridgeman & Abazia, 2017; Williams, 2016). The improved access and limited restriction to marijuana have led to tremendous studies on the safety, efficacy, and use of marijuana in many disease conditions (Aggarwal et al., 2009; Babson et al., 2017; Payne et al., 2019).

Age-Related Risk Factors and Treatment Disparities in OUD

OUD affects people of all ages; however, OUD's prevalence is reportedly highest among young adults. Latimer & Goldberg (1981) utilized New York Medicaid claims data to examine the age-related medication addiction treatment (MAT) for people diagnosed with OUD. In their method, they categorized the data into six sociodemographic variables, including age group (18–29, 30–39, 40–49, 50–59, 60–64 years), place of residence, race and ethnicity, sex (female, male), and Medicaid eligibility months. They conducted a two-sample *z*-test and *t* test to compare the outcome measures and covariates across ages.

Of the 88,637 OUD patients identified, 64% (56,926 individuals) received some MAT in 2015; the age range with the most significant proportion (25%) of OUD was young adults (ages 18–29) (Shover et al., 2019). This age group was also the least likely to receive MAT. Only 50% of young adults received MAT for OUD, whereas 85% of older patients were more likely to receive MAT. Shover et al.'s (2019) study clarified the need for treatment providers to consider age group effects in designing interventions for patients to enhance the engagement of the age group more at risk of OUD. Not only is younger age a risk factor for OUD and unwillingness to receive MAT but it is also associated with higher odds of having a physical or psychiatric comorbid disorder (Naji et al., 2017).

Edlund et al. (2010) carried out a study to estimate the risk factors for OUD and dependence in patients on continuous opioid therapy utilizing the Arkansas Medicaid or registered in the HealthCore Integrated Research Database. They reported that younger patients (ages 18 and 30 years) were at increased risk of OUD, with the highest odds ratio of 5.88, 9.08, when the age group of 18-30 years old was compared with 65 and over age group, in HealthCore and Arkansas respectively. In their study, Edlund et al. identified 1,188 patients in the HealthCore sample (n = 36,605) and 277 patients in the Arkansas Medicaid Sample (n = 9,651) with OUD. The authors noted limitations because the study design was observational; therefore, the statistics described are associations and should not be considered causal relationships. Also, the study's findings may not represent the general population despite the large sample used.

Boyd et al. (2009) analyzed data from the National Epidemiologic Survey on Alcohol and Related Conditions to examine whether prescription opioids' nonmedical use determined its relationship to continued nonmedical use and substance use disorders 3 years later. 34,653 adults were interviewed at Wave 1 (2001–2002) and re-interviewed at Wave 2 (2004–2005). They used multivariate logistic regression analyses and reported that younger age (18 to 24 years) and nonmedical use at Wave 1 was associated with higher odds of a general substance or OUD at Wave 2 (adjusted odds ratio = 3.42, 95% confidence interval = 1.45, 8.07). Additionally, they reported that nonmedical use of opioids is associated with an increased risk of future opioid or other substance use disorders. In all three studies (Boyd et al., 2009; Edlund et al., 2010; Neighbors et al., 2019), younger age had an increased risk of OUD, respectively.

Sex Differences in Opioid Overdose Deaths

Several studies have indicated that more males die from OUD than females. In 2016, 9,978 men and 7,109 women died from prescription opioid overdose, representing an ORD of about 27 men per day compared to 19 women per day (NIDA, 2018). Before 2016, women were more likely than men to die of opioid overdose (CDC & National Center for Health Statistics, 2018). Gladstone et al. (2016) used administrative mortality data from 2004 to 2013 to examine sex differences in ORDs in British Columbia; they reported that men had higher overall rates of prescription ORDs in British Columbia than women.

Gladstone et al. (2016) used a serial cross-sectional study design to examine deaths from opioid-related causes in the United States between January 1, 2001, and

December 31, 2016, as determined by death certificates. They reported a 345% (from 9489 to 42 245 deaths) increase in ORDs, and males accounted for 67.5% of all ORDs. Like earlier reports, Gladstone et al. found that young adults between 15 and 34 were most affected.

Opioid-Related Mortality

An average of 115 people die per day in the United States from opioid abuse (Jette, 2018; NIDA, 2018). Over 33,000 deaths were related to opioid overdose in the United States in 2015 (Gomes et al., 2017; HCUP Fast Stats, 2018; Rudd et al., 2016; Skolnik, 2017; Tadrous et al., 2018). The Centers for Disease Control and Prevention (2017) reported a fivefold increase in ORDs in the United States from 8,050 in 1999 to 42,250 in 2016 (CDC, 2017).

Gomes et al. (2018) used a serial cross-sectional study design to investigate deaths from opioid-related causes across the United States between January 1, 2001, and December 31, 2016. They reported a total of 335,123 ORDs in the United States within their study period, with a sharp increase of 345% from 9,489 in 2001 (33.3 deaths per million population) to 42,245 in 2016 (130.7 deaths per million population). They noted that adults aged 24 to 35 years had the highest (20%) death rate in 2016.

Gomes et al. (2018) reported that adults aged 24 to 35 years have the highest (15.8%) increase in the death rate from 4.2% in 2001 to 20.0% in 2016) death rate in 2016 followed by those aged 15 to 24 years (9.4% increase from 2.9% to 12.4%). Although older adult generally has lower ORD rates compared to younger adults, the most relative increases observed were among adults aged 55 to 64 years (754% increase

from 0.2% to 1.7%) and those aged 65 years and older (635% increase from 0.01% to 0.07%).

Between 2016 and 2020, an estimated 15,393 Canadians died from an opioid overdose (Belzak & Halverson, 2018). The years of life lost due to Canada's opioid-related mortality it was increased by 142% between 1990 and 2014 (Belzak & Halverson, 2018). Within the same period, there were 5,935 premature opioid deaths in Ontario, Canada; this represents 242% in the mortality rate (Gomes et al., 2014).

ORH

An estimated 835 people per 100,000 population visited the emergency room due to opioid overdose in the United States in 2015 (Gomes et al., 2017; HCUP Fast Stats, 2018; Rudd et al., 2016; Skolnik, 2017; Tadrous et al., 2018). Over 2,800 ORDs and 5,840 emergency room visits in 2016 in Canada (Health Canada, 2017). These values represent a tremendous increase compared to previous years (Health Canada, 2014, 2015, 2016).

Weiner et al. (2020) reported that 1 in 20 patients treated for a nonfatal opioid overdose in an emergency department (ED) died within 1 year of their visit. Two-thirds of these deaths resulted from subsequent opioid-related overdoses (Weiner et al., 2020). Rajbhandari-Thapa et al. (2019) used a cross-sectional study to examine whether the prevalence of ORH has increased due to opioid abuse, addiction, poisoning, and dependence. They analyzed data from the National Inpatient Sample (NIS) from January 1, 2011, to September 30, 2015, for 18 years and older. They identified 3,239,136 ORHs; 704,670 ORHs(the highest prevalence) occurred in 2014; the age group most affected

was patients aged 35–54 years (5-year average, 37%). They reported that the prevalence was highest among White patients (5-year average, 72%) and in urban hospitals (5-year prevalence range, 58%–64%) than in rural hospitals (5-year prevalence range, 36%–42%) and among patients with two or more comorbid conditions (94%).

Singh and Cleveland (2020) examined the hospitalizations and associated mortality rates due to OUD, using the United States NIS data from 1998–2016 to verify ORHs and associated mortality. Singh and Cleveland reported 781,767 ORHs within the study period of 1998 to 2016; younger adults, male and White race, had a higher prevalence of ORHs, had a higher prevalence of ORHs. Like earlier reports, Singh and Cleveland reported an increasing prevalence of ORH with time. ORH increased by 219%, from 59.8 per 100,000 in 1998–2000 to 190.7 per 100,000 NIS hospitalizations in 2015–2016.

Jones et al. (2016) reported an increasing rate of ORH and significant correlations between opioid dispensing and ORH in the province of Quebec ($r = 0.87$, CI: 0.49–0.97; $p = 0.002$), New Brunswick ($r = 0.85$; CI: 0.43–0.97; $p = 0.004$), and Nova Scotia ($r = 0.78$; CI:0.25–0.95; $p = 0.012$), using a retrospective study design involving data from annual volumes of medical opioid dispensed from a representative, stratified sample of retail pharmacies across Canada. Their finding supports opioid dispensing levels as a systemic driver of OUD in a population.

Tadros et al. (2015) used a retrospective cohort study to examine data from the Nationwide Emergency Department between 2006 and 2011. They reported a total of

250,000 visits to the United States emergency room between 2006 and 2011 with a primary diagnosis of prescription opioid poisoning.

Related Public Health Measures to Reduce OUDs

Opioid Agonist Therapy on ORD and Hospitalization

Methadone was developed in 1937 by Gustav Ehrhart and Max Bockmhl in response to the post-World War II shortage of morphine. It was introduced to the United States in 1947 as an analgesic; by the early part of 1970, methadone became used for addiction treatment (Courtwright, 1997). Essentially, methadone maintenance treatment is an opioid substitution therapy; the long duration of action with tolerable withdrawal symptoms of methadone compared to most other opioids, especially the short-acting ones, makes methadone appropriate for managing opioid withdrawal symptoms (Mattick et al., 2004).

ORD is relatively lower among individuals living with OUD who receive methadone maintenance treatment than those who do not (National Consensus Development Panel on Effective Medical Treatment of Opiates, 1998). Pearce et al. (2020) used a population-based retrospective cohort study to compare the risk of mortality among people with OUD on and off opioid agonist treatment (OAT). They reported that people with OUD not on the opioid agonist therapy have a 65% increase in relative risk of death compared to OUD clients on OAT.

Pearce et al. (2020) obtained their data from the PharmaNet database (to identify OAT dispensations), the Vital Statistics database (to identify all deaths and their underlying cause during the follow-up period), the DAD (to obtain all hospital

admissions with diagnostic codes), and Medical Services Plan and the National Ambulatory Care Reporting System (NARCS) databases (to identify comorbidities related to OUD). They identified 55,347 OAT recipients in British Columbia between January 1, 1996, and September 30, 2018. The relative risk of mortality in patients who went off OAT was 2.1 (95% confidence interval 1.8 to 2.4) times higher than in those on OAT before the introduction of fentanyl. It increased to 3.4 (2.8 to 4.3) at the end of the study period (65% increase in relative risk).

In Australia, Degenhardt et al. (2014) reported that OAT produced a 29% reduction in mortality across the entire cohort in 2009. In Australia, 40,000 treatment recipients reported a standardized mortality ratio of 4.5 (4.3 to 4.8) on OAT and 8.0 (7.7 to 8.3) off OAT (Degenhardt et al., 2014). Their study method utilized data from the New South Wales (NSW) Pharmaceutical Drugs of Addiction System (which contains the information on "authority to dispense" methadone or Buprenorphine as opioid replacement therapy between 1985-2006) and the National Deaths Index (all death records in Australia) and calculated crude mortality rates and standardized mortality ratios. Their finding that OAT significantly reduces death from OUD accords with reports from similar studies in the United States discussed above.

Methadone maintenance treatment effectively reduced injection-related risk behaviors. It decreased infectious diseases among substance users (Longshore et al., 1994; Metzger et al., 1995; Ward et al., 1998; Wells et al., 1996). Individuals living with OUD and are on methadone maintenance treatment have improved quality of life, well-being, and chances of being employed compared to those not receiving the treatment

(Dazord et al., 1998; Dole et al., 1995; Gearing & Schweitzer, 1998; Lowinson et al., 1997; Simpson & Sells, 1995;).

Despite the approval and widespread use of methadone therapy in treating OUD, there are reports of methadone-related death and poisonings (Caplehorn, 1998; Zador & Sunjic, 2002). Zador and Sunjic (2002) reported an overall mortality rate of 7.1 deaths per 10,000 people inducted with methadone; death occurred within the first 2 weeks of initiating methadone therapy. Although earlier reports claimed that methadone fatalities are primarily due to respiratory depression during methadone induction (Williamson et al., 1997), recent studies revealed that methadone deaths are also associated with methadone-related QTc prolongation that results in fatal ventricular arrhythmia or Torsade de Pointes (Modesto-Lowe et al., 2010).

In a cross-sectional study by Zador and Sunjic (2002) to explore the circumstances in which methadone-related deaths occurred, they reported that 238 methadone-related death occurred between 1990–1995, 21% of the death occurred within the first week of methadone dose initiation, 88% involved polysubstance use with methadone. Other limitations to the use of methadone treatment are severe constipation (Veillardd & Hallinan, 2017), sexual dysfunction (Hosseini et al., 2013), significant inconvenience to the patient who may need to visit the pharmacy or clinic daily for dose administrations (Kermode et al., 2020), becoming dependent on their prescriber, and sometimes, suffering significant stigma (Earnshaw et al., 2013).

Buprenorphine, like methadone, is a synthetic opioid discovered in 1969 by the Reckitt and Colman research group in England; it showed success in reducing opioid

withdrawal in animals. The first human clinical trial with buprenorphine was in 1971, and buprenorphine was first used in the United Kingdom to treat pain the same year. The United States approved buprenorphine alone or in combination with naloxone to treat OUD in 2002. (Welsh & Valadez-Meltzer, 2005).

Buprenorphine is a partial agonist with high affinity but low intrinsic activity for the mu-opioid receptor and an antagonist at the kappa-opioid receptor. These pharmacologic properties make buprenorphine have less painkilling and euphoric effects but effectively reduce opioid withdrawal symptoms, and it is likely a safer alternative to methadone. Buprenorphine and methadone share similarities in the mode of action in treating OUD; however, there are differences between them.

Mattick et al. (2003) compared the effectiveness of methadone versus buprenorphine in treating OUD. Their systematic review study consisted of 24 randomized controlled trials (RCTs) with 4,497 participants. Buprenorphine was significantly less effective in retaining patients in treatment than methadone; however, both have a similar outcome in suppressing opioid withdrawal in managing OUD.

Connock et al. (2007), in a cross-sectional study, found buprenorphine to have less potential for overdose, respiratory depression, and death compared to methadone (Connock et al., 2007). Furthermore, buprenorphine had a significantly higher potential for abuse than methadone, especially among injection drug users (Smith et al., 2007); the abuse potential of buprenorphine is due to the ease of diversion of buprenorphine compared to methadone (Winstock et al., 2008).

Naloxone Distribution, Overdose Education Program, and ORD and Hospitalization

Naloxone is a synthetic, nonselective, and competitive opioid receptor antagonist with an extremely high affinity for the μ-opioid receptor; it also binds to the δ and κ opioid receptors but with a lesser degree of affinity (Kim et al., 2009)—several reports on the effectiveness of the naloxone distribution and overdose education program. Alexander et al. (2015) used an uninterrupted time-series study to evaluate opioid-related overdose death and acute care utilization of naloxone from 2002 to 2009. They reported a significant reduction in opioid overdose poisoning in communities that implemented the naloxone distribution and an overdose education program (Alexander et al., 2015).

Naloxone reverses the analgesia, sedation, euphoria, and respiratory suppression caused by opioids and has no addictive effect. Naloxone is not orally active; therefore, naloxone is administered intranasally or by injection (Lavonas et al., 2015). Naloxone is very safe and effective in reversing opioid overdose and prevents ORD (Boyer, 2012; Buajordet et al., 2004; Clarke et al., 20165; Dahan et al., 2010). While naloxone effectively prevents opioid-related harm, its effects are helpful only if administered immediately after respiratory depression (Ngai et al., 1976).

Significant limitations with the use of naloxone are the timing of the administration and the dose administered. Too high a dose of naloxone will cause severe opioid withdrawal syndromes (Shaw et al., 2009), hypertensive emergencies, ventricular dysrhythmias (Michaelis et al., 1974), pulmonary edema (Nath et al., 2009), delirium, and seizures (Kim & Nelson, 2015) and even death (Sivilotti, 2016). Timely access to naloxone, when needed for opioid poisoning reversal, is crucial because opioid

poisonings are unplanned, and the population at risk does not readily have access to naloxone.

Bird et al. (2016) investigated the effectiveness of Scotland's National Naloxone Program for reducing opioid-related deaths: a before (2006–10) versus after (2011–2013) comparison, utilizing data from the National Records of Scotland and reported a 36% reduction in ORD among recipients of naloxone kit (2011-2013) compared to those that did not (2006-2010). Precisely, Bird et al. (2016) reported that from 2006–2010, 9.8% of ORDs (193 of 1970) were in people released from prison within 4 weeks of death before the start of the naloxone program in Scotland. However, only 6.3% of ORDs in 2011–13 followed prison release (76 of 1212, $P < 0.001$; this represented a difference of 3.5% [95% confidence interval (CI) = 1.6–5.4%)]. This reduction in the proportion of prison-release ORDs translates into 42 fewer prison-release ORDs (95% CI = 19–65) during 2011–2013, when 12,000 naloxone kits were issued.

The Prescription Drug Monitoring Programs and ORD and Hospitalization

The prescription drug monitoring program (PDMP) is an electronic database that tracks controlled substance prescriptions in a given jurisdiction, such as a state or province (CDC, 2020). It provides health authorities with real-time information about "prescribing and patient behaviors that contribute to the epidemic and facilitate a nimble and targeted response" (CDC, 2020). Despite the widespread use of MDMPs in the United States and Canada, most studies have reported a lack of association between PDMP and reducing OUD harm.

Rhodes et al. (2019), in a systematic review study involving 22 studies and 49 types of PDMPs, reported minimal evidence to support the overall associations between reductions in opioid-related harm and the PDMP. Despite their finding, the authors argued that the presence of PDMPs continuously reminds prescribers of the need to be cautious when prescribing opioids; this may be why most pharmacists and prescribers use PDMPs for prescribing and dispensing decisions (Freeman et al., 2018).

Despite the numerous public health intervention programs targeted at reducing the opioid crisis over the past decades, the problematic use of opioids continues to rise steadily in the United States and Canada (Belzak & Halverson, 2018; Fischer et al., 2016). In searching for an effective measure to limit the opioid epidemic, some researchers have proposed that recreational marijuana may be the game-changer. There have been several claims suggesting that increasing access to cannabis through its decriminalization can reduce ORHs and deaths from overdose (Bachhuber et al., 2014; Bradford et al., 2018; Li & Chihuri, 2020; Livingston et al., 2017; Shi et al., 2019; Vyas et al., 2018).

Medical Cannabis and ORD and Hospitalization

A report by Williams (2020) claimed that marijuana use, especially during adolescence age, can "meaningfully introduce de novo risk for the initiation of opioid use and development of opioid use disorder" but agreed that his claim requires further studies. In the United States, Bachhuber et al. (2014) reported a 24.8% annual reduction in opioid overdose mortality rate in states with medical cannabis laws than in states with a complete prohibition of cannabis use from 1999 to 2010.

Shi et al. (2019) also reported a 29.6% reduction in the number of opioid prescriptions, a 29.9% reduction in opioid dosage, and a 28.8% reduction in opioid-related Medicaid spending in states with medical cannabis legalization compared with states without such law. Contrary to the claim that enhancing access to marijuana use has the potential to reduce opioid-related harms, Shover et al. (2019) reported that states with medical cannabis law experienced a 22.7% increase in opioid overdose deaths, a complete reversal of the earlier reports by Bachhuber et al. (2014). Shover et al. (2019) findings accord with the theory that marijuana is a companion drug rather than a substitution drug and that its use may be contributing to the opioid crisis (Finn, 2018).

Several other researchers demonstrated that marijuana use increases rather than reduces OUD (DiBenedetto et al., 2018; Olfson et al., 2018). Bachhuber et al. (2014) used a time-series analysis to study the association between medical cannabis laws and ORDs from 1999 to 2010. They reported a significant association between medical cannabis laws and lower state-level opioid overdose mortality rates. Livingston et al. (2017) used an interrupted time-series study to examine the monthly changes in ORDs before and after Colorado stores began selling recreational cannabis and reported that recreational marijuana was associated with reductions in ORDs.

Vyas et al. (2018) examined the role of medical cannabis laws on the opioid crisis in the United States using a literature review. They reported a reduction in opioid-related mortality in States with medical cannabis laws compared to states without such laws. Lucas (2017) discussed the evidence-based rationale for the use of Marijuana as an

opioid substitute to reduce opioid-related adverse effects. He utilized the conceptual frame of the harm reduction theory.

Contrary to the reports of an association between cannabis law and reduced OUD, Li and Chihuri (2020) reported a strong correlation between marijuana and opioid use. In a cross-sectional study, Li and Chihuri found that drivers who test positive for marijuana are significantly more likely to test positive for opioids and alcohol.

Olfson et al. (2018) used a structured interview to determine the relationship between cannabis and prescription OUD, using logistic regression models; they reported that increased use of cannabis is associated with the risk of OUD. Shover et al. (2019) used a time series analysis like the works of Bachhuber et al. (2014) to study the association between medical cannabis laws and ORDs.

Unlike the work of Bachhuber et al. (2014), Shover et al. (2019) extended their study beyond 1999 and 2010. They reported that states passing a medical cannabis law experienced a 22.7% increase in OUD. Grotenhermen and Müller-Vahl (2012) extensively used a selective literature review study to discuss cannabis preparations' therapeutic benefits; these therapeutic effects include antispastic, analgesic, antiemetic, and neuroprotective and anti-inflammatory actions, and are effective against certain psychiatric diseases. The big question remains: Will increased access to marijuana reduces the opioid crisis in Canada? Several mixed reports on this claim in the United States (Olfson, 2018; Piper et al., 2017; Powell et al., 2018; Wendelboe et al., 2019).

Summary and Conclusions

Several of the research studies reviewed in this chapter examined the impact of OUD, risk factors for OUD, the effectiveness of past and current public health interventions to limit ORD and hospitalization, and evidence for and against the potential role of medical cannabis in limiting the problematic opioid use. There was a strong consensus with the findings of most of the studies in this literature review regarding the magnitude of the opioid crisis in the United States and Canada (Belzak & Halverson, 2018; Degenhardt et al., 2014; Gomes et al., 2014; Murphy et al., 2014; Singh &Cleveland, 2020).

All of the studies agreed that OUD and its consequences of decreased quality of life, increased hospitalization rate, increased health care costs, and death of tens of thousands of Americans and Canadians annually continued to rise at an alarming rate over the years (Gomes et al., 2014, 2018; Jette, 2018; Jones et al., 2016; NIDA, 2018). Most studies reviewed also agreed that the opioid crisis defiled most current public health efforts (Fischer et al., 2016).

Most studies considered the harm reduction approaches of MAT and Overdose Education and Naloxone Distribution (to be the most effective intervention (Bird et al., 2016; Lucas, 2017). Despite the claimed effectiveness of the harm reduction approaches, several studies in this review reported severe limitations to their use in practice (Caplehorn, 1998; Zador & Sunjic, 2002). They agreed that there is a need for a better approach. Some studies claimed that cannabis would provide a better substitution

treatment for OUD and reported a significant reduction in ORD in states with limited access to medical cannabis (Bachhuber et al., 2014; Shi et al., 2019; Vyas et al., 2018).

Some of the studies reviewed in this chapter reported the medicinal use and safety of cannabis in clinical practice (Amin & Ali, 2019; Bridgeman & Abazia, 2017; Freeman et al., 2019; Tapley & Kellett, 2019;). There was no study on any community with fully legalized recreational marijuana and its impact on OUD. My dissertation seeks to fill the gap by examining the role of the nationwide legalization of recreational marijuana on the opioid crisis in Canada. Canada enacted an entire recreational marijuana law in June 2018.

Chapter 3: Research Method

Introduction

This chapter will describe the research method used to test this study's hypotheses. This study utilized a GEE analysis of a time series with the time of legalization as an independent variable. The number of deaths and hospitalizations among hospital patients in Ontario were the dependent variables, and the months were the unit of analysis for this study. I extracted data on ORDs and hospitalizations in the Province of Ontario, Canada, from June 2015 to June 2021 from the Public Health Infobase database, Canada.

By analyzing changes in data on ORDs and hospitalizations in the 36-month exposure period (March 2018 to March 2021) to those in the 36-month unexposed period (March 2015 to March 2018), I examined the effects of the legalization of marijuana (medical and recreational) on ORDs and hospitalizations.

The 36-month period of exposure in this study represented the period of nationwide recreational cannabis use (March 2018 to March 2021), while the 36-month unexposed period consisted of March 2015 to March 2018, 3 years before nationwide recreational cannabis use. The findings from this study provided additional evidence to support or refute the claim that increased access to cannabis through legalization could solve the opioid crisis.

Methodology

Setting and Sample

Analyzing the Ontario province ORDdeaths and hospitalization data (Public Health Infobase Canada, Opioid- and Stimulant-related Harms in Canada, March 2021) from March 15, 2015, to March 15, 2018, and March 15, 2018, to March 15, 2021, provided data to answer the RQ: Did the decriminalization of marijuana reduce ORDs and hospitalization in Ontario, Canada?

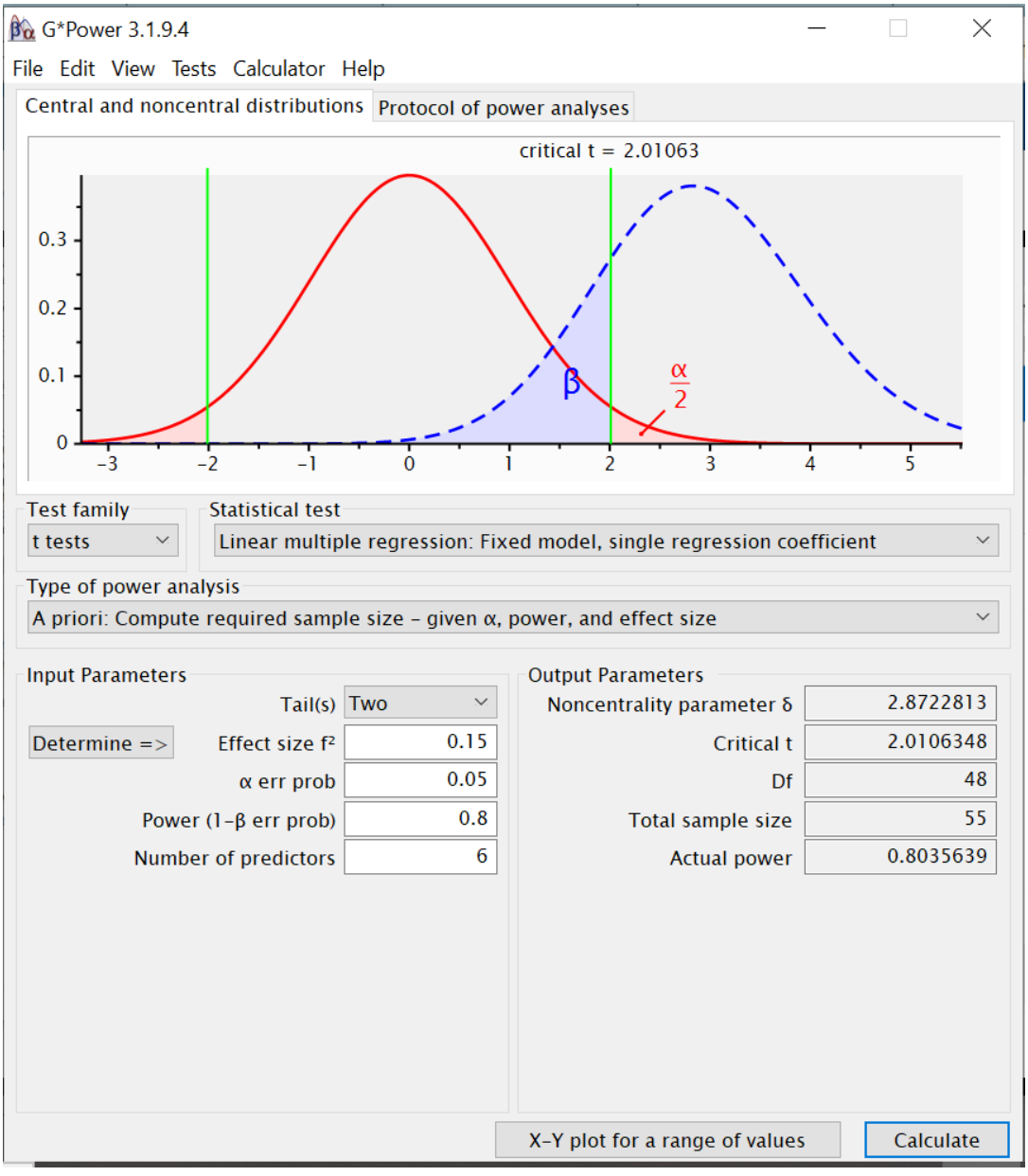
Opioid-Related Deaths and Hospitalization Data

Data on ORHs and deaths were extracted from the Public Health Infobase website. To obtain the data, I requested it through the CIHI. The data request process involved our acknowledgment, which maintained the confidentiality of the information accessed. These annual data on ORDs and hospitalizations provided information on the characteristics of individuals who died or visited public and publicly funded private hospitals in Ontario, Canada. Canada has a universal health care system, and all physicians are required to report all opioid-related hospital visits or deaths to the local or national databases.

The Public Health Infobase system was a part of more extensive statistical information-gathering systems. I used the *G*-Power sample size calculator to estimate the sample size needed for my analysis, as shown in Figure 1.

Figure 1

Power Analysis Calculation for Sample Size



Limitation of Data Used in the Study

Some significant limitations deserve to be mentioned because they may have affected the validity of our study outcome. Investigations into the cause of death occur at the provincial level involving either the medical examiner system, the coroner system, or both, resulting in potential variation in the definition of the cause of death. Due to the potential differences between provinces and territories in the death investigation process, death classification method, toxicology testing, and the manners of death reported, there may be a problem with the interpretation and comparability of the data over time and between provinces and territories.

In the absence of postmortem toxicology results, some deaths could be misclassified as not opioid-related, resulting in underestimating the ORD. Some of the data reported are based on ongoing investigations by coroners and medical examiners and are, therefore, subject to change. Furthermore, data on opioid toxicity deaths and stimulant toxicity deaths are not mutually exclusive. A high proportion of deaths involving a stimulant also involved an opioid; therefore, combining these numbers will result in the wrong estimate. The observation unit for this analysis for this study was time in months. Not every case of opioid poisoning ends in a hospital visit; some get resolved at home and never reported.

Instrumentation and Materials

The Public Health Infobase database contains data on opioid- and stimulant-related harms in Canada that are extracted from the hospital DAD, Emergency Department Database (ED), the NACRS and the Hospital Morbidity Database (HMDB).

DAD is a national administrative database from the CIHI that compiles information on hospital discharges (including deaths, sign-outs, and transfers) from acute care institutions in all provinces and territories, except Quebec NACRS contains data for all ambulatory care data such as day surgery, outpatient and community-based clinics and emergency departments, while the HMDB records administrative, clinical and demographic information on inpatient separations from acute care hospitals (Special Advisory Committee on the Epidemic of Opioid Overdoses, 2020).

The CIHI receives the data from acute care facilities, their health/regional authority, or the ministry/health department. The extracted data are analyzed using the CIHI Portal by Health Canada. Only inpatient hospitalizations from acute care facilities were included in the analyses.

Only hospital admission and discharge records for all patients with significant diagnoses of opioid-related poisoning were included in the data as opioid-related poisoning hospitalizations. Poisoning diagnoses were based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada (ICD-10-CA), which is used to code up to 25 diagnoses per hospital record, as it is the national standard for reporting morbidity (Special Advisory Committee on the Epidemic of Opioid Overdoses, 2020). In the raw data set, a case would be an ORH if the opioid-related poisoning diagnosis were considered influential to the time spent and treatment received while in hospital (Special Advisory Committee on the Epidemic of Opioid Overdoses, 2020).

The Public Health Infobase database receives death counts or record-level information from the provinces and territories that collect data from their respective offices of chief coroners or chief medical examiners (Public Health Agency of Canada, 2021). The Canadian universal healthcare system requires accurate and continuous client-level data reporting for research use.

This study utilized a GEE analysis with the time of legalization as the primary independent variable. The dependent variables were the number of ORDs and ORHs among hospital patients in Ontario. The unit of analysis was time in months. Table 1 shows the operational measures for the key independent and dependent variables in the study.

Table 1

Description of Operational Measures for Key Independent and Dependent Variables

Variables	Description/specific measures	Response category	Type of variable
Opioid-related hospitalization	Emergency room visit		Continuous
Opioid-related death	Died from opioid overdose		Continuous
Age	Age in years	1 = 18-24 2 = 25-34 3 = 35-44 4 = 45-54 5 = 55-64 6 = 65-older	Continuous (%)

Variables	Description/specific measures	Response category	Type of variable
Race/Ethnicity	Group best represents race	1 = White 2 = Black or African Canadian 3 = Hispanic White or Black 4 = Asian 5 = Other	Continuous (%)
Primary independent variable	Legalization	0 = Before legalization. 1 = After legalization	Dichotomous

Procedures for Recruitment, Participation, and Data Collection

Records of all ORDs in Ontario were retrieved and extracted from the DAD, ED, the NACRS, and the HMDB from March 15, 2015, to March 15, 2018, and March 15,

2018, to March 15, 2021. Records of all ORHs in Ontario were extracted and retrieved from the DAD, the NACRS, and the HMDB from March 15, 2015, to March 15, 2018, and March 15, 2018, to March 15, 2021. For both ORD and ORH, data from March 2015 to March 2018 were compared with those from March 2018 to March 2021 using GEE with time as an independent variable.

Table 1 shows the scaling of the variables. Legalization was the primary independent variable, and it was a dichotomous variable with only two possible outcomes: before legalization (scored as 0) and after legalization (scored as 1). ORD was a dependent variable that described the number of deaths caused by opioid poisoning per month in Ontario. ORH was a dependent variable representing the number of hospital visits/admissions caused by opioid poisoning per month in Ontario.

Data Analysis Plan

I used the Box-Jenkins multivariate model for analyzing data as described by Bachhuber et al. (2014) in their study, which verified the association between cannabis law and opioid-related mortality in the United States. I determined the association between cannabis legalization and opioid analgesic–related deaths and hospitalization using GEE. I used the logarithm of the monthly opioid analgesic overdose mortality rate and hospitalization for the dependent variables. In my GEE analysis, I included an indicator for the absence of cannabis law in Canada (March 2015 to March 2018). The months before the enactment of the medical cannabis law were coded as 0. All months after the passage of the cannabis law were coded as 1.

To estimate the absolute difference in opioid-related mortality and hospitalizations due to cannabis legalization, I calculated the difference in the number of opioid analgesic overdose deaths and hospitalizations between March 2015 to March 2018 and March 2018 to March 2021. I also examined the graphs of the time series patterns before and after the cannabis law for differences likely due to the cannabis law.

Threats to Validity

Not all cases of opioid poisoning end up in the hospital setting. Sometimes, the patients may reverse the poisoning using naloxone. Therefore, this study might have underestimated the number of ORHs, which is a threat to the validity of our study. Furthermore, investigations into the cause of death occur at the provincial level involving either the medical examiner system, the coroner system, or both, resulting in potential variation in the cause of death definition. ORD misclassification may have occurred, resulting in an underestimation of the ORD problem.

Cannabis legalization in Canada is age-dependent; only a person 19 years and above can purchase and use cannabis. This age limit excludes a significant age group affected by the opioid crisis and may likely not be affected by cannabis law. Additionally, the impact of the COVID-19 pandemic on data obtained from March 2020 to March 2021 is uncertain and may have affected the validity of this study. Since prescription opioid medications are covered by most Canadian health insurance for all citizens, individuals who take advantage of the accessible prescription opioids may not be influenced by cannabis legalization because they have to pay for cannabis.

Ethical Procedures

Client information (Opioid- and Stimulant-related Harms in Canada, June 2021) in the Public Health Infobase Canada is protected in several ways. Any information that reveals the identity of the client is removed. All variables that may identify a client are removed, categorized, and coded to protect the client's information. Confidentiality is maintained throughout the collecting process. In general, personal information such as names, telephone numbers, addresses, and dates of birth were not included in the CIHI data that were accessed in this study.

Summary

This study relied on quantitative analysis of the relationship between independent and dependent variables. The Public Health InfoBase for Canada was the data source. The sample size needed was calculated by performing a power analysis. IBM SPSS Statistics version 28 was used to perform a time series analysis to determine changes in ORD and hospitalization due to legalization.

Chapter 4: Results

Introduction

The overarching purpose of this study was to verify the plausibility of the claim that increased access to marijuana may be a game-changer in the fight against the opioid crisis. For this purpose, the study was designed to confirm whether ORDs and hospitalization rates would change in Ontario due to the nationwide decriminalization of marijuana in Canada in 2018.

As discussed in Chapter 1, this study sought to answer the following RQs and hypotheses:

RQ1: Is there a correlation between the decriminalization of Marijuana and ORDs per month in Ontario, Canada?

$H_0$1: There is no correlation between the decriminalization of marijuana and ORDs per month in Ontario, Canada.

H_a1: There is a correlation between the decriminalization of marijuana and ORDs per month in Ontario, Canada

RQ2: Is there a correlation between decriminalization of marijuana and ORHs per month in Ontario, Canada?

$H_0$2: There is no correlation between the decriminalization of marijuana and ORHs per month in Ontario, Canada.

H_a2: There is a correlation between the decriminalization of marijuana and ORHs per month in Ontario, Canada.

Data analyzed in this study included records of all ORDs. ORHs in Ontario were retrieved and extracted from the DAD, ED, the NACRS, and the HMDB from March 15, 2015, to March 15, 2018, and March 15, 2018, to March 15, 2021. I used the GEE method to analyze data.

Results

Descriptive Statistics

Table 2 shows the pattern of ORH from 2015 to 2021. The overall mean of ORHs was 930.36 (*SD* 330.707). The yearly mean of ORHs increased from 405.56 (38.67) in 2015 to 1486.33 (*SD* 49.803) in 2021. In 2016, the mean of ORH was 565.33 (*SD* 54.10); this increased by 56.7% in 2017 to 886.08 (*SD* 200.655). There was an additional 13% increase between 2017 and 2018 (1002.42, *SD* 127.80), representing a total increase of 98.7% in ORH visits between 2015 and 2018. These findings demonstrate the worsening trend of opioid-related harm as reported in several pieces of literature (Gomes et al., 2017; Rudd et al., 2016).

Although there has been a consistent increase in ORHs from 2015 to 2017, the increase became very steep in 2018 and most significant in 2021 (1486.33, *SD* 49.803). Table 1 further shows the steep increase in ORHs during the years 2018 to 2021 when recreational cannabis was legalized in Canada. The hospitalization rate increased slightly more than twofold (1275.58, *SD* 143.957) in 2020 and up to threefold 1486.33, *SD* 49.803) in 2021 compared to 2015 (504.56 *SD* 38.67).

ORD followed a similar pattern seen with ORH. As shown in Table 1, there was zero death in 2015 and 2016; however, in 2017, the mean ORD was 4.50 (*SD* 4.503),

6.00 (*SD*3.54) in 2018, 6.50 (*SD* 6.10) in 2019, 9.0 (*SD*7.60) in 2020 and 17.33 (*SD* 2.517) in 2021. This represents a 285% rise in ORD between 2017 (4.50, *SD* 4.503) and 2021 (17.30, *SD* 2.52).

Table 2

Descriptive Statistics for Opioid-Related Deaths and Hospitalization in Ontario From 2015-2021

Year		*N*	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean Lower Bound	95% Confidence Interval for Mean Upper Bound	Minimum	Maximum
	2015	9	504.56	38.666	12.889	474.83	534.28	434	571
	2016	12	565.33	54.093	15.615	530.96	599.70	464	647
	2017	12	886.08	200.655	57.924	758.59	1013.57	606	1281
	2018*	12	1002.42	127.754	36.879	921.25	1083.59	745	1145
	2019	12	1102.75	275.507	79.532	927.70	1277.80	738	1553
	2020	12	1275.58	143.957	41.557	1184.12	1367.05	942	1512
	2021	3	1486.33	49.803	28.754	1362.62	1610.05	1440	1539
	Total	72	930.36	330.707	38.974	852.65	1008.07	434	1553
	2015	9	.00	.000	.000	.00	.00	0	0
	2016	12	.50	1.732	.500	-.60	1.60	0	6
	2017	12	4.50	4.503	1.300	1.64	7.36	0	16
	2018*	12	6.00	3.542	1.022	3.75	8.25	0	11
	2019	12	6.50	6.068	1.752	2.64	10.36	0	17

Year		*N*	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean Lower Bound	Upper Bound	Minimum	Maximum
	2020	12	9.00	7.592	2.192	4.18	13.82	0	22
	2021	3	17.33	2.517	1.453	11.08	23.58	15	20
	Total	72	5.14	6.054	.714	3.72	6.56	0	22

Note. *Years of recreational cannabis legalization in Canada

Table 3 shows ORDs over time. The death rate increased linearly over the years but showed a steeper increase between the years 2018 and 2021, the period of cannabis legalization in Canada. Table 3 shows the means of ORH over the years. The hospitalization rate increased linearly over the years but showed a steeper increase between the years 2018 and 2021, the period of cannabis legalization in Canada. Table 3 shows the seasonal ORDs and hospitalizations in Ontario, Canada, from 2015 to 2021. Each season (summer, fall, and winter) was compared against spring.

Table 3

Seasonal Opioid-Related Death and Hospitalization in Ontario, Canada, From 2015 to 2021

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean Lower Bound	95% Confidence Interval for Mean Upper Bound	Minimum	Maximum
1	18		990.28	386.208	91.030	798.22	1182.33	483	1553
2	18		924.11	294.815	69.488	777.50	1070.72	494	1312
3	18		881.78	304.288	71.721	730.46	1033.10	434	1398
4	18		925.28	348.908	82.238	751.77	1098.79	464	1512
Total	72		930.36	330.707	38.974	852.65	1008.07	434	1553
1	18		5.67	6.894	1.625	2.24	9.10	0	22
2	18		3.61	3.600	.848	1.82	5.40	0	10
3	18		5.50	5.762	1.358	2.63	8.37	0	16
4	18		5.78	7.488	1.765	2.05	9.50	0	21
Total	72		5.14	6.054	.714	3.72	6.56	0	22

*Spring=1, Summer=2, Fall=3, Winter =4 All seasons' analyses against Spring *N=3(span of one season in months) ×6(complete years between 2015 and 2021)

Visual examination of the seasonal changes in ORDs and hospitalizations showed no differences across all seasons. This observation was later proven accurate, as shown in Table 4; there were no significant differences (hospitalization: *p*-value= 0.81, death: *p*-value= 0.68) in ORDs and hospitalization across all seasons.

Table 4

Seasonal Means of Opioid Hospitalization and Deaths in Ontario, Canada, Between 2015-2021

		N	Min	Max	M	SD	SE	CI	
Cases								Upper	Lower
	1	18	483	1553	990.28	386.208	91.030	798.22	1182.33
	2	18	494	1312	924.11	294.815	69.488	777.50	1070.72
	3	18	434	1398	881.78	304.288	71.721	730.46	1033.10
	4	18	464	1512	925.28	348.908	82.238	751.77	1098.79
	Total	72	434	1553	930.36	330.707	38.974	852.65	1008.07
Deaths	1	18	0	22	5.67	6.894	1.625	2.24	9.10
	2	18	0	10	3.61	3.600	.848	1.82	5.40
	3	18	0	16	5.50	5.762	1.358	2.63	8.37
	4	18	0	21	5.78	7.488	1.765	2.05	9.50
	Total	72	0	22	5.14	6.054	.714	3.72	6.56

*1= Spring, 2= summer, 3= Fall, 4= winter.

Table 5 shows the means of opioid hospitalization and deaths per month in Ontario between 2015 and 2021.

Table 5

Means of Opioid Hospitalization and Deaths per Month in Ontario, Canada, Between 2015-2021

	Months	Opioid Hospitalizations	Opioid Deaths
Mean	36.50	116.30	1.82
Median	36.50	81.00	.00
SD	20.801	101.462	3.119
Maximum	72	517	15

Figure 2 shows a line graph showing ORDs over time. The death rate increased linearly over the years but showed a steeper increase between the years 2018 and 2021, the period of cannabis legalization in Canada.

Figure 2

Trend of Annual Opioid-Related Deaths From 2015-2021

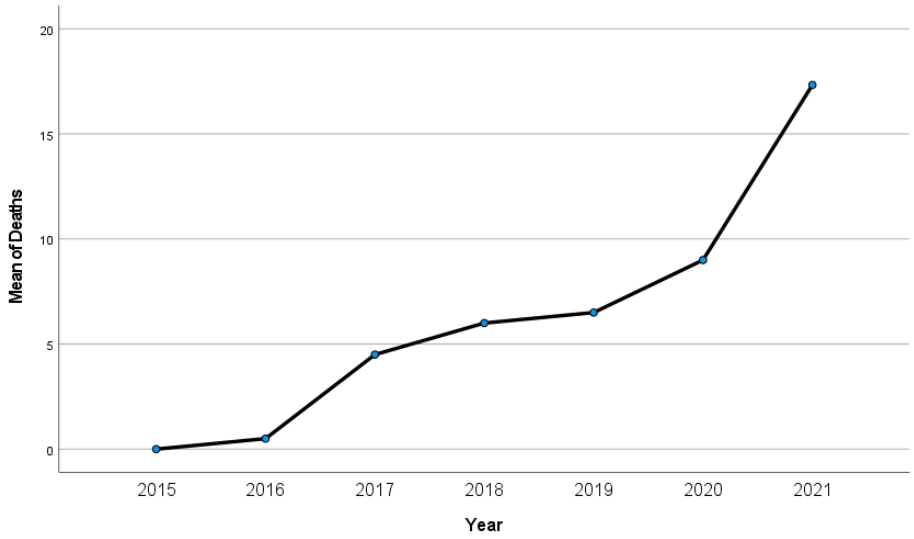
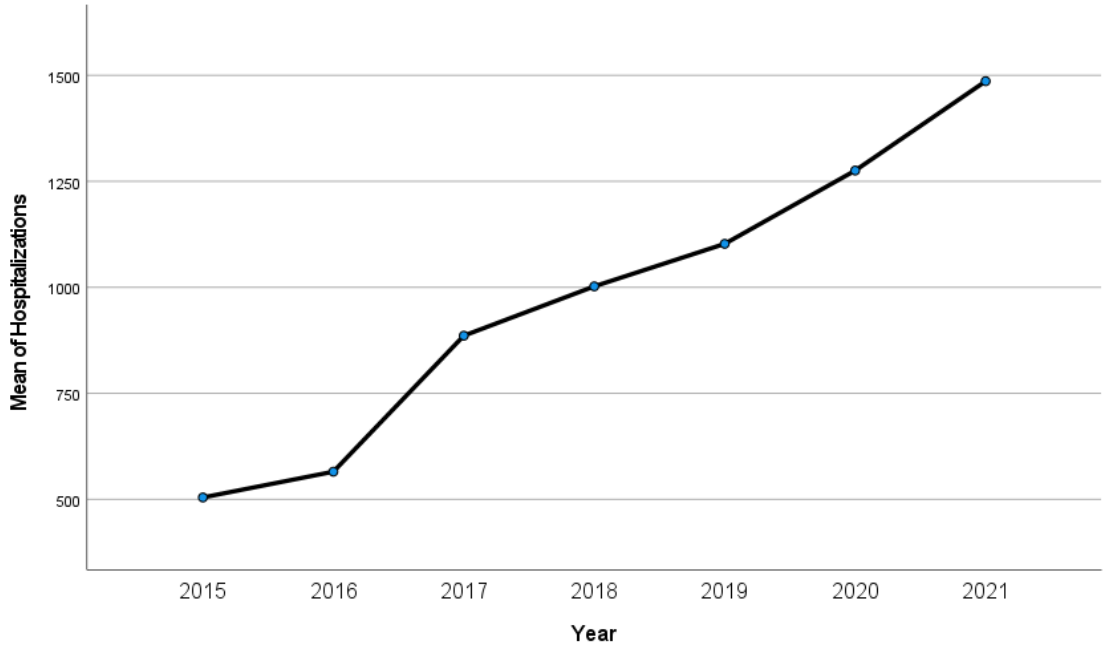


Figure 3 shows a line graph for the means of ORH over time. The hospitalization rate increased linearly over the years but showed a steeper increase between the years 2018 and 2021, the period of cannabis legalization in Canada.

Figure 3

Trend of Annual Opioid-Related Hospitalizations From 2015 to 2021



The Q-Q plots shown in Figure 4 and Figure 5 revealed that the data are relatively normally distributed. The sample data points on the Q-Q plot lie approximately along the reference line.

Figure 4

Q-Q Plot Hospitalization Cases

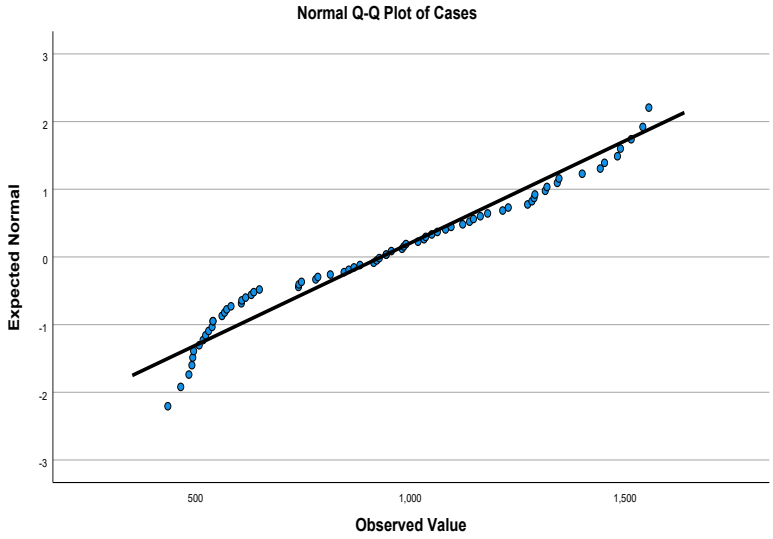
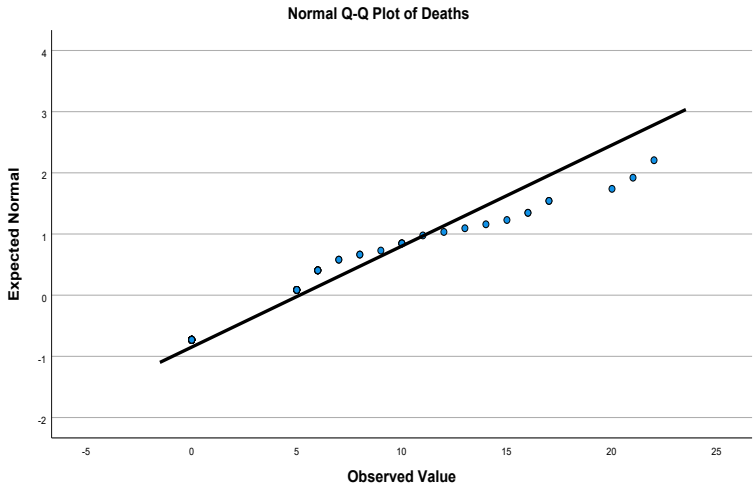


Figure 5

Normal Q-Q Plot Deaths



Similar to the observation found with Q-Q in Figure 4 and Figure 5, the probability plots for ORH (see Figure 6) and ORD (see Figure 7) showed that the data are typically distributed; in both cases, the data points on the p-p plot lie approximately along the reference line.

Figure 6

Hospitalization Cases P-P Plot Regression

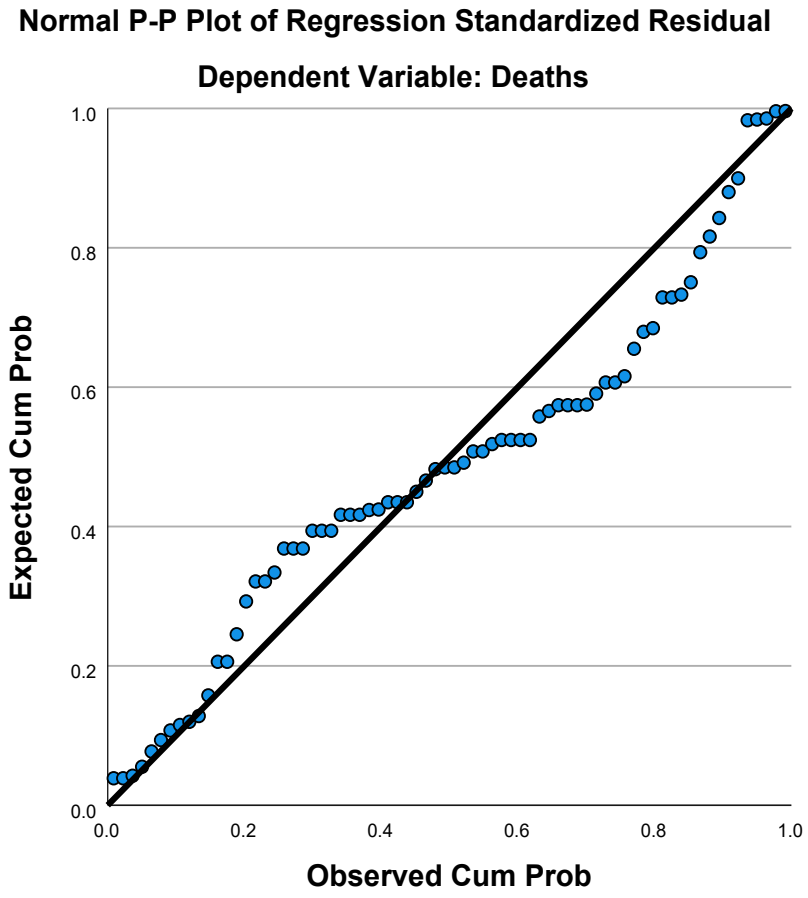
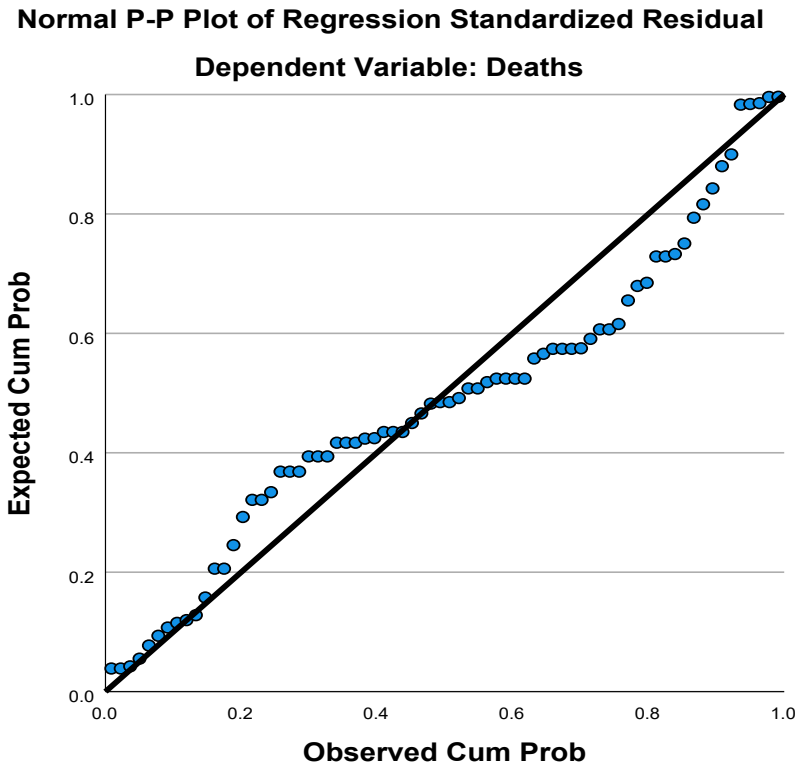


Figure 7

Death P-P Plot Regression



ANOVA

The assumption of normality (skewness and kurtosis statistics) and homogeneity of variance (Levene's Test of Equality of Variances) were checked. When both assumptions were met, a one-way ANOVA analysis was performed to test for significant main effects. Post hoc testing was performed when a significant main effect was detected. Means and standard deviations were reported and interpreted for each year and season.

Statistical significance was assumed at an alpha value of 0.05, and all analyses were performed using SPSS Version 29 (Armonk, NY: IBM Corp).

Statistical Results

Table 6 shows the result of one-way ANOVA for years. For the analysis related to years, a statistically significant main effect was detected for hospitalizations, $F(6,65) = 37.67$, $p < 0.001$. Using 2015 as the reference, there were significant differences with 2017, 2018, 2019, 2020, and 2021, $p < 0.001$, but no difference with 2016, $p = 1.0$. A significant main effect was detected for the death analysis, $F(6,65) = 8.67$, $p < 0.001$. Post hoc tests with 2015 used as the reference found significantly higher levels of death in 2020, $p = 0.001$, and 2021, $p < 0.001$, but not in 2016, $p = 1.0$, 2017, $p = 0.72$, 2018, $p = 0.11$, and 2019, $p = 0.06$. See Table 2 for all the means and standard deviations associated with the year analyses.

Table 6

One-Way ANOVA for Years

Outcome	Group/Level	*M* (SD)	*p*-value
Hospitalizations			
	2015	504.56 (38.67)	
	2016	565.33 (54.09)	
	2017	886.08 (200.66)	
	2018	1002.42 (127.75)	
	2019	1102.75 (275.51)	
	2020	1275.58 (143.96)	
	2021	1486.33 (49.80)	< 0.001
Deaths			
	2015	0.00 (0.00)	
	2016	0.50 (1.73)	
	2017	4.50 (4.50)	
	2018	6.00 (3.54)	
	2019	6.50 (6.07)	
	2020	9.00 (7.59)	
	2021	17.33 (2.52)	< 0.001

Note. M (*SD*) – Mean (standard deviation)

Table 7 demonstrates that the data for death and hospitalization were typically distributed (p-value = 0.002, 0.001, respectively).

Table 7

Tests of Normality

	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	Sig	Statistic	Df	Sig
Cases	.124	72	.008	.941	72	.002
Deaths	.206	72	< .001	.813	72	<.001

The means and standard deviations for the Season analyses are presented in Table 8. For the analysis related to seasons, there was no significant main effect for hospitalizations, $F(3,68) = 0.32$, $p = 0.81$. There was also no significant main effect on deaths, $F(3,68) = 0.51$, $p = 0.68$.

Table 8

One-Way ANOVA for Seasons

Outcome	Group/Level	*M* (SD)	*p*-value
Hospitalizations			
	Spring	990.28 (386.21)	
	Summer	924.11 (294.82)	
	Fall	881.78 (304.29)	
	Winter	925.28 (348.91)	0.81
Deaths			
	Spring	5.67 (6.89)	
	Summer	3.61 (3.60)	
	Fall	5.50 (5.76)	
	Winter	5.78 (7.49)	0.68

Note. M (*SD*) – Mean (standard deviation)

As shown in Table 9, there was a statistically significant difference between hospitalization groups as determined by one-way ANOVA ($F(37.668) = 4.467$, $p = .021$).

Table 9

One-Way ANOVA

Variable	Sum of squares	df	Mean square	F	p	η2	CI
Hospitalization	7765068.61	71	1005106.34	37.668	<.001	.777	.650, .820
Deaths	2602.61	71	192.82	8.670	<.001	.445	.213, .541

Estimated Equation Model Results

Two primary outcomes of interest for the study were hospitalizations and deaths. Due to the hierarchical nature of the data and, thus, the violation of independence of observations, GEE were used to test the primary hypotheses. Beta coefficients (B), their respective standard errors (SE), their associated 95% Wald confidence intervals (95% CI), and *p*-values were reported for the GEE analyses. Marginal means (M) with 95% CI were reported for the periods when marijuana was legal and illegal. Statistical significance was assumed at an alpha value of 0.05, and all analyses were performed using SPSS Version 29 (Armonk, NY: IBM Corp.).

Statistical Results

For the GEE analysis related to hospitalizations, the primary independent variable was a binary, categorical grouping variable of 0 = illegal period and 1 = legal period. There were 38 months of observation for the illegal period, with eight data points per month representing different age groups (n = 304 total observations). For the legal period, there was a total of 34 months of observation, with the same eight data points per month reflecting the age groups (n = 272 total observations). When performing the GEE analysis, there was a statistically significant increase in the number of monthly hospitalizations from the illegal period (M = 87.02, 95% CI 78.54 – 95.50) to the legal period (M = 149.01, 95% CI 1.39.84 – 158.19), B = 61.99, SE = 6.37, Wald 95% CI 49.50 – 74.49, $p < 0.001$.

The exact primary independent variable, which focused on monthly deaths, was utilized for the GEE analysis. However, out of a total of N = 576 possible observations, there were n = 373 (64.8%) missing observations and n = 203 (35.2%) observations included in the current analysis spread across the 72 total months represented in the study. There was at least one possible observation for 71 out of the 72 months within the study, and the maximum number of observations in any month was six. Out of the n = 203 observations included in the analysis, n = 116 (57.1%) were during the illegal period, and n = 87 (42.9%) were during the legal period. The GEE analysis found a statistically significant increase in the number of monthly deaths from the illegal period (M = 0.65, 95% CI 0.28 – 1.01) to the legal period (M = 3.39, 95% CI 2.74 = 4.05), B = 2.74, SE =

0.38, Wald 95% CI 1.99 – 3.50, $p < 0.001$. Table 10 below shows the generalized estimating equations for hospitalizations and deaths per month.

Table 10

Generalized Estimating Equations

Outcome	Group	*B* (Wald 95% CI)	SE	*M* (95% CI)	*p*-value
Hospitalizations per month					
	Illegal	Referent		87.02 (78.54 – 95.50)	
	Legal	61.99 (49.50 – 74.48)	6.37	149.01 (139.84 – 158.19)	< 0.001
Deaths per month					
	Illegal	Referent		0.65 (0.28 – 1.01)	
	Legal	3.39 (2.74 – 4.05)	0.38	3.39 (2.74 – 4.05)	< 0.001

Note. B – beta coefficient, 95% CI – 95% confidence interval, SE – standard error, M – marginal mean

Summary

The results of the descriptive statistics showed that the overall mean of ORHs is 930.36 (*SD* 330.707). This increased from 405.56 (38.67) in 2015 to 1486.33 (*SD* 49.803) in 2021. In 2016, the mean of ORH was 565.33 (*SD* 54.10); this increased by 56.7% in 2017 to 886.08 (*SD* 200.655). There was an additional 13% increase between 2017 and

2018 (1002.42, *SD* 127.80), representing a total increase of 98.7% in opioid-related hospital visits between 2015 and 2018.

The hospitalization rate increased slightly more than twofold (1275.58, *SD* 143.957) in 2020 and up to threefold (1486.33, *SD* 49.803) in 2021 compared to 2015 (504.56 *SD* 38.67). Descriptive statistics showed zero death in 2015 and 2016; however, in 2017, the mean ORD was 4.50 (*SD* 4.503), 6.00 (*SD* 3.54) in 2018, 6.50 (*SD* 6.10) in 2019, 9.0 (*SD* 7.60) in 2020 and 17.33 (*SD* 2.517) in 2021. This represents a 285% rise in ORD between 2017 (4.50, *SD* 4.503) and 2021 (17.30, *SD* 2.52).

The analysis of seasonal effects showed no significant main effect for hospitalizations, $F(3,68) = 0.32$, $p = 0.81$. There was also no significant main effect on deaths, $F(3,68) = 0.51$, $p = 0.68$.

The result of one-way ANOVA for years showed a statistically significant main effect detected for hospitalizations, $F(6,65) = 37.67$, $p < 0.001$. A significant main effect was detected for the death analysis, $F(6,65) = 8.67$, $p < 0.001$. Post hoc tests with 2015 used as the reference found significantly higher levels of death in 2020, $p = 0.001$, and 2021, $p < 0.001$, but not in 2016, $p = 1.0$, 2017, $p = 0.72$, 2018, $p = 0.11$, and 2019, $p = 0.06$.

The GEE analysis showed a statistically significant increase in the number of monthly hospitalizations from the illegal period ($M = 87.02$, 95% CI 78.54 – 95.50) to the legal period ($M = 149.01$, 95% CI 1.39.84 – 158.19), $B = 61.99$, $SE = 6.37$, Wald 95% CI 49.50 – 74.49, $p < 0.001$.Tthere were significant increases in ORDs for 2017 ($B = 4.60$, $SE = 2.11$, $p = 0.033$), 2018 ($B = 6.10$, $SE = 2.11$, $p = 0.005$), 2019 ($B = 6.60$, $SE = 2.11$,

$p = 0.003$), 2020 ($B = 9.10$, $SE = 2.11$, $p < 0.001$), and 2021 ($B = 17.74$, $SE = 3.29$, $p < 0.001$).

Chapter 5: Discussion, Conclusions, and Recommendations

Discussion

Numerous studies have posited that increasing access to cannabis through marijuana decriminalization could mitigate ORHs and overdose deaths (Bachhuber et al., 2014; Bradford et al., 2018; Li & Chihuri, 2020; Livingston et al., 2017; Shi et al. 2019; Vyas et al., 2018). For instance, in the United States, Bachhuber et al. (2014) reported a 24.8% annual reduction in opioid overdose mortality rates in states with medical cannabis laws compared to those with complete cannabis prohibition from 1999 to 2010. Similarly, Shi et al. (2019) documented a 29.6% reduction in opioid prescriptions, a 29.9% reduction in opioid dosage, and a 28.8% reduction in opioid-related Medicaid spending in states where medical cannabis was legalized relative to those without such laws.

However, contradicting the notion that increased access to marijuana might reduce opioid-related harms, Shover et al. (2019) found that states with medical cannabis laws experienced a 22.7% increase in opioid overdose deaths, directly opposing the earlier findings of Bachhuber et al. (2014). Shover et al.'s findings align with the theory that marijuana serves as a complementary rather than a substitute drug, potentially exacerbating the opioid crisis (Finn, 2018). Other studies have similarly suggested that marijuana use may increase, rather than decrease, the prevalence of OUD (DiBenedetto et al., 2018; Olfson et al., 2018).

Given the disparate opinions and mixed findings regarding marijuana's potential role in addressing the opioid epidemic, critical questions arise: Would marijuana indeed reduce opioid-related adverse outcomes if patients substituted cannabis for opioids?

Would similar studies conducted in Canada yield comparable results? Notably, Canada differs from the United States in that it enacted nationwide decriminalization of recreational marijuana in October 2018, which could, in theory, exert a more pronounced effect on the opioid crisis than observed in the United States.

Over the past 2 decades, ORHs and deaths have risen significantly worldwide, particularly in North America (Gomes et al., 2018; Jette, 2018; Schuchat et al., 2017). The incidence of opioid-related fatalities and hospitalizations has sharply increased in both the United States and Canada (Gomes et al., 2017; Rudd et al., 2016).

This study sought to assess the validity of claims that increased access to marijuana could be transformative in combating the opioid crisis. Specifically, the study aimed to determine whether ORD and hospitalization rates in Ontario changed following the nationwide decriminalization of marijuana in Canada in 2018. Contrary to expectations that increased cannabis access might reduce opioid-related harms, the study found that ORDs and hospitalizations increased during the period of cannabis legalization. While the COVID-19 pandemic, which coincided with this period, may have contributed to the rise in opioid misuse, the study was unable to establish this link conclusively. The findings were interpreted based on this study's RQs and hypotheses restated below:

RQ1: Is there a correlation between decriminalization of marijuana and ORDs per month in Ontario, Canada?

$H_0$1*:* There is no correlation between the decriminalization of marijuana and ORDs per month in Ontario, Canada.

*H*a1*:* There is a correlation between the decriminalization of marijuana and ORDs per month in Ontario, Canada

RQ2: Is there a correlation between decriminalization of marijuana and ORHs per month in Ontario, Canada?

*H*02*:* There is no correlation between the decriminalization of marijuana and ORHs per month in Ontario, Canada.

*H*a2*:* There is a correlation between the decriminalization of marijuana and ORHs per month in Ontario, Canada.

Interpretation of Findings

Descriptive Statistics

The data revealed an upward trend in opioid-related admissions and mortality in Ontario between 2015 and 2021, with significant spikes, particularly between 2018 and 2019, following the legalization of recreational marijuana. This trend illustrates the deterioration of public health in the region, as hospitalization rates escalated from an average of 405.56 in 2015 to 1486.33 in 2021. Similarly, ORDs, which were not reported between 2015 and 2016, surged to 17 cases in 2021. These patterns raise critical questions about the interplay between substance use behaviors and cannabis legalization, suggesting that opioid misuse has increased in parallel.

Several factors may contribute to this trend. First, the legalization of marijuana may have reduced the public's perception of the risks associated with substance use, normalizing drug consumption. As cannabis became more accessible and socially accepted, individuals might have felt more comfortable experimenting with other

substances, such as opioids, leading to increased misuse. Additionally, the use of cannabis for self-medication, particularly for pain relief, may have blurred the line between appropriate use and dependence, potentially resulting in greater opioid prescriptions and misuse.

The lack of seasonal and geographical variation in opioid-related outcomes suggests that social and policy factors, rather than temporal influences, are driving the epidemic. This persistence underscores the need for further exploration into the broader factors at play, such as the role of socioeconomic disparities, common mental health conditions, and the effectiveness of current harm reduction strategies. Understanding the connection between cannabis legalization and rising opioid-related harms provides critical insights into the shaping of modern public health policy. The expectation that cannabis would serve as a safer alternative for pain management contrasts with the dramatic rise in hospitalizations and deaths following decriminalization, suggesting a possible relationship between the two.

These findings emphasize the necessity of a comprehensive approach to drug policy, one that addresses both cannabis and opioid use, and provides crucial considerations for shaping future legislation. The data indicate that Ontario's efforts to decriminalize cannabis may have inadvertently exacerbated the opioid crisis rather than alleviating it. This calls for a reassessment of current strategies and highlights the importance of evaluating the broader public health implications of drug legalization. Stakeholders must engage in a thorough investigation of these issues and develop

interventions that address the risks of both opioids and potential cross-addiction. Only by doing so can we arrive at practical solutions to this urgent public health challenge.

ANOVA Results

The ANOVA results underscore significant trends in opioid-related admissions and deaths over the study period from 2015 to 2021, revealing sharp increases in both measures. Specifically, the quantitative analysis demonstrated a statistically significant main effect for hospitalizations ($F(6,65) = 37.67$, $p < 0.001$) and deaths ($F(6,65) = 8.67$, $p < 0.001$), indicating that the observed trends are not coincidental but statistically significant. Post-hoc comparisons further confirmed that hospitalizations increased significantly each year following 2015, suggesting that the opioid crisis represents a long-term, worsening public health issue rather than an isolated event.

Although the analysis showed a significant rise in deaths, a closer comparison of mortality data from 2016-2019 to figures from 2020-2021 suggests little change before the pandemic, with the situation worsening dramatically afterward. This may be attributed to the availability of more potent opioids, changes in prescribing practices, and inadequate support services for individuals with substance use disorders. Additionally, the lack of seasonal variation in ORHs and deaths ($p = 0.81$ and $p = 0.68$, respectively) suggests that the crisis is a persistent, year-round public health issue rather than a seasonal phenomenon.

Taken together, these findings highlight the urgent need for intervention strategies that address both the immediate consequences of opioid misuse for individuals and families, as well as the underlying systemic factors driving the epidemic. The results

underscore the importance of policy considerations, particularly in light of shifting drug legislation, and suggest that future research could further elucidate the connections between drug use and public health outcomes, contributing to the development of more effective public health policies.

GEE Model Results

The GEE analysis offers compelling evidence of the impact of marijuana legalization on ORHs and deaths. The sharp increase in monthly hospitalizations from an average of 87.02 before marijuana legalization to 149.01 afterward ($B = 61.99$, $p < 0.001$) indicates that legalization may have contributed to higher opioid use or abuse, potentially due to new perceptions of risk and availability of substances. Similarly, the rise in monthly deaths from 0.65 in the prelegalization period to 3.39 after legalization ($B = 2.74$, $p < 0.001$) supports the notion that the opioid crisis worsened during this time. This increase in mortality may be due to interactions between different substances, as individuals could be using marijuana in combination with opioids, thereby compounding their health risks.

The findings raise critical questions about the current public health and harm reduction approaches in light of cannabis legalization. Despite the policy shift, hospitalization and death rates increased, suggesting that legalizing marijuana may not uniformly reduce opioid-related harms. The data challenge the hypothesis that cannabis decriminalization has no bearing on opioid-related outcomes and underscore the need for further research to understand the relationship between these substances better. This

could inform the design of more effective policies and intervention mechanisms aimed at mitigating the opioid crisis.

Implication for Social Change

The finding from this study provides crucial information for all groups involved in the fight against opioid-related harm, including policymakers, health care providers, and government agencies. The outcome that cannabis failed to prevent ORD and hospitalization provides an evidence-based ground for practitioners to avoid the use of cannabis as a substitution drug for OUD. This finding is contrary to the reported reduction in opioid-related mortality in states with medical cannabis laws compared to states without such laws by Vyas et al. (2018).

Finding an effective intervention program that will prevent ORDs and hospitalizations remains a current and significant public challenge in Canada; therefore, it would be a massive success if marijuana possesses the claimed ability to reduce the opioid crisis. Additionally, marijuana is a psychoactive substance and has the potential for abuse and behavioral changes. Therefore, it is crucial to be very sure of its importance before recommending its use in the fight against the opioid epidemic; this study disagrees with any potential benefit of cannabis in the fight against opioid-related harms.

The finding from this study not only opposed the claim that cannabis legalization may reduce opioid-related harm, but the study demonstrated a rise in opioid use with cannabis legalization. This finding agrees with the works of Li and Chihuri (2020) and Olfson et al. (2018). Li and Chihuri reported a strong correlation between marijuana and OUD. Olfson et al. used a structured interview to determine the relationship between cannabis

and prescription OUD, using logistic regression models; they reported that increased use of cannabis is associated with the risk of OUD. Shover et al. (2019) used a time series analysis like the works of Bachhuber et al. (2014) to study the association between medical cannabis laws and ORDs. The understanding that cannabis is not a safe substitute drug to opioid, rather, it may be a gate way drug may help prevent worsening opioid epidemics.

Limitations of the Study

One of the primary limitations of this study is the relatively brief exposure period. Extending the exposure period to 3 to 5 years or more would enhance the reliability of the study's findings by providing a more robust dataset for analysis. While annual data would offer a broader temporal perspective, the use of monthly data introduces multiple variables for more granular statistical analysis. Given the rapid accumulation of ORHs and deaths due to the epidemic's nature, monthly data should suffice to discern any potential impact of marijuana legalization on opioid-related outcomes.

Another noteworthy limitation is the potential confounding effect of the COVID-19 pandemic. This study was unable to control for the pandemic, which may have significantly contributed to the observed increase in opioid-related harms. Previous research by Kurdyak et al. (2021) indicated a 57% increase in suspected opioid overdoses and a 60% increase in fatal opioid overdoses in Ontario since the onset of COVID-19 compared to the pre-pandemic period. Similarly, Ghose et al. (2022) reported a significant rise in monthly overdose deaths during the pandemic. Given these findings,

the results of this study should be interpreted with caution, acknowledging the lack of adjustment for the potential confounding effects of the COVID-19 pandemic.

Recommendations

It is strongly recommended that future research extend the exposure period to 3 to 5 years or longer. Such an extension would enhance the reliability of the study's findings by allowing for a more comprehensive and robust dataset, thereby improving the validity of the analysis. Additionally, it is essential to consider the potential confounding effects of the COVID-19 pandemic on the study's results. To mitigate this, the study should be replicated during a period without the influence of COVID-19, ensuring that the findings accurately reflect the variables of interest without pandemic-related distortions.

Conclusion

Contrary to the multiple claims that increasing access to cannabis may reduce opioid-related harms (Vyas et al., 2018), the findings from this study showed that ORDs and hospitalization increased during the era of cannabis legalization. Additionally, the degree of increase was higher during the 3 years of cannabis legalization compared to the three years prior to cannabis legalization. Although the impact of the COVID-19 pandemic on this study could not be verified, there are reports that the COVID-19 pandemic was associated with a rise in substance use, including opioids (Kurdyak et al., 2021). Ghose et al. (2022) reported a significant rise in ORDs and hospitalizations during the COVID-19 pandemic compared to the pre-COVID-19 era. Additionally, there are reports of the association between cannabis use and a rise in opioid-related overdose (Li & Chihuri, 2020; Olfson et al., 2018). Access to cannabis was the primary treatment in

this study; therefore, it was impossible to control its use in the design. I suggest that the findings of this study be used with caution.

Summary

This research rigorously examines the correlation between increased opioid use following legalization and the corresponding rise in hospitalization and mortality rates, strengthening the argument that opioid misuse constitutes a significant public health issue. The GEE analysis reveals a statistically significant increase in monthly hospitalizations, with an average of 87.02 during the prelegalization period and 149.01 in the postlegalization period ($\beta = 61.99$, $p < 0.001$). This finding underscores not only a change but also a substantial rise in healthcare costs due to opioid-related complications. Furthermore, the GEE analysis for monthly mortality rates demonstrates a similar upward trend, with average deaths increasing from 0.65 to 3.39 per month. These findings suggest that despite regulatory changes intended to control access, opioid use remains a significant threat to public health, with heightened risk for misuse leading to severe health outcomes.

Additionally, descriptive statistical analysis supports these alarming trends, indicating a sharp, exponential increase in opioid-related hospital readmissions and mortality between 2017 and 2021. Notably, hospitalization rates surged from an average of 405.56 in 2015 to 1486.33 in 2021, representing more than a threefold increase. Similarly, ORDs, which were absent in 2015 and 2016, escalated to an average of 17.33 in 2021, contributing significantly to the opioid-related mortality rate. Importantly, the data did not reveal any significant seasonal variations in these outcomes, as evidenced by

non-significant *F*-tests, indicating that the opioid crisis persists year-round. Collectively, these findings provide a compelling scientific basis for the detrimental consequences of opioid legalization and raise critical questions about the adequacy of current legal frameworks in addressing the opioid crisis.

This study also challenges the prevailing assumption that increased cannabis legalization would mitigate opioid misuse and its associated harms. In contrast to previous studies suggesting that cannabis could reduce opioid dependence due to its relatively lower risk profile, the current research contradicts these claims, demonstrating that marijuana did not serve as an effective substitute for opioids as anticipated. In fact, the findings suggest that some users may have employed marijuana and opioids interchangeably, contributing to the rise in ORHs and deaths. These insights highlight the urgent need for policy reforms grounded in robust research to address both the opioid epidemic and the potentially adverse effects of marijuana legalization in this context.

References

Aggarwal, S. K., Carter, G. T., Sullivan, M. D., ZumBrunnen, C., Morrill, R., & Mayer, J. D. (2009). Medicinal use of cannabis in the United States: Historical perspectives, current trends, and future directions. *Journal of Opioid Management*, *5*(3), 153–168. https://doi.org/10.5055/jom.2009.0016.

Alexander, G. C. (2015). *The prescription opioid epidemic: an evidence-based approach*. Johns Hopkins Bloomberg School of Public Health. https://www.pacificresearch.org/wp-content/uploads/2017/06/2015-prescription-opioid-epidemic-report.pdf

Amin, M. R., & Ali, D. W. (2019). Pharmacology of medical cannabis. *Advances in Experimental Medicine and Biology*, *1162*, 151–165. https://doi.org/10.1007/978-3-030-21737-2_8

Babson, K. A., Sottile, J., & Morabito, D. (2017). Cannabis, cannabinoids, and sleep: a review of the literature. *Current psychiatry reports*, *19*(4), 1-12. https://doi.org/10.1007/s11920-017-0775-9

Bachhuber, M. A, Saloner, B., Cunningham, C. O, & Barry, C. L. (2014). Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *Journal of American Medical Association Internal Medicine*, *174*, 1668-1673. https://doi.org/10.1001/jamainternmed.2014.4005

Baker, D. W. (2017). History of the joint commission's pain standards: Lessons for today's prescription opioid epidemic. *Journal of American Medical Association*, *317*(11), 1117-1118. https://doi.org/10.1001/jama.2017.0935

Belzak, L., & Halverson, J. (2018). The opioid crisis in Canada: A national perspective. La crise des opioïdes au Canada: une perspective nationale. *Health Promotion and Chronic Disease Prevention in Canada: Research, Policy and Practice*, *38*(6), 224–233. https://doi.org/10.24095/hpcdp.38.6.02

Bennett, C. (2010). Early/ancient history. In J. Holland (Ed.), *The pot book*: *A complete guide to cannabis. Its role in medicine, politics, science, and culture* (pp. 15-23). Park Street Press. https://books.google.com/books?hl=en&lr=&id=tV0oDwAAQBAJ&oi=fnd&pg=PT28&dq=Bennett,+C.+(2010).+Early/ancient+history.+In+J.+Holland+(Ed.),+The+pot+book:+A+complete+guide+to+cannabis.+Its+role+in+medicine,+politics,+science,+and+culture+(pp.+15-23).+Park+Street+Press%5D&ots=pvXdMRCknW&sig=9ZjOfAkvaHoXg8JcQrXfqOVow3Y

Bradford, A. C., Bradford, W. D., Abraham, A., & Bagwell Adams, G. (2018). Association between US state medical cannabis laws and opioid prescribing in the Medicare Part D population. *Journal of American Medical Association Internal Medicine*, *178*(5), 667–672. https://doi.org/10.1001/jamainternmed.2018.0266

Bridgeman, M. B., & Abazia, D. T. (2017). Medicinal cannabis: History, pharmacology, and implications for the acute care setting. *P&T: A Peer-Reviewed Journal for Formulary Management, 42*(3), 180–188. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5312634/

Cameron, J. M., & Dillinger, R. J. (2011). Narcotic Control Act. In M. A. R. Kleiman &

J. E. Hawdon (Eds.), *Encyclopedia of drug policy* (pp. 543–545). SAGE Publications. https://sk.sagepub.com/reference/drugpolicy

Caplehorn, J. R. (1998). Deaths in the first two weeks of maintenance treatment in NSW in 1994: Identifying cases of iatrogenic methadone toxicity. *Drug Alcohol Review*. *17*(1), 9-17. https://doi.org/10.1080/09595239800187551

Centers for Disease Control and Prevention. (2020). *Wide-ranging online data for epidemiologic research (WONDER)*. http://wonder.cdc.gov

Cerdá, M., Wall, M., Keyes, K. M., Galea, S., & Hasin, D. (2012). Medical marijuana laws in 50 states: Investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence. *Drug and Alcohol Dependence*, *120*(1-3), 22–27. https://doi.org/10.1016/j.drugalcdep.2011.06.011

Cheung, A., Marchand, J., & Mark, P. (2020). Loss of life and labour productivity: The Canadian opioid crisis. Working Paper No. 2020-13. *Nanaimo Regional General Hospital*. https://sites.ualberta.ca/~econwps/2020/wp2020-13.pdf

Chimbar, L., & Moleta, Y. (2018). Naloxone effectiveness: A systematic review. *Journal of Addictions Nursing*, *29*(3), 167–171. https://doi.org/10.1097/JAN.0000000000000230

Clarke, J. L., Skoufalos, A., & Scranton, R. (2016). The American Opioid Epidemic: Population Health Implications and Potential Solutions. Report from the National Stakeholder Panel. *Population health management*, 19 Suppl 1, S1–S10. https://doi.org/10.1089/pop.2015.0144

Connock, M., Juarez-Garcia, A., Jowett, S., Frew, E., Liu, Z., Taylor, R. J., Fry-Smith,

A., Day, E., Lintzeris, N., Roberts, T., Burls, A., & Taylor, R. S. (2007). Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health technology assessment* (Winchester, England), 11(9), 1–iv. https://doi.org/10.3310/hta11090

Dasgupta, N., Beletsky, L., & Ciccarone, D. (2018). Opioid Crisis: No Easy Fix to Its Social and Economic Determinants. *American Journal of Public Health*, 108(2), 182–186. https://doi.org/10.2105/AJPH.2017.304187

Degenhardt, L., Charlson, F., Mathers, B., Hall, W. D., Flaxman, A. D., Johns, N., & Vos, T. (2014). The global epidemiology and burden of opioid dependence: results from the global burden of disease 2010 study. *Addiction* (Abingdon, England), 109(8), 1320–1333. https://doi.org/10.1111/add.12551

DiBenedetto DJ, Weed VF, Wawrzyniak KM, Finkelman M, Paolini J, Schatman ME, Herrera D, Kulich RJ. (2018) The Association Between Cannabis Use and Aberrant Behaviors During Chronic Opioid Therapy for Chronic Pain. *Pain Medicine*. 19(10):1997-2008. doi: 10.1093/pm/pnx222. PMID: 29947796.

D'Onofrio, G., O'Connor, P. G., Pantalon, M. V., Chawarski, M. C., Busch, S. H., Owens, P. H., Bernstein, S. L., & Fiellin, D. A. (2015). Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. *Journal of American Medical Association*, 313(16), 1636–1644. https://doi.org/10.1001/jama.2015.3474

Earnshaw, V., Smith, L., & Copenhaver, M. (2013). Drug addiction stigma in the context of methadone maintenance therapy: An investigation into understudied sources of

stigma. *International Journal of Mental Health and Addiction*, 11(1), 110–122. https://doi.org/10.1007/s11469-012-9402-5

Finn, K. (2018). Why Marijuana will not fix the opioid epidemic. *Missouri Medicine*, 115(3), 191–193.

Fischer, B., Rehm, J., & Tyndall, M. (2016). Effective Canadian policy to reduce harms from prescription opioids: learning from past failures. *Canadian Medical Association journal = journal de l'Association medicale canadienne*, 188(17-18), 1240–1244. https://doi.org/10.1503/cmaj.160356

Freeman, P. R., Curran, G. M., Drummond, K. L., Martin, B. C., Teeter, B. S., … Edlund, M. J. (2019). Utilization of prescription drug monitoring programs for prescribing and dispensing decisions: Results from a multi-site qualitative study. *Research in Social & Administrative Pharmacy*, 15(6), 754–760. https://doi.org/10.1016/j.sapharm.2018.09.007

Freeman, T. P., Hindocha, C., Green, S. F., & Bloomfield, M. (2019). Medicinal use of Cannabis-based products and cannabinoids. *British Medical Journal (Clinical research ed.),* 365, l1141. https://doi.org/10.1136/bmj.l1141

Ghose R, Forati AM, Mantsch JR (2022) Impact of the COVID-19 Pandemic on Opioid Overdose Deaths: a Spatiotemporal Analysis. J Urban Health. Apr;99(2):316-327. doi: 10.1007/s11524-022-00610-0. Epub 2022 Feb 18. PMID: 35181834; PMCID: PMC8856931.

Gomes T, Tadrous M, Mamdani MM, Paterson JM, Juurlink DN. (2018) The Burden of Opioid-Related Mortality in the United States. *Journal of American Medical*

Association Netw Open. 1(2):e180217. https://doi.org/10.1001/jamanetworkopen.2018.0217

Gomes, T., Greaves, S., Martins, D., Bandola, D., Tadrous, M., Singh, S et al. (2017). Latest trends in opioid-related deaths in Ontario: 1991 to 2015. *Ontario Drug Policy Research Network*. Retrieved from https://odprn.ca/wp-content/uploads/2017/04/ODPRN-Report_Latest-trends-in-opioid-related-deaths.pdf

Gomes, T., Mamdani, M. M., Dhalla, I. A., Cornish, S., Paterson, J. M., & Juurlink, D. N. (2014). The burden of premature opioid-related mortality. *Addiction*, 109(9), 1482– 1488. doi: 10.1111/add.12598

Gomes, T., Tadrous, M., Mamdani, M.M., Paterson, J.M., & Juurlink, D.N. (2018). The burden of opioid-related mortality in the United States. *Journal of American Medical Association Network*, 1(2), e180217. doi:10.1001/jamanetworkopen.2018.0217.

Government of Canada (2021). Cannabis laws and regulations. Retrieved on August 29, 2021, retrieved from https://www.canada.ca/en/health-canada/services/drugs-medication/Cannabis/laws-regulations.html

Grotenhermen, F., & Müller-Vahl, K. (2012). The therapeutic potential of Cannabis and cannabinoids. *Deutsches Arzteblatt International*, 109(29-30), 495–501. https://doi.org/10.3238/arztebl.2012.0495

Haley DF, Saitz R (2020) The Opioid Epidemic During the COVID-19 Pandemic.

Han, B., Compton, W.M., Blanco, C., Crane, E., Lee, J., & Jones, C.M. (2017).

Prescription opioid use, misuse, and use disorders in U.S. adults: *2015 National Survey on Drug Use and Health.* 167(5), 293-301.

Hawk, K. F., Vaca, F. E., & D'Onofrio, G. (2015). Reducing fatal opioid overdose: Prevention, treatment, and harm reduction strategies. *The Yale Journal of Biology and Medicine*, 88(3), 235–245.

Hollander, M., Donohue, J. M., Stein, B. D., Krans, E. E., & Jarlenski, M. P. (2020). Association between Opioid Prescribing in Medicare and Pharmaceutical Company Gifts by Physician Specialty. *Journal of general internal medicine*, 35(8), 2451–2458. https://doi.org/10.1007/s11606-019-05470-0

Hosseini, S. H., Isapour, A., Tavakoli, M., Taghipour, M., & Rasuli, M. (2013). Erectile dysfunction in methadone maintenance patients: A cross sectional study in northern Iran. *Iranian Journal of Psychiatry*, 8(4), 172–178.

Jette, A. (2018). Responding to the opioid epidemi in the Unitced States. *Physical Therapy*, 98(3), 147–148.

Jones, M. R., Viswanath, O., Peck, J., Kaye, A. D., Gill, J. S., & Simopoulos, T. T. (2018). A Brief History of the Opioid Epidemic and Strategies for Pain Medicine. *Pain and therapy*, 7(1), 13–21. https://doi.org/10.1007/s40122-018-0097-6

Jones, M. R., Viswanath, O., Peck, J., Kaye, A. D., Gill, J. S., & Simopoulos, T. T. (2018). A brief history of the opioid epidemic and strategies for pain medicine. *Pain and Therapy*, 7(1), 13–21. https://doi.org/10.1007/s40122-018-0097-6

Joranson, D. E., Ryan, K. M., Gilson, A. M., & Dahl, J. L. (2000). Trends in medical use and abuse of opioid analgesics. *Journal of American Medical Association*,

283(13), 1710–1714. https://doi.org/10.1001/jama.283.13.1710

Joranson, D.E., Gilson, A.M., Dahl, J.L., Haddox, J.D. (2002). Pain management, controlled substances, and state medical board policy: A decade of change. *Pain Symptom Manage*, 23(2), 138-47.

Journal of American Medical Association. 324(16):1615–1617. doi:10.1001/jama.2020.18543

Kermode, M., Choudhurimayum, R. S., Rajkumar, L. S., Haregu, T., & Armstrong, G. (2020). Retention and outcomes for clients attending a methadone clinic in a resource-constrained setting: A mixed methods prospective cohort study in Imphal, Northeast India. *Harm Reduction Journal*, 17(1), 1–17. https://doi.org/10.1186/s12954-020-00413-z

Kerr, T., Tyndall, M., Li, K., Montaner, J., & Wood, E. (2005). Safer injection facility use and syringe sharing in injection drug users. The Lancet, online Research Letter. Retrieved May 9, 2008, from http://image.thelancet.com/extras/04let9110web.pdf

Kidorf, M., Brooner, R. K., Leoutsakos, J. M., & Peirce, J. (2018). Treatment initiation strategies for syringe exchange referrals to methadone maintenance: A randomized clinical trial. *Drug and alcohol dependence*, 187, 343–350.

Kim, D., Irwin, K.S., & Khoshnood, K. (2009). Expanded access to naloxone: Options for critical response to the epidemic of opioid overdose mortality. *American Journal of Public Health*, 99(3):402-7.

Kim, H. K., & Nelson, L. S. (2015). Reducing the harm of opioid overdose with the safe

use of naloxone: a pharmacologic review. *Expert opinion on drug safety*, 14(7), 1137–1146. https://doi.org/10.1517/14740338.2015.1037274

Klimkiewicz, A., & Jasinska, A. (2018). The health effects of Cannabis and cannabinoids. In Psychiatria (Vol. 15, Issue 2). https://doi.org/10.17226/24625.

Krebs, E. E., Gravely, A., Nugent, S., Jensen, A. C., DeRonne, B., Goldsmith, E. S., Kroenke, K., Bair, M. J., & Noorbaloochi, S. (2018). Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial. *Journal of American Medical Association*, 319(9), 872–882. https://doi.org/10.1001/jama.2018.0899

Krikorian A. D. (1975). Were the opium poppy and opium known in the ancient Near East?. *Journal of the history of biology*, 8(1), 96–114.

Krishnamurti, C., & Rao, S. C. (2016). The isolation of morphine by Serturner. *Indian journal of anaesthesia,* 60(11), 861–862. https://doi.org/10.4103/0019-5049.193696

Kurdyak EL, Gomes T, et al. (2021) The impact of the COVID-19 pandemic on opioid-related harm in Ontario. Science Briefs of the Ontario COVID-19 Science Advisory;2(42). https://doi.org/10.47326/ocsat.2021.02.42.1.0

Latimer, D. & Goldberg, J. (1981). *Flowers in the Blood: The Story of Opium*. New York: Franklin Watts. Page 306. https://books.google.com/books?hl=en&lr=&id=-y51EAAAQBAJ&oi=fnd&pg=PT7&dq=Latimer,+D.+%26+Goldberg,+J.+(1981)

.+Flowers+in+the+Blood:+The+Story+of+Opium.+New+York:+Franklin+Watts.+Page+306.&ots=Ou9KEhPOI7&sig=yvxUn2Hjnal0PXAQd76BfazG4nc

Lavonas, E. J., Drennan, I. R., Gabrielli, A., Heffner, A. C., Hoyte, C. O., Orkin, A. M., Sawyer, K. N., & Donnino, M. W. (2015). Part 10: Special Circumstances of Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*, 132(18 Suppl 2), S501–S518. https://doi.org/10.1161/CIR.0000000000000264

Li, G., & Chihuri, S. (2020). Is Marijuana use associated with decreased use of prescription opioids? Toxicological findings from two US national samples of drivers. *Substance Abuse Treatment, Prevention, and Policy*, 15(1), 12. https://doi.org/10.1186/s13011-020-00257-7

Livingston, M. D., Barnett, T. E., Delcher, C., & Wagenaar, A. C. (2017). Recreational Cannabis Legalization and Opioid-Related Deaths in Colorado, 2000-2015. *American journal of public health,* 107(11), 1827–1829. https://doi.org/10.2105/AJPH.2017.304059

Lucas, P. (2017). Rationale for Cannabis-based interventions in the opioid overdose crisis. *Harm Reduction Journal,* 14(1), 10–15. https://doi.org/10.1186/s12954-017-0183-9. https://link.springer.com/article/10.1186/s12954-017-0183-9

Manubay, J., Davidson, J., Vosburg, S., Jones, J., Comer, S., Sullivan, M. (2015). Sex differences among opioid-abusing patients with chronic pain in a clinical trial, *Journal of Addiction Medicine,* 9(1), 46-52. https://doi.org/10.1097/ADM.0000000000000086

Marlatt, G. A., Blume, A. W., & Parks, G. A. (2001). Integrating harm reduction therapy and traditional substance abuse treatment. *Journal of psychoactive drugs*, 33(1), 13–21. https://doi.org/10.1080/02791072.2001.10400463

Marshall, B. D., Milloy, M. J., Wood, E., Montaner, J. S., & Kerr, T. (2011). Reduction in overdose mortality after the opening of North America's first medically supervised safer injecting facility: a retrospective population-based study. *Lancet* (London, England), 377(9775), 1429–1437. https://doi.org/10.1016/S0140-6736(10)62353-7

Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2003). Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *The Cochrane database of systematic reviews,* (2), CD002209. https://doi.org/10.1002/14651858.CD002209

Mattick, R. P., Kimber, J., Breen, C., & Davoli, M. (2004). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *The Cochrane database of systematic reviews,* (3), CD002207. https://doi.org/10.1002/14651858.CD002207.pub2

Max M. B. (1990). Improving outcomes of analgesic treatment: is education enough?. *Annals of internal medicine,* 113(11), 885–889. https://doi.org/10.7326/0003-4819-113-11-885. https://www.acpjournals.org/doi/abs/10.7326/0003-4819-113-11-885

McDonald, R., & Strang, J. (2016). Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction*

*(*Abingdon, England), 111(7), 1177–1187. https://doi.org/10.1111/add.13326

McGinty, E. E., Goldman, H. H., Pescosolido, B., & Barry, C. L. (2015). Portraying mental illness and drug addiction as treatable health conditions: effects of a randomized experiment on stigma and discrimination. *Social science & medicine* (1982), 126, 73–85. https://doi.org/10.1016/j.socscimed.2014.12.010

Michaelis, L. L., Hickey, P. R., Clark, T. A., & Dixon, W. M. (1974). Ventricular irritability associated with the use of naloxone hydrochloride. Two case reports and laboratory assessment of the effect of the drug on cardiac excitability. *The Annals of thoracic surgery*, 18(6), 608–614. https://doi.org/10.1016/s0003-4975(10)64408-6

Modesto-Lowe, V., Brooks, D., & Petry, N. (2010). Methadone deaths, risk factors in pain and addicted populations. *Journal of General Internal Medicine*, 25(4), 305–309. https, //doi.org/10.1007/s11606-009-1225-0

Morgan J. P. (1985). American opiophobia: customary underutilization of opioid analgesics. *Advances in alcohol & substance abuse*, 5(1-2), 163–173. https://doi.org/10.1300/J251v05n01_11

Nath, S. S., Tripathi, M., Pandey, C., & Rao, B. (2009). Naloxone-induced pulmonary edema: a potential cause of postoperative morbidity in laparoscopic donor nephrectomy. *Indian journal of medical sciences,* 63(2), 72–75. https://doi.org/10.4103/0019-5359.49240.

Ng, J., Sutherland, C., & Kolber, M. R. (2017). Does evidence support supervised injection sites? *Canadian family physician Medecin de famille canadien*, 63(11),

866. https://www.cfp.ca/content/63/11/866.short

Ngai, S.H., Berkowitz, B.A., Yang, J.C., Hempstead, J., Spector, S. (1976). Pharmacokinetics of naloxone in rats and in man: Basis for its potency and short duration of action. *Anesthesiology,* 44(5), 398–401. https://europepmc.org/article/med/1267205

NIDA. (2018, July 2). As Opioid Use Disorders Increased, Prescriptions for Treatment Did Not Keep Pace. Retrieved from https://www.drugabuse.gov/news-events/nida-notes/2018/07/opioid-use-disorders-increased-prescriptions-treatment-did-not-keep-pace

Olfson, M., Wall, M. M., Liu, S. M., & Blanco, C. (2018). Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States. *The American journal of psychiatry*, 175(1), 47–53. https://doi.org/10.1176/appi.ajp.2017.17040413

Payne, K., Mazur, D.J., Hotaling, J.M., & Pastuszak, A.W. (2019). Cannabis and Male Fertility: A Systematic Review. *The Journal of Urology*, 202, 674-681, https://doi.org/10.1097/JU.0000000000000248

Pergolizzi, J., Böger, R. H., Budd, K., Dahan, A., Erdine, S., Hans, G., Kress, H. G., Langford, R., Likar, R., Raffa, R. B., & Sacerdote, P. (2008). Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). Pain practice: *the official journal of World Institute of Pain,* 8(4), 287–313. https://doi.org/10.1111/j.1533-

2500.2008.00204.x

Phillips JK, Ford MA, B. R. (2017). *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use.* https://doi.org/https://www.ncbi.nlm.nih.gov/books/NBK458655/

Piomelli, D., Solomon, R. Abrams, D., Balla, A. Grant, I. & Yoder, J. (2019). Regulatory barriers to research on Cannabis and cannabinoids: A proposed path forward. *Cannabis and Cannabinoid Research,* 4(1). https://doi.org/10.1089/can.2019.0010

Piper, B. J., DeKeuster, R. M., Beals, M. L., Cobb, C. M., Burchman, C. A., Perkinson, L., Lynn, S. T., Nichols, S. D., & Abess, A. T. (2017). Substitution of medical Cannabis for pharmaceutical agents for pain, anxiety, and sleep. *Journal of psychopharmacology* (Oxford, England), 31(5), 569–575. https://doi.org/10.1177/0269881117699616hv

Platt, L., Minozzi, S., Reed, J., Vickerman, P., Hagan, H., French, C., Jordan, A., Degenhardt, L., Hope, V., Hutchinson, S., Maher, L., Palmateer, N., Taylor, A., Bruneau, J., & Hickman, M. (2018). Needle and syringe programmes and opioid substitution therapy for preventing HCV transmission among people who inject drugs: findings from a Cochrane Review and meta-analysis. *Addiction* (Abingdon, England), 113(3), 545–563. https://doi.org/10.1111/add.14012

Powell, D., Pacula, R. L., & Jacobson, M. (2018). Do medical Marijuana laws reduce addictions and deaths related to pain killers?. *Journal of health economics*, 58, 29–42. https://doi.org/10.1016/j.jhealeco.2017.12.007

Public Health Agency of Canada. (2021). Apparent Opioid and Stimulant Toxicity Deaths (Issue December). https://health-infobase.canada.ca/src/doc/SRHD/UpdateDeathsMarch2021.pdf

Rhodes, E., Wilson, M., Robinson, A., Hayden, J. A., & Asbridge, M. (2019). The effectiveness of prescription drug monitoring programs at reducing opioid-related harms and consequences: A systematic review. *British Medical Council Health Services Research,* 19(1), 784. https://doi.org/10.1186/s12913-019-4642-8

Riley D, Pates R, Monaghan G, O'Hare P (2012) . A brief history of harm reduction. In: Pates R, Riley D, editors. Harm reduction in substance use and high-risk behaviour: international policy and practice. Oxford, UK: Wiley-Blackwell; 2012. https://books.google.com/books?hl=en&lr=&id=3Nh6aV8RXn8C&oi=fnd&pg=PT16&dq=Riley+D,+Pates+R,+Monaghan+G,+O%E2%80%99Hare+P+(2012)+.+A+brief+history+of+harm+reduction.+In:+Pates+R,+Riley+D,+editors.+Harm+reduction+in+substance+use+and+high-risk+behaviour:+international+policy+and+practice.+Oxford,+UK:+Wiley-Blackwell%3B+2012&ots=lU2oTQn3Uy&sig=2nLk9Gk9XQOoWSfzzJ-hGw7mXJ0

Rudd, R. A., Seth, P., David, F., & Scholl, L. (2016). Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. MMWR. *Morbidity and mortality weekly report,* 65(50-51), 1445–1452. https://doi.org/10.15585/mmwr.mm655051e1

Ruder, J., Wally, M. K., Oliverio, M., Seymour, R. B., Hsu, J. R., & PRIMUM Group

(2017). Patterns of opioid prescribing for an orthopaedic trauma population. *Journal of Orthopaedic Trauma*, 31(6), e179–e185. https://doi.org/10.1097/BOT.0000000000000834

Salas, J., Scherrer, J. F., Lustman, P. J., & Schneider, F. D. (2016). Racial differences in the association between nonmedical prescription opioid use, abuse/dependence, and major depression. *Substance abuse*, 37(1), 25–30. https://doi.org/10.1080/08897077.2015.1129523

Saloner, B., McGinty, E., Beletsky, L., Bluthenthal, R., Beyrer, C., Botticelli, M., & Sherman, S. (2018). A public health strategy for the opioid crisis. *Public Health Reports,*133(Supplement 1) 24S-34S. https://doi.org/10.1177/0033354918793627

Shaw L. V., Moe J., Purssell R., Buxton J., Godwin J., Doyle-Waters M. et al. (2009) Naloxone interventions in opioid overdoses: A systematic review protocol. *Systematic Reviews* 8:138. https://doi.org/10.1186/s13643-019-1048-y

Shi, Y., Liang, D., Bao, Y., An, R., Wallace, M. S., & Grant, I. (2019). Recreational Marijuana legalization and prescription opioids received by Medicaid enrollees. *Drug and alcohol dependence,* 194, 13–19. https://doi.org/10.1016/j.drugalcdep.2018.09.016

Shover. C, Davis, C., Gordon. S, Humphreys, K. (2019). Association between medical Cannabis laws and opioid overdose mortality has reversed over time. *Proceedings of the National Academy of Sciences,* 116 (26) 12624-12626. https://doi.org/10.1073/pnas.1903434116

Smith, M. Y., Bailey, J. E., Woody, G. E., & Kleber, H. D. (2007). Abuse of

buprenorphine in the United States: 2003-2005. *Journal of addictive diseases*, 26(3), 107–111. https://doi.org/10.1300/J069v26n03_12

Special Advisory Committee on the Epidemic of Opioid Overdoses. (2020). Opioid and Stimulant Poisoning Hospitalizations (Issue January 2016). https://health-infobase.canada.ca/substance-related-harms/opioids-stimulants/

Tapley, P., & Kellett, S. (2019). Cannabis-based medicines and the perioperative physician. *Perioperative Medicine* 8, 19. https://doi.org/10.1186/s13741-019-0127-x

Thomas, G. (2005). Harm Reduction Policies and Programs Involved for Persons Involved in the Criminal Justice System. *Ottawa: Canadian Centre on Substance Use*. https://www.academia.edu/5670450/Harm_reduction_policies_and_programs_for_persons_involved_in_the_criminal_justice_system

Tucker, K.L. (2004). Medico-legal case report and commentary, inadequate pain management in the context of terminal cancer. The case of Lester Tomlinson. *Pain Medicine*. Volume 5, pages 214–228. doi.10.1111/j.1526-4637.2004.4029

Veillardd, R.H. (2017). Constipation and other common symptoms reported by women and men in methadone and buprenorphine maintenance treatment. *Drug and Alcohol Dependence*, 181(1), 132-139. https://www.sciencedirect.com/science/article/pii/S0376871617305161

Vyas, M. B., LeBaron, V. T., & Gilson, A. M. (2018). The use of Cannabis in response to the opioid crisis: A review of the literature. *Nursing outlook*, 66(1), 56–65.

https://doi.org/10.1016/j.outlook.2017.08.012

Webster L. R. (2017). Risk Factors for Opioid-Use Disorder and Overdose. *Anesthesia and analgesia*, 125(5), 1741–1748. https://doi.org/10.1213/ANE.0000000000002496

Weiner, S. G., Baker, O., Bernson, D., & Schuur, J. D. (2020). One-Year Mortality of Patients After Emergency Department Treatment for Nonfatal Opioid Overdose. *Annals of emergency medicine*, 75(1), 13–17. https://doi.org/10.1016/j.annemergmed.2019.04.020

Welsh, C., & Valadez-Meltzer, A. (2005). Buprenorphine: A (relatively) new treatment for opioid dependence. Psychiatry, 2(12), 29–39. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2994593/

Wendelboe, A. M., Mathew, R., Chongsuwat, T., Rainwater, E., Wendelboe, M. A., Chou, A. F. (2019). Is there less opioid abuse in states where Marijuana has been decriminalized, either for medicinal or recreational use? A Clin-IQ. *Journal of patient-centered research and reviews,* 6(4), 267–273. https://doi.org/10.17294/2330-0698.1704

Whelan, P. J., & Remski, K. (2012). Buprenorphine vs methadone treatment: A review of evidence in both developed and developing worlds. *Journal of Neurosciences in Rural Practice,* 3(1), 45–50. https://doi.org/10.4103/0976-3147.91934

Wiese, B., & Wilson-Poe, A. R. (2018). Emerging Evidence for Cannabis' Role in Opioid Use Disorder. *Cannabis and cannabinoid research*, *3*(1), 179–189. https://doi.org/10.1089/can.2018.0022

Williams, A.R. (2020). Cannabis as a Gateway Drug for Opioid Use Disorder. *The Journal of Law, Medicine & Ethics*, 48(2), 268-274. https://journals.sagepub.com/doi/abs/10.1177/1073110520935338

Williams, A.R. (2016). Medical and Recreational Marijuana Policy: From Prohibition to the Rise of Regulation. In M. Compton (Ed.), *Marijuana and Mental Health* (pp. 39-69). *American Psychiatric Publishing* Inc. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6358421/

Williamson, P. A., Foreman, K. J., White, J. M., & Anderson, G. (1997). Methadone-related overdose deaths in South Australia, 1984-1994. How safe is methadone prescribing? *The Medical journal of Australia,* 166(6), 302–305. https://onlinelibrary.wiley.com/doi/abs/10.5694/j.1326-5377.1997.tb122318.x

Winstock, A. R., Lea, T., & Sheridan, J. (2008). Prevalence of diversion and injection of methadone and buprenorphine among clients receiving opioid treatment at community pharmacies in New South Wales, Australia. *The International journal on drug policy*, 19(6), 450–458. https://doi.org/10.1016/j.drugpo.2007.03.002

World Health Organization. (1986). Cancer pain relief. *World Health Organization*. https://iris.who.int/bitstream/handle/10665/43944/9241561009_eng.pdf

Zador, D. A., & Sunjic, S. D. (2002). Methadone-related deaths and mortality rate during induction into methadone maintenance, New South Wales, 1996. *Drug and alcohol review,* 21(2), 131–136. https://doi.org/10.1080/09595230220139028

Zenz, M. & Willweber-Strumpf, A. (1993). Opiophobia and cancer pain in Europe. *Lancet*, 341(8852), 1075–6. https://elibrary.ru/item.asp?id=1851112

Zias, J., Stark, H., Sellgman, J., Levy, R., Werker, E., Breuer, A., Mechoulam, R. (1993). Early medical use of Cannabis. *Nature*, 363(6426), 215. https://www.nature.com/articles/363215a0