Naloxone distribution and administration in hospital emergency departments

By

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Abstract

The opioid crisis continues to worsen throughout North America. Alberta has been particularly impacted, with approximately two Albertans dying of an opioid overdose every day. Opioid overdose deaths can be prevented with the timely administration of naloxone, an opioid antagonist that reverses the potentially life-threatening respiratory depression that occurs during an opioid overdose. Naloxone is used by Emergency Medical Services (EMS) and hospital emergency department (ED) providers to manage opioid overdoses. Additionally, take-home naloxone programs are public health interventions that prevent opioid-related mortality by distributing naloxone to non-medical personnel who may witness an opioid overdose, such as people who use opioids or their peers. In recent years, take home naloxone programs have been increasingly incorporated into hospital emergency departments in an effort to reach individuals who are at high risk of opioid overdose. It is particularly critical to provide naloxone kits to patients who present to the ED with an opioid overdose, since they are at high risk for future overdose death.

This thesis contains two distinct studies. Both studies use data collected through a retrospective chart review of medical records from emergency department (ED) visits for opioid overdose at Edmonton's Royal Alexandra Hospital between May 2016 and April 2017.

Study 1: Factors associated with being offered take home naloxone in a busy, urban emergency department

Objectives: I sought to evaluate the implementation of the ED-based take home naloxone program at the Royal Alexandra Hospital by i) determining the proportion of individuals who visit the ED for an overdose who are offered a naloxone kit, and ii) identifying whether certain patients were more likely to be offered naloxone kits than others.

Methods: I used multivariate analyses to identify patient characteristics associated with being offered a take home naloxone kit after visiting the ED for an opioid overdose.

Results: I found that 50% of patients who visited the ED for an opioid overdose were offered a naloxone kit before leaving the ED. Patients were more likely to be offered a kit if they overdosed on an illegal opioid, or if they had a severe overdose as measured by their level of consciousness upon EMS arrival. In contrast, patients were less likely to be offered take home naloxone if they had an active prescription for an opioid at the time of their ED visit, if they were admitted to the hospital, or if they left the ED unexpectedly.

Conclusions: Only half of patients with opioid overdose were offered THN. ED staff readily identify patients who use illegal opioids or experience a severe overdose as potentially benefitting from THN, but may miss others at high risk for opioid mortality. I recommend that hospital EDs provide guidance to staff to ensure that all eligible patients at risk of overdose receive THN.

Study 2: A comparison of naloxone administration between patients admitted to an Emergency Department for illegal and pharmaceutical opioid overdose

Objectives: Previous studies have suggested that EMS may under-administer naloxone to patients who overdose on pharmaceutical opioids compared to heroin. I sought to assess how different factors may influence EMS providers' decision to administer naloxone, and whether patients who do not receive naloxone from first responders (including EMS, fire rescue services, or bystanders with naloxone kits) are more likely to subsequently require naloxone in the ED.

Methods: I used multivariate analyses to test whether patients who overdose on illegal opioids are more likely to received naloxone from i) EMS and ii) ED staff, controlling for potentially confounding variables such as route of administration, level of consciousness, and other patients characteristics.

Results: Compared to patients who overdosed on a pharmaceutical opioid, patients who overdosed on an illegal opioid (heroin or illegally manufacture fentanyl) were more likely to receive pre-hospital

naloxone from EMS, bystanders with naloxone kits, and fire rescue services, but less likely to receive

naloxone in the ED. Whether patients received naloxone from these first responders was not associated

ED naloxone administration.

Conclusions: Although EMS were less likely to administer naloxone to patients who overdosed on

pharmaceutical opioids, this did not appear to impact whether naloxone is needed in the ED. Further

research is needed to determine why EMS appear to manage illegal and pharmaceutical opioid

overdoses differently.

Preface

This thesis is original work by Daniel O'Brien. Chapters 2 and 3 of this thesis were written in collaboration with Dan Dabbs, Dr. Paul Veugelers, Dr. Kathryn Dong, and Dr. Elaine Hyshka. D. Dabbs conducted the retrospective chart review that this thesis is based on. The abstraction protocol was developed by D.Dabbs in collaboration with K. Dong, and E. Hyshka.

K. Dong, and E. Hyshka conceived and designed the first study, and collaborated with Daniel O'Brien to conceive and design the second study. D. O'Brien designed the analysis of both studies in collaboration with K. Dong, E. Hyshka, and P.J. Veugelers. D. O'Brien conducted the analyses and drafted the manuscripts.

No part of this thesis has been previously published, although chapter 2 has been submitted for peer-review and possible publication to *BMC Health Services Research* journal (special issue on opioid crisis). Parts of this thesis have been presented a scientific conferences and knowledge translation meetings, including:

- o University of Alberta Chancellor's forum | The Opioid Crisis: Perspectives on health and harm. Edmonton AB. (2019, April)

- Alberta Health Services Emergency Strategic Clinical Network quality improvement & innovation forum. Red Deer, AB. (February, 2019).
- Annual General Meeting of the Prairie node of the Canadian Research Initiative in Substance Misuse. Saskatoon, SK (2018, November).
- Clinical Nurse Educators meeting at the Royal Alexandra hospital. Edmonton, AB. (2018, November)
- School of Public Health "This is Public Health Week" oral presentation. Edmonton, AB. (2018, November).
- Stimulus conference: Drugs, Policy, and Practice in Canada. Edmonton, AB. (2018, October)
- Canadian Society for Addiction Medicine scientific meeting and conference. Vancouver, BC. (2018, October)
- Presentation at the Emergency Department Physicians meeting at the Royal Alexandra Hospital. (2018, Steptember).
- Alberta Health Services harm reduction steering committee meeting. Edmonton AB. (July, 2018).
- Canadian Society for Epidemiology and Biostatistics conference. Thunder Bay, ON. (2018, June)
- University of Alberta Department of Emergency Medicine research day. Edmonton AB. (2018, June)
- Alberta Health/Alberta Health Services take home naloxone working group committee meeting. Edmonton AB. (2018, May)

Acknowledgement

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List of abbreviations

ACCH- Alberta Community Council on HIV

AMA- Against Medical Advice

AOR- Adjusted Odds Ratio

CDC- Centre for Disease Control

ED- Emergency Department

EMS- Emergency Medical Services

GCS- Glasgow Coma Scale

GEE- Generalized Estimating Equation

MCAR- Missing Completely at Random

MAR-Missing at Random

OME- Oral Morphine Equivalents

PEG- Percutaneous Endoscopic Gastrostomy

PIN-Pharmaceutical Information Network

PMP- Prescription Monitoring Program

PO- Pharmaceutical Opioid

RAH- Royal Alexandra Hospital

THN- Take Home Naloxone

Chapter 1: Introduction

1.1 Opioid crisis in North America

The opioid epidemic in the United States and Canada continues to worsen.[1,2] In both these countries, opioid-related mortality and morbidity have increased steeply since the 1990s and now constitute a major public health crisis.[1,3-5] In the United States, there were 70,237 drug overdose deaths in 2017, of which 46,600 (67.8%) involved an opioid.[6] This amounts to an opioid overdose death rate of 14.9 per 100,000 population.[6] Notably, this trend has driven drug-poisoning to replace motor vehicle collisions as the leading cause of accidental injury fatalities,[7] and has led to a decrease in life-expectancy among middle-aged white Americans for the first time in decades.[8] In Canada, available provincial-level data shows that trends of opioid-related mortality and morbidity are similar to those in the US, with 4,034 apparent opioid-related deaths occurring in 2017 and a death rate of 11.1 per 100,000 population.[9-13] The origins and evolution of the opioid crisis in North America are complex, and involve intertwining epidemics of overdose caused by prescription opioids, heroin, and illegally manufactured fentanyl.[2]

1.1.1 Prescription opioid epidemic

In the late 1990's and 2000's, the emerging crisis of opioid-related harm in North America was driven largely by the rise in high dose prescription opioid medications, such as hydrocodone, hydromorphone, fentanyl, and oxycodone.[1,14-16] While these prescription opioids have historically played an important role in the treatment of pain, they carry a serious risk of iatrogenic addiction and overdose. In the United States, the number of prescription opioids sold to hospitals, pharmacies, and clinics quadrupled from 1999 to 2010.[17]

Although opioid-prescription increased globally during this time, no other country reached the same per capita levels of consumption as the United States.[4] The U.S. alone was consuming about 80% of the world's opioid supply, despite containing only 4.7% of the global population.[16] In Canada, opioid consumption doubled from 2000 to 2010, making Canada the second largest per-capita consumer of prescription opioids globally.[5] The volume of opioids consumed in different countries is measured by the United Nations International Narcotics Control Board as "defined daily doses for statistical purposes per million inhabitants per day," which is a standardized metric used to converted the volume (in milligrams) of various opioid substances to an arbitrarily defined standard dose. In terms of standardized daily doses for statistical purposes, the US (47,807) and Canada (26,380) had higher levels of opioid consumption than any other country in the world during 2008-2010.[18] By comparison, the European average during this period was 7,023, and the next highest country was Germany (21,494).[18]

Several factors contributed to the rise of prescription opioids, including the liberalization of guidelines that previously restricted the use of prescription opioids for chronic non-cancer pain patients, advocacy for improved recognition and treatment of pain, and aggressive marketing of prescription opioids by pharmaceutical companies.[15,16,19] In particular, the initial acceleration of opioid prescribing was driven by the 1995 introduction of OxyContin®, a highly potent long-acting formulation of oxycodone that is now known to have a high risk of addiction and overdose.[16,19,20] Although Oxycontin pills were designed to act slowly over a long period, they became a popular target for non-medical use because the pills would rapidly release a large dose of oxycodone if they were crushed, chewed, injected, or snorted.[21]

The manufacturers of OxyContin®, Purdue Pharma, carried out an aggressive marketing campaign to consumers and physicians which falsely promoted OxyContin® as a safe, long-term therapy for a wide range of common chronic conditions.[21,22] In 2007, Purdue Pharma and three top executives pled guilty to federal charges related to misleading regulators, physicians, and patients regarding the

risk of addiction associated with OxyContin®.[23] Other marketing tactics employed by pharmaceutical companies included promoting the off-label use of certain opioids,[24] giving lucrative speaking fees and honoraria to physicians,[25] incentivizing physician prescribing of opioids through kickback schemes,[26] and lobbying.[27]

The promotion of opioid analgesics largely capitalized on a movement within the medical community around this time to improve the identification and treatment of pain.[28] Although efforts to improve pain management were needed and well-intentioned, several medical organizations facilitated the overuse of opioids by downplaying the risks involved and overstating the benefits of opioids to physicians.[19,21,29-32] For instance, in 1996 the American Pain Society and the American Academy of Pain Medicine, both organizations that received substantial drug company funding, issued a consensus statement that endorsed the long-term use of opioids to treat both cancer and non-cancer pain patients.[30] The statement claimed that the risk of opioid addiction among pain patients was low, that developing opioid tolerance does not preclude long-term opioid use, that respiratory depression is not a significant concern, and that there was no defined upper limit for dosage beyond which opioids are dangerous.[30]

In subsequent years, the Federation of State Medical boards created policy guidelines that endorsed the movement to more aggressively treat pain, and assured physicians that they would not be sanctioned for prescribing opioids for legitimate medical reasons.[33] Similarly, the Joint Commission on Accreditation of Healthcare Organizations released guidelines for treating hospitalized patients that endorsed the idea that pain was "the fifth vital sign," and recommended establishing policies supporting the provision of effective pain medications.[34] Much of the rhetoric surrounding this movement was aimed at reducing physician fears of addiction and misuse of pharmaceutical opioids, an attitude that was referred to as "opiophobia." [31]

Unfortunately, the claims made to physicians regarding long-term opioid use in chronic non-cancer patients often invoked insufficient or low-quality evidence.[35-39] In particular, one article that was widely cited as evidence that addiction is rare in patients treated with opioids consisted of a one-paragraph letter to the editor in the New England Journal of Medicine in 1980.[39] The generalization of the findings in this article was highly problematic because it only contained five sentences, and did not describe any methodology or include a clear definition of addiction.[35] In hindsight, the safety and efficacy of long-term opioid treatment had not yet been properly evaluated among a population of chronic non-cancer pain patients before it was used to treat this population.[19]

As opioid prescribing rates continued to rise throughout the 2000's, several opioid-related harms, including mortality, substance use treatment admissions, and emergency room visits, increased in parallel.[17,40] In the U.S. from 1999 to 2008, the number of overdose deaths caused by prescription opioids quadrupled such that in 2008, they were involved in 54% of drug-related deaths[17]. More deaths were caused by prescription opioids during this time than any other illegal drugs, such as heroin and cocaine.[17] During the same period, the rate of substance use treatment admission in the U.S. increased 6-fold.[17] Similarly, from just 2002 to 2009, the number of emergency room visits involving pharmaceutical drugs doubled to 1.2 million per year.[40]

In the Canadian context, available data show similar patterns of concurrent increases in opioid prescribing and opioid-related harms throughout the 1990's and 2000's.[5,11,20,41] For instance, in Ontario from 1991 to 2007, the prescribing of opioid analgesics increased by 29% overall, with an 850% increase of oxycodone prescriptions in particular.[20] Similarly, prescriptions of hydromorphone, fentanyl, and morphine also increased over this period.[20] In parallel with increases in opioid prescribing, the opioid-related mortality rate doubled from 13.7 per million in 1991 to 27.2 million in 2004, with a substantial increase in opioid–related mortality occurring following the introduction of long-acting oxycodone (ie OxyContin©) in 2000.[20] Prescription opioid related deaths continued to increase each year throughout

the 2000's, from 153 in 2002 to 540 in 2012 in Ontario.[41] Similar increases in opioid-related mortality driven by prescription opioid overdose were observed in Quebec and British Columbia over this period.[41,42]

There is strong evidence from both the United States and Canada that the volume of opioids being prescribed in the population correlated with increased levels of opioid-related morbidity and mortality.[43-48] This "volume-effect" occurred in-part because the greater availability of prescription opioids in the population increased diversion of opioids for non-medical reasons.[5,49] Diversion occurs when individuals obtain prescription opioids from someone with a prescription, and either use the pills themselves, or sell them in illegal drug markets.[49] Individuals seeking prescription opioids might also visit multiple doctors or clinics to obtain multiple prescriptions, or visit multiple pharmacies to get prescriptions filled for personal use, or for resale. These practices are commonly referred to as "double doctoring," "doctor shopping," or "prescription shopping.[49] Other forms of diversion included forging prescriptions, drug theft, or online prescription opioid sales.[49] There is evidence from the U.S and Canada that both diversion and doctor/prescription shopping contributed to opioid-related mortality.[49-53]

In addition to increasing the opportunity for diversion, prescription opioid consumption can cause morbidity and mortality among individuals prescribed opioids. For example, a review of 38 studies found that among chronic pain patients, rates of prescription opioid misuse averaged between 21 to 29%, and rates of addiction averaged between 8 to 12%.[54] Furthermore, several studies have shown that a dose-response relationships exists between the daily dose of prescription opioids prescribed to patients and overdose, with the risk of overdose increasing progressively at dosages exceeding 20, 50, and 100 MME per day. [50,55-59] These results show that although high daily doses opioids are associated with the greatest risk of overdose (>100 MME per day), many opioid-related

deaths occur in patients prescribed low to moderate dose ranges (50-100 MME per day), since such dosages are commonly prescribed.[55,57-59]

Additionally, individuals prescribed opioids are at greater risk of overdose if they concurrently using other central nervous system depressants such as alcohol or benzodiazepines.[60] Overdoses involving both prescription opioids and benzodiazepines are particularly frequent, with benzodiazepines playing a role in as many as 80% of fatal prescription opioid overdoses in some studies.[60] While alcohol and benzodiazepines cause minimal respiratory depression on their own, they can interact with opioids to increase and prolong respiratory depression.[60,61]

A growing awareness of the risks associated with prescription opioids led to various efforts to curb the use of prescription opioids and prevent their diversion.[62] In the US, several states introduced mandatory provider review laws in an attempt to reduce diversion and doctor shopping by requiring clinicians to review data from prescription monitoring programs before prescribing opioids. Similarly, pain clinic laws were implemented to crackdown on "pill mills," which were pain clinics that notoriously supplied a large volume of prescription opioids without proper medical justification or follow-up.[63,64] In 2010, Purdue Pharma released a 'tamper-resistant' formulation of oxycodone (OxyNEO®), which they claimed was more difficult to inject or insufflate than previous medications.[65] However, it should be noted that the utility of such formulations for curbing problematic patterns of prescription opioid use are questionable.[66]

Efforts to crack down on prescribing have reduced opioid prescribing in the US from its peak in 2010, and appear to have slowed the rate of deaths related to prescription opioids in several states.[62-64,67,68] Similar interventions occurred in the Canada over this period, with several provinces implementing Prescription Monitoring Programs (PMP) and the delisting long-acting formulations of oxycodone (OxyContin® & OxyNEO®) in an effort to reduce inappropriate opioid prescriptions.[10,41,69]

1.1.2 Illegal opioid epidemic

Despite increasing recognition of the harms caused by prescription opioids and efforts to crackdown on their overuse, opioid-related overdose deaths have continued to increase since 2010.[41,70] However, the nature of the opioid epidemic has shifted. While increasing opioid-related harms throughout the 1990's and 2000's was predominately driven by the use and misuse of prescription opioids, recent increases in overdose morality have been driven by illegal opioids, namely heroin and illegally manufactured synthetic opioids.[42,70-72] For instance, in the United States, national surveillance data shows that rates of heroin use have increased dramatically since 2010.[62] In parallel, the heroin-related death rate, which had been rising steadily since 2006, spiked by 400% from 2010 to 2015.[70] In Canada, available data from Ontario show similar trends. Specifically, heroin deaths rose 975% between 2006 and 2015 and contributed to 86 deaths in 2015.[11] Additionally, ED visits related to heroin also rose fourfold from 2013 to 2017, culminating in a rate of 5.7 per 100,000 population.[73]

Heroin use and prescription opioid use are interrelated epidemics.[74,75] This is evidenced by studies showing an association between prescription opioid- and heroin- related harms. For example, one study of opioid-related hospitalization rates between 1993 and 2009 found that increases in prescription opioid overdose hospitalization predicted subsequent increases in heroin overdose hospitalization one year later, with the converse being true as well.[75] Similarly, Rudd *et al.* showed that from 2010-2012, increases in rates of heroin-related death were associated with increases in rates of prescription-opioid related death among 28 states.[76]

Since heroin and pharmaceutical opioids are pharmacologically similar, some individuals who initially use prescription opioids non-medically may eventually switch to heroin as they develop an opioid use disorder.[75,77-79] Indeed, several qualitative studies have described a typical pattern in which individuals initiate opioids via the non-medical use of oral prescription opioid pills, which are mainly

obtained through friends, family, and personal prescriptions.[77,80,81] Eventually, some individuals who use prescription opioids non-medically may transition to more efficient routes of transmission, such as smoking, injection, or insufflation. As the opioid use disorder progresses and obtaining prescription opioids becomes increasingly expensive, some individuals may initiate heroin, which had become cheaper and more widely available since the 1990s as a result of shifting illegal drug distribution networks.[77,79,82,83]

Several cross-sectional and cohort studies have confirmed that the non-medical use of prescription opioids is a strong risk factor for future heroin use.[79,84-87] Data from the National Survey on Drug Use and Health in the United States from 2002 to 2011 showed that among people who use heroin, a large proportion of individuals (nearly 80%) reported using prescription opioids non-medically before initiating heroin use.[85] During this time, the risk of heroin initiation was 19 times higher among those who reported non-medical prescription opioid use compared to those who did not.[85] Similarly, a prospective cohort study of young individuals in Ohio who used prescription opioids non-medically but were not opioid dependent at baseline found that within three years, 7.5% participants had initiated heroin use.[87]

There is evidence that the transition to heroin may have also been facilitated by various "supply side" interventions that made prescription opioids either less desirable or more difficult to access, including the reformulation of OxyContin into abuse deterrent pills , implementation of prescription monitoring programs, cracking down on pill mills, and stricter guidelines for prescribing opioids.[62,65,88-90] While certain supply side interventions have shown success in reducing overall opioid-related mortality, such efforts are often not accompanied by sufficient care for individuals who are already struggling with opioid use disorders or opioid dependence.[89,91] Consequently, many individuals who lose access to prescription opioids may subsequently turn to heroin or other illegal street opioids.[79,92]

Since 2013, the opioid crisis in Canada and in the United States has been further complicated by the emergence of fentanyl in the illegal drug supply.[42,70] Fentanyl is a synthetic opioid that is 50-100 times more potent than morphine (CDC) and 30-50 times more potent than heroin.[71] Increasingly, illegally manufactured fentanyl powder is being sold in street markets as a substitute or additive to heroin, or cut with other ingredients to produce powders or counterfeit pills.[42,93,94] Fentanyl has also been detected in other non-opioid illegal drugs seized by law enforcement, such as cocaine, benzodiazepines, and methamphetaphine.[95-97] People using these substances are often unaware that they contain fentanyl.[93] Since the consumption of life-threatening doses of fentanyl is typically unintentional, some medical professionals and activists argue that the term opioid "poisoning" is more appropriate than "overdose" in the context of the current fentanyl crisis. This is because term overdose negatively and incorrectly implies that individuals know the dosage of their drugs, and that they chooses to take too much.[98]

Originally, pharmaceutical fentanyl was developed in the 1960's, and has long been used as an anesthetic during surgery.[99,100] In the 1990's, transdermal fentanyl patches also became available for the treatment of chronic pain.[99,100] Like other pharmaceutical opioids, the sales of pharmaceutical grade fentanyl rose dramatically throughout the 2000's, with transdermal fentanyl patches becoming popular targets for diversion and non-medical use.[16,42,101] However, in recent years, fentanyl and its analogues (i.e. carfentanil, furanylfentanyl, acetylfentanyl, butyrylfentanyl) are being manufactured in clandestine drug laboratories using precursors smuggled across the border, often from China.[42,93,94]

Fentanyl has several advantages for individuals involved in the illegal drug trade compared to heroin or diverted pharmaceutical grade opioids. Because of its high potency, less volume and weight is necessary to transport fentanyl powder, which makes it much easier to smuggle through borders.[89,94] Fentanyl can also be cheaply mass produced. A single kilogram of powder can be bought for a few thousand dollars and used to manufacture millions of counterfeit pills, each of which can be sold for

$10-20.[94,96,100] The lucrative nature of fentanyl has driven its sharp increase in the illegal drug market, to the point where it has almost entirely replaced heroin among certain populations.[72,96,102]

The high potency of fentanyl makes it more dangerous than other opioids such as heroin, oxycontin, morphine or hydrocodone. Whereas the dosing of other opioids is measured in milligrams (MME), the dosage of fentanyl is measured on the order of micrograms.[103] Therefore, there is an extremely small margin of error between a lethal dose and a dose sufficient to produce euphoria.[103] Since illegal drug manufacturers imprecisely dilute fentanyl when producing powders and counterfeit pills, the illegal street drug supply in communities with illegal manufactured fentanyl has become highly unpredictable and toxic.[2,93]

An additional issue concerning fentanyl is that the length of time between drug consumption and death is significantly less than with other opioids.[2] Whereas heroin overdose death typically occurs between 20-30 minutes after the drug is consumed, fentanyl can induce life-threatening respiratory depression within minutes.[104,105] Thus, the window of time in which it is possible may to intervene and reverse an overdose caused by fentanyl is greatly reduced, and the likelihood of death and severe complications is increased.[2] The rapidity with which fentanyl causes respiratory depression is attributable its high lipophilicity, which allows it to readily enter and exits the central nervous system, especially when injected.[2] Additionally, injected fentanyl can quickly produce muscle rigidly in the jaws and chest, which can interfere with ventilation and may complicate the overdose response.[106,107]

Communities with fentanyl in the street drug supply have seen acute increases in the number of opioid deaths.[93] From 2013 to 2015, the incidence of deaths in the United States related to synthetic opioids other than methadone tripled, resulting in almost 10,000 deaths.[7] Although the CDC opioid surveillance does not differentiate between illegally manufactured synthetic opioids and pharmaceutical synthetic opioids such as tramadol or pharmaceutical fentanyl, there is evidence that this increase in deaths is mainly driven by clandestinely manufactured fentanyl.[71,72] Specifically, the number of synthetic

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opioid-related deaths coincided with a sharp increase in the number of illegal drugs seized by law enforcement that tested positive for fentanyl, whereas the rate of pharmaceutical fentanyl prescribing did not change.[71,72]

Fentanyl is not distributed evenly in the United States, and has mostly impacted states where "white heroin" is prevalent, including the Northeast, Midwest, and Southeast regions.[97] In some regions, fentanyl has become the main driver of opioid-related fatalities. For example, in the northeastern states, between 60 and 90% of opioid overdose deaths tested in 2016 involved fentanyl.[108] Deaths-related to illegally manufactured fentanyl appear to be geographically spreading and increasing in number.[6]

In the Canadian context, a similar trend has developed in the western provinces of British Columbia and Alberta. In British Columbia, fentanyl was detected in 1,510 deaths in 2018, which represents 87% of all illegal drug deaths. This was an increase from 2017, in which 1,486 (82%) illegal drug deaths involved fentanyl.[109] Although case-definitions for opioid deaths vary between provinces, the proportion of opioid overdose deaths involving fentanyl appears to be similar in the province of Alberta, where 673 opioid overdose deaths (~88%) in 2018 involved fentanyl.[110] This represents an increase over 2017, in which 566 (81%) opioid overdose deaths involved fentanyl.[110] The rapid rise of fentanyl in Canada may have been fueled in-part by drug substitution after OxyContin[©] was delisted from the majority of provincial drug formularies in 2012. [10,42] Following this intervention, the number of fentanyl-related overdose deaths began to increase rapidly in several provinces, driving increases in overall opioid-related mortality.[42]

The opioid crisis continues to evolve, with an expanding array of synthetic opioids and fentanyl analogs being manufactured and added to the illegal drug supply.[100] Of particular concern is carfentanil, a synthetic opioid used for the sedation of large animals that is approximately 10,000 times more potent than morphine.[95] Carfentanil is increasingly being implicated in opioid-overdose deaths. In 2016 from

July to December, it was contributed to 350 deaths in Ohio, and was also detected in West Virginia.[95] In

Alberta, carfentanil has been detected 155 deaths in 2018.[110]

Beletsky *et al.* (2017) posit that the increasing potency of the drug supply (from heroin to

fentanyl and now carfentanil), is a predictable pattern that results from drug prohibition.[89] This pattern

occurs because illegal drugs that have a greater potency to volume ratio are more profitable and less

easily interdicted by law enforcement.[89] Notably, a similar progression was observed during the alcohol

prohibition era in the United States, in which thousands of people died from drinking contraband liquor

(moonshine).[89]

1.1.3 Social determinants of the opioid crisis

Despite recent declines in the amount of opioids prescribed in the United States, the rate of

opioid overdose deaths has accelerated in recent years.[28] As previously discussed, many opioid overdose

deaths are presumed to have involved individuals who were initiated into opioid use through

pharmaceuticals, but subsequently transitioned to using dangerous street opioids such as heroin and

illegally manufactured fentanyl.[2,77] However, the current state of the opioid crisis in North America

cannot be singularly blamed on exposure to pharmaceutical opioids. This is evidenced by the

observation that as of 2015, a higher proportion of individuals entering drug treatment in the US now

report initiating opioid use with heroin (33.3%) compared to either oxycodone or hydromorphone

(24.1% and 27.8% respectively).[111]

To understand the persistence of overdose death rates, it is necessary to consider the deeper

social and economic determinants that lead individuals to develop opioid use disorders. One well-

subscribed theory is that opioid deaths are part of a larger phenomenon of increasing "deaths of

despair," a grouping that also includes death from suicide and chronic liver disease.[8] From 1999-2015,

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the increasing rate of deaths from these causes has driven premature mortality in mid-life Americans, especially among rural, working-class whites without a high school education.[112]

There are numerous structural factors contributing to deaths related to substance use, including poverty, lack of economic opportunity, social isolation, and growing income inequality.[8,28,112] In particular, rural areas in the US have been challenged by deindustrialization and the loss of steady manufacturing jobs, which has led to long-term unemployment in many communities.[113] Economic conditions were further exacerbated by the 2008 financial crisis, such that individuals entering the work force now face lower-paying job opportunities compared to the previous generation.[8] Poverty and bleak employment prospects can produce feelings of hopelessness and stress, leading some individuals to cope through drug use.[112,114]

While much of the social and political attention regarding the opioid crisis in the US has been focused on the dramatic increases in overdose deaths among white, rural, and suburban communities, more recent data from the CDC show increasing rates of overdose death among black Americans.[6] Black Americans face the additional disadvantage of being disproportionately criminalized for their substance use as oppose to receiving treatment.[115] For instance, black Americans represent 12.5% of people who use illegal drugs, but 38% of those arrested for drug offenses and 33% of those incarcerated in state prisons for drug offences.[116] Former inmates with a history of substance use often face significant social and economic barriers upon their release from prison, making abstinence from substance use extremely difficult for many.[117] Further, the prolonged period of relative abstinence experienced during incarceration leaves people who use opioids vulnerable to overdose death given their loss of tolerance.[118]

At the community level, there is epidemiological evidence that social capital is closely associated with overdose rates in US counties.[119] Social capital refers to the level of social trust, norms and

networks in a community and has been shown to mediate a range of health outcomes.[119] Social capital is a proxy for connectedness with others, and can buffer against the feelings of hopelessness, stress, and isolation that contribute to the development and continuation of addiction. [119] In one qualitative study of residents living in a poor, rural community in Pennsylvania, social isolation and a lack of community were identified as drivers of the town's high burden of addiction and drug overdose.[114]

At the level of individuals and families, adverse childhood experiences and childhood trauma are strongly associated with both the earlier initiation of and lifetime use of substances.[120] There exists a robust dose-response relationship between cumulative traumas experienced in childhood and subsequent substance use in adolescence and adulthood. [120] In contrast, family cohesion can be a protective factor against the development of problematic substance, and can build resilience to the impacts of economic and social distress.[121,122] For adolescents, the more parental support and responsible monitoring they receive and the more time they spend with family outside of school, the less likely they are to engage in substance use.[123]

In Canada, Indigenous peoples share a disproportionate burden of opioid-related harms. For instance, indigenous people in British Columbia are five times more likely than non-indigenous individuals to experience a drug overdose, and three times more likely to die from an apparent overdose.[124] Similar patterns have been described in Alberta.[125] Higher rates of substance use and mental illness among indigenous people are attributable to intergenerational trauma, colonization, racism, and reduced access to mental health and addiction treatment.[124] In particular, the trauma caused by residential schools in terms of forced relocation and assimilation, and physical, sexual, and emotional abuse have left lasting impacts on survivors and their descendants.[126] Feelings of shame, hopelessness, and loss of cultural identity can be passed from survivors to their children and families, leaving them vulnerable to mental illness and substance use.[126]

From a social determinants of health perspective, it is clear that there are many other causal factors besides the availability of opioids that have fueled the current crisis. Therefore, it is important to focus on policies other than "supply side" interventions to address the opioid epidemic. Effective prevention of problematic substance use requires a more long-term health promotion approach that is focused on social determinants of health. While a comprehensive discussion of substance use prevention is out of the scope of this thesis, research in preventative science has shown that investments in schools, communities, leisure activities, and family supports can develop the social environment of children and youth in ways that decrease rates of substance use and delinquency.[123,127-130] For instance, governments can invest in funding for participation in organized youth activities, such as sports and recreation, extracurricular activities, and mentorship programs.[123,128] Further, efforts can be taken within the education system to strengthen connections between schools, parents, and other youth programs in the community.[123,127]

While tackling the root causes of addiction are long-term goals, several public health strategies are available to mitigate the immediate crisis of opioid-related deaths. These include expanded access to opioid agonist treatments (e.g. buprenorphine, methadone, slow release oral morphine and injectable options), and several harm reduction interventions, including naloxone distribution and overdose education, supervised consumption services, and potentially the provision of a safe supply of opioids to individuals at-risk of fentanyl poisoning.[131,132]

1.2 Take Home Naloxone (THN) programs

In response to escalating overdose morbidity and mortality, programs that distribute naloxone, the antidote to opioid overdose, have expanded substantially over the last two decades. [2,133] Take-Home Naloxone (THN) programs prevent opioid-related mortality by distributing naloxone to individuals

who are likely to witness an overdose, such as people who use opioids, their family and/or peers, and service providers.[134] Typically, these programs train individuals to recognize overdoses, administer naloxone, provide first aid, and call 911.[135] Some programs also educate program participants to recognize and address modifiable risk factors for opioid overdose, such as mixing opioids with other central nervous system depressants, using high doses of prescription opioids or illegally manufactured synthetic opioids, and using opioids alone.[136] When combined with training and education programming, THN programs are sometimes referred to as Opioid Education and Naloxone Distribution (OEND) programs or Opioid Overdose Prevention Programs (OOPPs).

THN programs are considered a harm reduction strategy for dealing with opioid-related mortality and morbidity. Harm reduction is an approach to psychoactive substance use that emphasizes pragmatic interventions to reduce health and social harm experienced by individuals and their communities, without necessarily requiring abstinence from the behaviour *per se.*[137,138] Other examples of harm reduction strategies used to mitigate opioid-related mortality and morbidity include syringe distribution programs and supervised consumption services.

THN programs have become a leading public health intervention in the opioid epidemic since they first emerged in the late 1990s. Today, the WHO strongly recommends that individuals who are likely to witness an opioid overdose have access to naloxone and be instructed on its administration,[139] and formal THN programs have been established in Canada, Australia, the United States, and at least 9 European countries.[133]

THN programs have also expanded to several different service settings and workforces.[133] Originally, the first THN programs were peer-based and mainly delivered to people who use opioids through existing community-based programs such as syringe distribution programs and methadone clinics. [2,133] However, more recently, THN programs have expanded to new service settings in an effort

to specifically target individuals at high risk for opioid overdose, such as those who are receiving

prescription opioids for pain, receiving hospital emergency care, or who have lost tolerance to opioids

following detoxification, prison, or participation in abstinence-based treatment programs.[2,133,135] In

addition to targeting individuals at-risk for opioid overdose themselves, THN programs may also

distribute naloxone to others who are likely to witness an overdose, such as the family and friends of

people who use drugs.[140,141] Several jurisdictions have also widened the availability of naloxone by

providing universal access to THN though pharmacies.[133] In Canada, the federal government facilitated

this intervention in 2015 by changing the prescription status of naloxone so that pharmacies would be

able to distribute naloxone to member of the public without requiring a prescription.[142]

1.2.1 Pharmacological considerations of naloxone

The effectiveness of naloxone is well-established. Naloxone is an opioid antagonist that can

rapidly reverse all signs and symptoms of opioid intoxication.[143-146] The signs and symptoms of opioid

intoxication include euphoria, miosis, analgesia, sedation, and respiratory depression.[143] Opioids exert

these effects on the central nervous system through the μ, δ, and κ opioid receptors.[146,147] Of these

three receptor subtypes, the μ-receptor is most important from a clinical perspective because it

mediates the positive reinforcing effects of opioids, and is therefore crucial in the development of opioid

use disorders.[146] Moreover, the μ-receptor mediates the respiratory depression caused by opioids,

which is the main hazard associated with an overdose.[143,145,146] Naloxone blocks the effects of all opioid

agonists by rapidly displacing them from all three receptor subtypes.[143,144,146,148] Thus, the timely

administration of naloxone can prevent opioid-related morbidity and mortality.

Typically, the effects of naloxone are seen within minutes of administration.[145] However, since

the effects of naloxone are shorter in duration than most opioid agonists, a repeated naloxone dose may

be necessary after the initial dose wears off.[146,149] Therefore, it is important for individuals who have

experienced an opioid overdose reversal with naloxone to be continuously monitored for a period of time, ideally in an emergency-care setting.[146]

Naloxone has a strong safety record and no misuse potential.[143,145,146,150] It has essentially no pharmacologic effect in the absence of opioid.[150] The main adverse effect of naloxone administration is that in people who chronically use opioids it can precipitate unpleasant withdrawal symptoms, such as nausea, vomiting, diarrhea, agitation, shivering, and aggressive or violent behavior.[149,151] To mitigate these painful withdrawal symptoms, it is recommended that naloxone be given at the lowest effective dose.[150]

There are currently several different delivery systems available for naloxone that vary in terms of dose and administration route.[2] Most THN programs distribute intramuscular naloxone that must be drawn out of an ampoule with a needle and injected.[2] Intramuscular naloxone ampoules typically contain 0.4mg of naloxone per 1ml injection. Also common is an improvised off-label intranasal spray that is assembled using a naloxone filled syringe attached to a nasal atomizer.[2] Using this system, a dose of 1mg naloxone is delivered into each nostril. Newer FDA-approved devices include an intramuscular autoinjector with a retractable needle that is similar to an epipen (Evzio[TM]), and a single step nasal spray (Narcan[TM]), both of which are available in different doses.[2] Although these newer FDA-approved devices are convenient and easy to use, their cost can be prohibitive for THN programs.[2] In Canada, most publicly funded naloxone kits contain naloxone in vials that must be drawn up into needles and injected intramuscularly.[152,153]

Currently the optimal delivery system for opioid overdose rescue is not clear.[136] Selecting the exact dosing of naloxone is a particularly difficult issue, because while an excessive dose of naloxone may lead to unpleasant withdrawal symptoms, a less than effective dose may prolong respiratory depression and increase the risk of injury or death.[149,150] In recent years, this issue has been further complicated by the rise of fentanyl and other synthetic opioids in the drug supply. Since these opioids

are so potent, repeated doses of naloxone may be necessary to reverse an opioid overdose.[154] In

response to the increasing prevalence of fentanyl, some THN programs have begun distributing a larger

number of doses and/or higher dose delivery systems.[2]

1.2.2 Epidemiological evidence for THN programs

The evidence base for THN programs has grown significantly since their initial

implementation.[133]   Several systematic reviews have concluded that Take-Home Naloxone (THN)

programs reduce opioid-related mortality among program participants and in the community.[140,141,148]

However, evaluating the effectiveness of THN programs has been challenging. Although a randomized

control trial (RCT) would provide the strongest evidence for the effectiveness of THN programs, there

are ethical concerns related to denying participants in the control group of a RCT access to potentially

life-saving medication.[141] Moreover, since opioid overdose is a relatively rare event, a very large

number of participants would needed to be enrolled to detect an effect on opioid-related mortality.[155]

Therefore, most evidence for the effectiveness of THN programs at reducing opioid-related mortality is

based on a variety of less rigorous observational study designs, including interrupted time-series

analysis, cohort studies, case series, and cross-sectional studies.[136]

Early studies of THN programs evaluated their feasibility by examining the attitudes,

knowledge, and experiences of program participants.[135,140] This was important because initially, there

were concerns regarding the willingness of bystanders without medical training to intervene in overdose

situations, as well as their ability to accurately identify opioid overdose symptoms and safely administer

naloxone. [140,156]

Several studies have confirmed that non-medical bystanders are willing to use naloxone to

rescue overdose victims.[157-162] One study of people who use heroin in Albuquerque found that 100 of

101 survey respondents reported willingness, if trained, to use rescue breathing and to inject naloxone

to aid an overdose victim.[157] A similar study of people who use injection drugs in San Francisco found that 87% were strongly in favor of participating in an overdose management training program to receive THN and training in resuscitation techniques.[160]

Studies that asses the effect of training on participants' knowledge have shown that lay people, including both people who use opioids and their friends and family, can be trained to recognize overdoses, identify risk factors for overdose, and administer naloxone. [163-169] For example, an evaluation of 6 THN programs concluded that trained program participants can identify opioid overdose scenarios and indicate when naloxone is needed more accurately than untrained participants.[170] Moreover, the trained program participants were as competent at these tasks as medical experts. In another study, a prospective cohort of 239 THN program participants had significant improvements in their knowledge of risk factors for overdose, signs of opioid overdose, and appropriate actions to take in an overdose situation compared to baseline measurements.[167] At 3 months follow-up, the participants' retention of knowledge related to opioid overdose and naloxone administration remained high.[167]

Particularly strong evidence that THN training can improve overdose-related knowledge comes from a 2014 RCT, in which 123 family members were randomly assigned to either group-based training or an information-only control.[171] It was found that participants who received THN training reported greater overdose-related knowledge and more positive overdose attitudes compared to the control group 3 months later.[171]

Although there is positive evidence that THN training can improve overdose-related knowledge, perhaps the best indication that non-medical bystanders can recognize overdoses and administer naloxone is through the demonstration of these abilities in real overdose situations. Several prospective cohort studies have determined that people who use opioids frequently witness opioid overdoses among their peers and, after being trained to use THN, are able to administer naloxone to rescue overdose victims.[163-169,172,173] A meta-analysis of nine prospective cohort studies estimated that for every

100 people who use opioids that are trained and supplied with THN, 9% will reverse an opioid overdose within 3 months of training.[174] This was a conservative estimate because it assumed that all program participants who were lost to follow-up did not administer a THN kit.[174] A more recent cohort study with a longer follow-up period found that 25% who people who use drugs that received a THN kit used it to reverse an overdose with one year.[175] Finally, a review of 7 prospective cohort studies found that that THN program participants subsequently administered naloxone in 67% of the overdoses that they witnessed.[148]

THN programs can also increase participants' use of rescue strategies other than naloxone administration. For instance, THN program participation has been associated with an increased use of recommended overdose response strategies, such as rescue breathing, sternal rubs, placing the victim into the recovery position, and remaining with the victim.[168,169,173] Similarly, THN training may reduce ineffective responses such as shouting at or slapping the victim, pouring cold water on the victim, or injecting them with saline or drugs other than naloxone.[163,168,173] However, the use of appropriate responses is highly variable between studies, and many overdose witnesses report still using inappropriate responses despite having participated in THN training.[135]

THN programs may be especially beneficial among individuals who use opioids that are reluctant to call 911 because they fear being arrested for illegal opioid possession or because they have outstanding warrants for their arrest.[157,176] Typically, THN programs train participants to activate emergency medical services as part of their response to opioid overdose situations.[135] However, some have expressed concern that after being provided THN and trained on its administration, people who use opioids may be less likely to call 911 because they feel comfortable responding to the overdose themselves.[135] This is potentially problematic because it is possible that an overdose victim will relapse into overdose after the THN dose wears off. Studies that have compared rates of 911 notification among people who use opioids before and after THN training have had mixed results.[135] While some

studies have found an increase[163,173] or no change[169] in 911 notification after THN training, others have

found a decrease.[168,177] These concerns may be ameliorated by legislation that shields bystanders from

criminal consequences if they call 911 or administer naloxone for an overdose, or by changes in local

enforcement policy where police only attend overdose calls when requested by EMS personnel.[178,179]

Two studies have sought to determine whether community-based THN programs can reduce

opioid-related mortality at the population level. The first of these was an evaluation of an early THN

program established by the Chicago Recovery Alliance in 2001.[180] The authors argued that the program

was associated with a reduction in heroin overdose deaths, since a trend of decreasing heroin deaths

started the same year the program was implemented and continued to decline over the next two years.

However, this study did not make any attempt to control for other confounding factors that may have

influenced the rate of heroin-related deaths during this time, such as the increase in prescription opioid

use during this time or other pre-existing trends.

One of the strongest evaluations of the impact of THN programs on opioid-related mortality

comes from an interrupted time-series analysis of a state-funded THN program in Massachusetts, which

was rolled out from 2006 to 2009 in 19 different communities.[181] This phased roll-out allowed for a

quasi-experiment, in which community opioid-overdose death rates were compared between time

periods in which THN programs had been implemented versus time periods in which there was no

implementation. The authors found that mortality rates were lower in communities after THN program

implementation compared to before, after controlling for other factors. Moreover, they observed a

dose-response relationship between THN distribution and mortality, such that communities that had

high THN program implementation (greater than 100 program participants per 100,000 in the

population), had lower mortality rates than communities with low implementation (1-100 program

participants per 100,000 in the population).

While most THN initiatives are based out of community syringe distribution or harm reduction programs, THN programs have also been shown to reduce mortality when targeted at individuals at high risk of opioid overdose in other service settings.[133] For example, Scotland's national naloxone program, which was implemented in 2011, targeted individuals recently released from prison.[182,183] A study comparing the risk of opioid-related death before and after this intervention found that the proportion of opioid-related deaths in Scotland that occurred in individuals within 4 weeks of prison release was reduced from 9.8% in 2006-2010 to 6.3% in 2011-2013.[182]

Another setting where THN may reduce opioid-related harm is in primary care among patients who are prescribed opioids. One non-randomized trial of individuals who use prescription opioids in San Francisco examined the effect of naloxone co-prescription on opioid-related ED visits.[184] It was found that patients who received a naloxone prescription had 47% fewer opioid-related ED visits in the 6 months after naloxone dispensation, and 63% fewer visits after 1 year.[184] The authors concluded that simply providing naloxone and overdose education resulted in behavior modification that prevented subsequent ED visits for opioid overdose.

Some prescribers, policymakers, and researchers have expressed concern related to "risk compensation" or "moral hazard," which is the notion that providing take home naloxone kits to people who use drugs will encourage riskier consumption practices by lowering the perceived negative consequences of drug use.[185,186] Fears of encouraging drug use are a common reaction to new harm reduction interventions among the public, and these perceptions have previously posed barriers to implementing needle exchange programs and supervised consumption services.[187,188] However, numerous cohort studies involving people who use opioids have shown no evidence that those who receive THN subsequently change their drug use in terms of either frequency or dosage.[166,169,189-191] In fact, several studies have suggested that participating in THN program training may even lead to decreased opioid use.[166,169,192] Finally, given that several high quality observational studies have shown

that implementing THN programs reduces population-level mortality rates, any negative effect of risk compensation appears to be outweighed by the number of lives that are saved.[181,182]

1.3 Emergency department based THN programs

In recent years, Emergency Departments have become increasingly recognized as an opportune settings for the distribution of THN.[193-195] Dispensing THN through the ED is particularly important because people who use opioids frequently present for emergency care, and those who have overdosed are at higher risk of future overdose death. [192,196,197] The few studies that have been published on ED-based THN programs have sought to establish their feasibility,[198] and examine barriers and facilitators to their implementation.[199-202] Factors that affect program implementation and uptake include ED staff willingness to provide THN,[203,204] patient acceptance of THN in the ED,[205] and other logistical considerations such as lack of ED staff time, training, and knowledge about THN.[200,201,206]

1.3.1 ED staff willingness to provide THN

ED staff willingness to provide THN from the ED is a necessary, but not sufficient factor in implementing ED-based THN distribution programs. Both Lacroix *et al.* (2017)[204] and Samuel *et al.* (2016)[203] conducted surveys with ED physicians and concluded that the majority seemed willing to provide THN. Specially, Lacroix *et al.'s* study of Canadian ED physicians showed that 86% of respondents reported that they would be willing to prescribe or dispense naloxone from the ED. Most of physicians either agreed or strongly agreed that certain groups would benefit from THN, such as friends and family of people at risk for opioid overdose, patients prescribed high doses of opioids, those enrolled in or recently discharged from opioid dependence treatment, those with known co-use of opioids and alcohol or benzodiazepines, those with a history of emergency visits for opioid overdose, and those with suspected prescription opioid dependence or heroin use. However, common perceived barriers to participation included lack of support from other health professionals for patient education, lack of

access to follow-up, inability to train the patient to use THN, lack of knowledge for the evidence of THN, lack of time, and lack of training in the prescription of naloxone.

Similarly, while S*amuel et al.* (2016)[203] found that while most participants in a sample of Massachusetts physicians had positive attitudes towards opioid harm reduction and were willing to prescribe naloxone, only 1.7% reported prescribing THN and only 10.3% had referred patients to a naloxone distribution program. Physicians identified lack of time, knowledge, training and institutional support as barriers to prescribing THN in the emergency department.

In contrast to previous studies which have found high willingness to provide THN among ED physicians, *Barbour et al.* (2018)[207] encountered resistance to prescribing THN to patients in ED physicians at a hospital in Irving, California. Specifically, among 43 ED patients who were identified as being at risk for opioid overdose and were willing to receive THN, the treating physician refused to prescribe naloxone for 16 (37%) patients. This shows that willingness to provide ED-based THN continues to vary between different settings.

1.3.2 Patient acceptance of ED-based THN

Patient uptake of ED-based THN distribution is necessary for program effectiveness. Kestler *et al.* (2017)[205] examined patient factors related to ED-based THN participation. This study surveyed patients at risk of opioid overdose at an ED in Vancouver about their demographic details, medical history, illegal drug-use history, previous overdose experience, and awareness and opinions of THN. Subsequently, participants were offered THN. In total, it was found that 68% of patients who visited the ED for an opioid overdose accepted a THN kit. In the multivariate analysis, factors associated with acceptance of THN kits included having previously witnessed an opioid overdose, concern about one's own overdose, female sex, and injection drug use. This study confirmed that majority of patients are accepting of THN from the ED, especially among females and those who have a greater risk of overdose.

In a follow-up study, Kestler *et al.* (2018)[208] analyzed reasons that study participants gave for accepting or declining THN from the ED. The authors found that most individuals who accepted THN said that they wanted to "save some else's life" or "save my own life." In contrast, most participants who declined a THN kit said that they did not think they were at risk. Patients who injected drugs were less likely give this reason than non-injection drug users. Additionally, some patients who were taking prescription opioids did not perceive themselves as being at risk of overdose because they were taking opioids as prescribed by their doctor. Based on these observations, the authors suggest that ED providers might increase uptake of THN in the ED by gently informing patients of their overdose risk in a non-judgmental manner. Additionally, ED providers can potentially encourage acceptance by appealing to patients' motivation to save the life of their at-risk peers.

1.3.3 Other barriers and facilitators to ED-based THN programs

Both Holland *et al.* (2019)[201] and Drainoni *et al.* (2018)[200] sought to identify various barriers and facilitators to distributing THN from the ED by conducting qualitative interviews with ED providers. Drainoni *et al.* (2018)[200] found that although the interviewees reported strong philosophical support for THN among staff, there were several barriers to providing it that were related to unclear policies/protocols, workflow logistics, and lack of education. In particular, some staff reported difficulties identifying the "right" patient to offer THN, confusion regarding prescription policy for THN, difficulty accessing THN, and lack of clarity on the best time to distribute naloxone. Staff also had difficulty incorporating THN training into the ED work flow, and there was a lack of consensus regarding which staff were responsible for THN dispensing and training.

Further, several staff perceived patient-related barriers to providing THN. Patients who use opioids were perceived as challenging to work with because they are impulsive and not willing to wait for THN and training, anxious to leave the ED once their overdose has been reversed, or insufficiently

motivated to participate in THN training. The author's recommended providing clear guidelines outlining who is at risk for overdose and initially narrowing the target population to reach those at highest risk, identifying site champions, providing consistent education for all staff, and developing training program for parents and caregivers that can be integrated into the ED workflow.

Similarly, Holland *et al.* (2019)[201] conducted interviews to explore ED physicians' and pharmacists' perspectives on take-home naloxone in Australia, where few hospitals distribute THN. While the majority of staff interviewed were supportive of supplying THN to patients, several staff expressed negative or stigmatizing attitudes, such as the belief that THN would simply encourage more drug use. Other staff expressed concerns related to possible clinical or logistical challenges. For instance, some staff anticipated challenges identifying eligible patients to receive THN, or expressed reluctance towards providing THN to patients prescribed opioids. Additionally, many participants recognized that it would be difficult for physicians to have the time to train and counsel patients in the use of THN, and suggested that this role should fall to nurse and pharmacists. Finally, staff education and awareness was identified as a key need to implement THN in the ED.

1.4 Naloxone administration by EMS and ED providers

Naloxone has long been used clinically in Emergency Departments (ED) and by Emergency Medical Services (EMS) to manage opioid overdoses. In the hospital setting, single boluses of naloxone administered intravenously are usually sufficient to reverse respiratory depression.[209] Typically, a low dose is administered initially and then carefully titrated so as to achieve overdose reversal without precipitating painful withdrawal symptoms.[210] If overdose reversal cannot be sustained, continuous infusions through intravenous drip may be necessary.[209]

In the pre-hospital setting, EMS may administer naloxone via intranasal spray, intravenously, or intramuscular injection.[211,212] Typically, EMS are trained to administer naloxone to patients presenting

with altered mental status, depressed respiratory rate (ie. ≤12 breaths per minute), miotic pupils, and

where there is circumstantial evidence of opioid overdose (ie. drug paraphernalia).[213,214] Altered mental

status is assessed using the Glasgow Coma Scale, which is a standard test that measures a patient's eye,

motor, and visual responsiveness, with higher scores signifying a higher level of consciousness.[215]

Previous studies by *Sumner et al.* (2016),[216] *Banta-Green et al.* (2018),[217] and *Levy et al.*

(2016),[218] have shown that EMS are more likely to administer naloxone to individuals who have

overdosed on heroin compared to pharmaceutical opioids. A common explanation for this difference in

naloxone administration is that heroin overdoses may be more easily recognized by EMS because there

is often more circumstantial evidence of drug use on scene, such as injection paraphernalia or injection

track marks. Further, the role of naloxone in reversing overdose has historically been emphasized for

heroin more than prescription opioids.[2,133]

Levy et al. (2016)[218] examined medical examiner records of opioid overdose decedents to

identify patient and overdose scene factors associated with being administered naloxone from EMS

providers. Using multivariate analysis, it was found that naloxone was more likely to be administered to

patients if there were signs of injection drug use or if the patient's death was witnessed. In contrast,

patients were less likely to be given naloxone if they died at home. The patient's opioid intoxicant was

not independently associated with naloxone administration in the multivariate analysis. However, the

authors found that naloxone was administered twice as often in heroin overdoses as in prescription

opioid overdoses, despite there being no differences in terms of CPR performance, paramedic calls, or

whether the death was witnessed. Based on this observation, the authors concluded that efforts are

needed to improve EMS naloxone administration to prescription opioid overdose victims.

Sumner et al. (2016)[216] found that among opioid overdose decedents, factors independently

associated with being administered naloxone by EMS included younger age, male sex, and visible signs

of potential drug abuse (e.g., paraphernalia, track marks). The authors note that these factors are

consistent with the historically higher rate of heroin overdose among younger males, although they did not attempt to directly test whether the patient's opioid intoxicant (heroin vs. prescription opioid) was associated with EMS naloxone administration. The author's concluded that first responders should be informed that there has been a changing demographic of individuals who overdose on opioids with the rising use and misuse of pharmaceutical opioids. Specifically, people who use pharmaceutical opioids tend to be older and have more balance between males and females.

Banta-Green et al. (2018)[217] conducted a descriptive case series of 98 heroin overdoses and 85 pharmaceutical opioid overdoses that were non-fatal. The authors used EMS medical records to examine the clinical presentation and EMS interventions provided. Patients with pharmaceutical opioid overdose were less likely to receive EMS naloxone, but were more likely to be intubated. There were no apparent differences between the two groups in terms of respiration rate or GCS that could account for this difference in EMS intervention, although heroin overdoses were more likely to present with miotic pupils. Similarly, the differential management of overdoses by EMS did not appear to be related to the presence of a benzodiazepine co-intoxicant. The authors speculated that differences in overdose management by EMS may be related to patient co-morbidities, polysubstance overdose, or other subtle environmental and social cues such as the patient's age or the location of the overdose. However, the authors did not examine whether these factors were associated with EMS naloxone administration.

1.5 Gaps in knowledge

1.5.1 ED-based THN programs

Previous research has shown the ED-based THN distribution is feasible[219], and that the majority of ED staff is willing to provide THN to patients who are at risk of opioid overdose.[199-202] Further, research has established that the majority of patients are accepting THN in the ED setting.[205] However,

even once ED-based programs are implemented, ensuring that patients at risk for overdose receive THN may be challenging.[200,207] In order to maximize the effectiveness of THN programs, ED staff should strive to offer THN to a range of at-risk patients, including those with a history of opioid overdose, those with a history of substance use disorder, those who are prescribed high doses of opioids, and those who present to the ED with signs suggestive of problematic substance use (ie. endocarditis, abscesses). The identification of these various patients is a crucial step in the pathway to providing THN to all patients who need it. However, it may be difficult for clinicians to recognize at risk patients in the context of a busy ED, especially if they are uncertain as to which patients should be targeted. To date, there has been no studies reporting on the extent to which ED staff are able to identify various patients who are at risk of opioid overdose and offer them THN.

1.5.2 Naloxone administration by EMS and ED staff

There are also several knowledge gaps that exist in the literature related to naloxone administration by EMS to reverse opioid overdoses. Although *Levy et al.* (2016)[218] and *Sumner et al.* (2016)[216] showed that decedents who overdosed on heroin were more likely to receive naloxone from EMS than those who overdosed with pharmaceutical opioids, neither of these studies were able to examine the effect of the patient's initial clinical presentation. For instance, it is possible that EMS were more likely to administer naloxone in cases of heroin overdose because the patients had clinically more severe overdose presentations (miosis combined with a depressed level of consciousness and respiratory rate). In contrast, *Banta-Green et al* (2018)[217] showed that EMS were more likely to administer naloxone in cases of non-fatal heroin overdose compared to non-fatal pharmaceutical opioid overdose, despite the clinical presentation of these groups being very similar. However, this study did not account for the effect of other potentially confounding variables, such as patient demographics, the presence of cues suggestive of illegal drug use (i.e. drug paraphernalia), or the overdose location.

Additionally, even if EMS do under-administer naloxone in cases of pharmaceutical opioid overdose, it is unknown whether this affects the patient's subsequent overdose recovery. It is possible that not receiving naloxone from EMS increases the risk of patient morbidity due to prolonged respiratory depression. Finally, while the previously mentioned studies have compared EMS naloxone administration between heroin and pharmaceutical opioid overdose, it is unknown whether these results would be similar in communities in which illegally manufactured fentanyl is present in the street drug market. Few studies have examined how the management of illegal opioid overdoses differs in communities struggling with high rates of illegal fentanyl-related morbidity and mortality.[136]

1.5.3 Local context

Alberta is a province of about 4.3 million located in western Canada. In 2017, 706 Albertans died of an opioid overdose, and according to most recently available data, 746 have died in 2018.[110] During this time, more than 80% of these opioid overdose deaths have involved fentanyl.[110] Additionally, the rate of Emergency Department (ED) visits in Alberta related to opioid overdose and other substances of misuse has increased dramatically in recent years. Specifically, there was an increase of 65% from the first quarter of 2015 to the third quarter of 2018, which culminated in a population rate of over 250 ED visits per 100,000 person years.[110] During this period, the Edmonton zone alone accounted for an average of 30% of all ED visits related to opioid use and substance misuse in the province.

In 2005, Edmonton became the first Canadian city to have a community-based THN program when it was initiated by street works, an organization that provides harm reduction, health promotion, and primary health care services to people who use drugs in Edmonton's inner city.[152] More recently in 2015, Alberta introduced a provincial THN program delivered in partnership with the Alberta Community Council on HIV (ACCH) and Alberta Health Services to address the rapidly increasing number of opioid

overdoses.[152] From January 2016 through December 2018, 121,854 naloxone kits were dispensed in

Alberta, and 7,709 overdose reversals were self-reported.[110] THN kits are dispensed from a variety of

sites, including the ACCH's harm reduction agencies, community pharmacies, walk-in clinics, addiction &

mental health centers, opioid dependency programs, correctional facilities, hospital EDs and others. [110]

Among these, the vast majority of THN kits are distributed through harm reduction agencies and

community pharmacies.[110]

The Royal Alexandra hospital (RAH), located in Edmonton's downtown core, is one of the biggest

inner city hospital in Canada with 895 beds.[220] It also has the most frequently visited ED facility for issues

related to opioids and other substances of misuse in the province.[110] In 2016, the RAH implemented an

ED-based THN program, the largest of its kind in Alberta. The implementation of this program has yet to

be evaluated.

1.6 Research objectives

My thesis consists of two studies. The first study aims to evaluate the Royal Alexandra Hospital

THN program's patient coverage and develop recommendations to optimize program implementation

by:

1) Identifying the proportion of ED visits for opioid overdose in which THN was offered to the

   patient; and

2) Identifying patient and ED visit characteristics associated with being offered THN.

My second study aims to compare the clinical interventions and outcomes of patients who visited

the ED for an illegal opioid overdose versus a pharmaceutical opioid overdose by:

1) Determining if EMS are more likely to administer naloxone to patients with an illegal opioid

   overdose

2) Determining if receiving EMS naloxone is related to requiring subsequent naloxone in the ED

3) Comparing clinical interventions and outcomes of patients who overdose on illegal opioids versus pharmaceutical opioids, including overdose severity, length of ED stay, overdose complications, need for hospitalization, and naloxone administrations from bystanders with THN, first responders, and ED staff.

1.6.1 Research questions

Study #1

- Among patients who visited the RAH ED for an opioid overdose between April 2016 and May 2017, what patient and overdose characteristics are associated with being offered a THN kit?

Study #2

- Among patients who visited the RAH ED for an opioid overdose between April 2016 and May 2017, are patients who overdosed on an illegal opioid more likely to have received naloxone from EMS compared to those that overdosed on a pharmaceutical opioid?

- Among this same group of patients, are those who received naloxone from EMS less likely to require naloxone from the ED staff compared to those that did not receive naloxone from EMS?

- Do patients who visit the RAH ED for an illegal opioid overdose differ from those with a pharmaceutical opioid overdose in terms of overdose severity, length of ED stay, overdose complications, need for hospitalization, or pre-hospital naloxone administration from other first responders (i.e. fire rescue and bystanders with naloxone kits).

1.7 Structure of this thesis

The second chapter reports the first study of this thesis, which involved a retrospective chart review of patients who visited the Royal Alexandra Hospital Emergency Department for an opioid

overdose. The third chapter includes my second study, which uses the same retrospective chart review

dataset used in the first study to compare clinical interventions and outcomes between individuals who

overdose on illegal opioids versus and those who overdose on pharmaceutical opioids. This study

specifically examines whether EMS naloxone administration is impacted by whether the patient

overdosed on an illegal opioid versus pharmaceutical opioid, and how this may affect overdose recovery

in the ED. The fourth chapter provides an overview of the main findings and general implications, with

conclusions and recommendations.

1.8 My contributions

The data used in both of the studies contained in this thesis was extracted by Daniel Dabbs (DD)

through a retrospective chart review in the summer of 2016. DD designed the data abstraction protocol

in consultation with Dr. Elaine Hyshka (EH) and Dr. Kathryn Dong (KD), and abstracted the data.

EH and KD conceived and designed the first study, and obtained research funding. I planned and

conducted the data analysis in consultation with Dr. Paul Veugelers (PV), KD and EH. I detailed the

existing literature and drafted the manuscript, and all authors contributed substantially to its revision.

I conceived and designed the second study, and conducted the analysis in consultation with EH,

KD, and PV. I detailed the existing literature and drafted the manuscript, and all authors contributed

substantially to its revision.

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Chapter 2: Factors associated with being offered take home naloxone in a busy, urban emergency department: a retrospective chart review

2.2 Introduction

2.2.1 Background

Opioid overdoses continue to increase and are a leading, yet preventable cause of death in North America and around the world.[1,2] Naloxone, an opioid antagonist, is commonly used in clinical settings to reverse the potentially lethal respiratory depression that occurs during opioid overdose.[3] "Take Home Naloxone" (THN) programs aim to prevent opioid overdose deaths by distributing naloxone to people likely to witness an opioid overdose, such as people who use drugs and their family and friends.[4-7] Typically, THN programs train people to recognize opioid overdoses and respond appropriately by providing basic life support and administering naloxone via either intranasal spray or intramuscular injection.[2,4-7] The World Health Organization has identified THN distribution as a key health intervention to prevent opioid overdose deaths.[2]

Research on THN programs has shown that THN kits are frequently used by people who use drugs to respond to overdoses.[8,9] Specifically, a meta-analysis found that between 9-19% of people who use drugs who are trained and supplied with naloxone will use it to reverse an overdose within 3 months.[9] At the population-level, reductions in overdose mortality have been observed following the implementation of THN programs, and higher rates of kit distribution lead to greater reductions in mortality.[10,11] While historically the majority of THN programs have been based in pharmacies or community-based harm reduction programs,[4] THN programs are increasingly being implemented in hospital Emergency departments (EDs).[11-13] Hospital EDs provide a critical opportunity to reach people at high risk of mortality, because people who use opioids frequently present for emergency care, and those who have overdosed are at higher risk of overdose death.[14-16] Previous investigations have

demonstrated that ED-based THN distribution is feasible,[17,18] and that the majority of clinicians are willing to provide THN in the ED.[19,20] Further, approximately 70% of at-risk ED patients who are offered THN accept it.[21]

For ED-based THN programs to have the greatest impact, THN should be offered to patients who report using illegal opioids, those taking high doses of prescribed opioids, and those using opioids who present with complications other than opioid overdose (e.g. abscesses, trauma, etc.).[21-23] However, ensuring all ED patients at risk of overdose are offered naloxone may be challenging.[19,23,24] A previous evaluation found that THN was offered to only 8% of ED patients with International Classification of Disease codes for opioid overdose, misuse, or dependence.[24] Commonly reported barriers to providing THN include lack of time, knowledge, training, and institutional support.[19] Additionally, ED providers may lack clarity about which patients should be offered naloxone.[24] This is especially problematic, because correctly identifying at-risk patients to offer THN is a crucial step in providing THN to those who need it. Despite the importance of this process, the extent to which different groups of patients are offered naloxone has not yet been studied in an ED setting.

2.2.2 Aims of the study

The present study evaluates a recently-implemented THN program in a busy urban ED to determine the extent to which THN was offered to patients at highest risk of fatal overdose: those who presented with a nonfatal opioid overdose. Our specific aims are to measure the proportion of ED visits for opioid overdose in which THN was offered, and identify factors associated with being offered a THN kit in the ED. Ideally, 100% of individuals who present to the ED with opioid overdose should have an opportunity to leave with a THN kit. However, we anticipated that even among this high-risk population, certain patients would be more likely to be offered THN than others. By identifying patients that may have been systematically missed, we aimed to develop new insights and recommendations for

optimizing the implementation of ED-based THN distribution. Additionally, while the primary outcome

of our study is whether THN was offered to patients, we also examined patient acceptance of THN after

it was offered.

2.3 Methods

2.3.1 Study design and setting

We conducted a retrospective chart review of all ED visits for which the primary diagnosis was

opioid overdose between May 1st, 2016 and April 31st 2017 at the Royal Alexandra Hospital, which is

located in Edmonton, Alberta, Canada. This large, urban, tertiary hospital received 73,163 ED visits in

2016-2017,[25] and sees the highest number of ED visits related to opioids and other substances of misuse

in the province of Alberta.[26] The hospital ED began offering and dispensing THN kits in February 2016.

During the study period, patients who were identified by either a physician or a nurse as being at risk for

opioid overdose would be offered a THN kit just before they were discharged from the ED. If the patient

accepted, a registered nurse would dispense the kit and provide overdose response training. Registered

nurses working in the ED were required to take a training module prior to distributing THN. The kits

distributed are publicly funded and provided at no cost to patients. They contain 3 vials of 0.4 mg/ml

naloxone, safety-engineered intramuscular syringes, gloves, a CPR face shield, alcohol swabs, and an

instructional pamphlet. Kits can be dispensed 24 hours per day, 7 days per week. Since THN kits are

dispensed directly to the patient from the ED, it is not necessary for patients to fill a naloxone

prescription after they leave.

2.3.2 Case identification and data collection

Cases were identified from the patient hospital administrative system according to ICD-10

codes, as any of the following: T40.0-T40.4, and T40.6. We excluded cases if the hospital chart could not

be retrieved, or if the patient died in hospital. All medical documents related to patient care were subject to review and data abstraction, including ED physician charts, ED nursing charts, EMS charts, inpatient hospital charts, laboratory reports, and the ED medication dispensation tracking system. The data abstraction protocol was developed by DD who is an experienced ED nurse, in consultation with KD (emergency medicine specialist) and EH (health services and policy researcher). To establish inter-rater reliability of the abstraction protocol, a second registered nurse independently reviewed a random subset of 70 (20%) medical records. Percent agreement and kappa statistics were calculated for variables collected and are included in appendix 1. For all variables, kappa was above or approaching 0.8, the commonly accepted standard for excellent inter-rater agreement.[27]

In addition to reviewing patient charts, each ED visit was linked to data from the provincial Pharmaceutical Information Network (PIN), which tracks prescription medication dispensations. The PIN data were obtained for all opioids dispensed to patients in the 6 months prior to their ED visit for opioid overdose, and included the date each opioid was dispensed, the type of opioid dispensed, the period it was prescribed for, and the quantity and dosage. Our research protocol received ethics approval from the University of Alberta's Health Research Ethics Board.

2.3.3 Variables of interest

Our primary outcome of interest was whether THN was offered during their hospital ED visit, or subsequent inpatient hospital stay if admitted. We also determined the number of patients that accepted a THN kit. Evidence that THN was offered and accepted was identified in ED physician and nursing charts, as well as inpatient hospital records. Additionally, ED medication dispensation data were reviewed to confirm cases in which THN was provided. Factors believed to be potentially associated with being offered THN included demographic characteristics: age (16-24, 25-34, 35-44, 45-54, +55), sex (female vs. male), residence in the inner city (yes vs. no), no fixed address (yes vs. no), relevant co-

morbidities: chronic pain (yes vs. no), mental health disorder (yes vs. no), overdose details: route of opioid consumption (inhalation, injection, oral and other), public overdose (yes vs. no), intentional overdose (yes vs. no), and other clinical details: required intubation (yes vs. no), required naloxone from EMS or ED (yes vs. no), admitted to hospital (yes vs. no), time of day at presentation and discharge (0:01-8:00, 8:01-16:00, 16:01-24:00), and length of ED stay (hours). We examined patient disposition, including whether the patient was discharged against medical advice (AMA, yes vs. no), or left ED without treatment or before treatment completion (yes vs. no). A patient was considered to have left the ED AMA if they disclosed to the providers that they intended to leave and signed an AMA form. In contrast, patients who left without treatment or before treatment completion would have registered with triage but then left either from the waiting room or their patient care space, typically without disclosing their intent to leave.

Several variables were used to assess overdose severity, including pre-hospital Glasgow Coma Scale (GCS) (3-8, 9-13, 14-15), and respiratory or cardiac arrest (yes vs. no). GCS is a standard test that measures a patient's eye, motor, and visual responsiveness, with higher scores signifying higher consciousness.[28] GCS was measured by EMS on arrival at the overdose scene, and was therefore only available for patients who arrived at the ED via ambulance. Respiratory and cardiac arrest may have occurred in either pre-hospital or hospital settings, as these variables were abstracted from EMS, ED, and inpatient hospital records.

PIN data were used to determine whether the patient had an active prescription for any opioid medication at the time of their ED visit, and whether the patient was prescribed a high average daily dose of opioids (≥50 Oral Morphine Equivalents). Average daily dose was calculated by: i) identifying opioid prescriptions that overlapped with the date of the ED visit, ii) calculating total dosage dispensed (number of pills dispensed multiplied by dosage of each pill), iii) calculating average dosage per day

(total dosage divided by number of days), and iv) converting average daily dosage to Oral Morphine Equivalents (OME's) with recommended conversion factors.[29]

The patient's primary opioid intoxicant was confirmed by patient self-report, or else suspected by EMS or ED staff, and categorized as either illegal or non-illegal. Illegal opioids included heroin, carfentanil, and non-prescribed fentanyl. Fentanyl was considered non-prescribed if the patient did not have an active prescription for fentanyl at the time of their ED visit. Non-illegal opioids included prescribed fentanyl, and all other pharmaceutical opioids (ie. oxycodone, hydromorphone, morphine) regardless of whether they were prescribed to the patient.

2.3.4 Analysis

We calculated the number and percentage of each independent variable among ED visits in which THN was offered and not offered. To determine whether each variable was associated with offering THN, we conducted a series of analyses using Generalized Estimating Equations (GEE) regressions for binary outcomes with logit link. Initially, we fitted separate regression models for each independent variable, with offering THN kits as the outcome and controlling for age and sex. We identified age and sex *a priori* as potential confounders to be considered in all regression analyses. We used GEE with logit link for all regression analyses because a significant portion of patients had multiple ED visits for opioid overdose within our study period, and the data collected for these patients were potentially correlated. With GEE, standard errors are calculated that adjust for multiple observations per patient, in this case using an exchangeable correlation structure.[30]

Variables that appeared statistically significant in the initial age-sex adjusted analyses at the 0.1-level were eligible for inclusion in the subsequent multivariable analysis, in which a purposeful selection procedure was followed to identify factors independently associated with being offered THN.[30] Specifically, variables were retained in the final multivariable model if they were significant at the level

of 0.05, or if they showed a confounding effect on a statistically significant covariate (that is, if removing the variable caused a coefficient to change by ≥15%). A significant portion of values were missing for pre-hospital GCS (14.9%), primary opioid intoxicant (12.8%), and primary intoxicant consumption route (18.1%). Missing data for these and other variables were imputed using chained equations with augmented regression and 30 imputations.[31] All variables were included in the imputation regressions, and the outcome was not imputed. Analyses were performed using STATA 14.0 IC.

2.4 Results

From May 1st 2016 to April 30th 2017, there were 347 visits to the ED in which the patient received a primary diagnosis of opioid overdose. Among these visits, only 344 patient charts were reviewed, as patient records could not be retrieved for 3 ED visits. Additionally, 2 visits were excluded because the patient died while hospitalized. The remaining 342 ED visits were made by 297 unique patients, of whom 67.3% were males and the median age was 36 (range 16-93, IQR 25-75). Repeat ED visits for opioid overdose were made by 35 patients during the study period, with a range of 1 to 4 ED visits per patient. Overall, THN was offered to the patient in 168 (49.1%) visits, and was accepted by patients in 128 (76.2%) visits (figure 2.1). Among the 40 visits in which the patient declined THN, the patients reported already possessing a kit in 11 (27.5%) cases.

Table 2.1 shows the breakdown of patient characteristics by ED visit. In 82 (24.0%) ED visits, the patient held a current prescription for an opioid medication, with 53 (15.5%) involving a daily dose of opioids of ≥50 OME. In the majority of ED visits (186 (62.4%)), the patient's primary intoxicant was an illegal opioid (heroin, non-prescribed fentanyl, or carfentanil). Patients' primary opioid intoxicant was confirmed by self-report in 273 (79.8%) visits, suspected by EMS in 12 (3.5%) visits, and suspected by ED staff in 13 (3.8%) visits. Among ED visits in which the patient arrived by ambulance, the patient's pre-hospital GCS was most frequently in the severe category (GCS 3-8; n=210, 72.2%).

Table 2.1 shows the results of the initial age-sex adjusted analysis. After adjusting for age and sex, patients were less likely to be offered THN if they overdosed in a public location (AOR=0.59 [0.36, 0.97], intentionally overdosed (AOR= 0.28 [0.12,0.65]), left the ED without treatment or before treatment completion (AOR=0.17 [0.06,0.46]), were admitted to hospital (AOR=0.40 [0.21,0.76]) or if they were in the 45-54 or 55+ age categories (AOR=0.47 [0.22, 1.04] and AOR=0.29 [0.12, 0.69], respectively). In contrast, patients were more likely to be offered THN if they were male [AOR=2.01 [1.22, 3.30]), if they inhaled or injected their primary opioid intoxicant (AOR= 5.03 [2.52,10.04] and AOR=6.01 [3.10,11.65] respectively), if they had a severe GCS score (AOR=4.16 [2.03, 8.53] for GCS 3-8 vs. GCS 14-15), if they required pre-hospital naloxone (AOR=2.51 [1.49,4.21], or if they experienced cardiac or respiratory arrest (AOR= 1.83 [1.04,3.23] & 2.23 [1.38,3.61], respectively).

Table 2.2 shows the results of the multivariable analysis. Factors that were independently and positively associated with being offered THN included using an illegal opioid intoxicant (AOR = 3.09 [1.32, 7.24]), and having a severe overdose as measured by GCS (AOR= 3.15 [1.46, 6.79] for GCS 3-8 vs. GCS 14-15). In contrast, patients were less likely to receive a THN kit if they left the ED without treatment or before treatment completion (AOR=0.15 [0.05, 0.42]), if they were admitted to hospital (AOR=0.46 [0.22,0.99]) or if they had an opioid prescription at the time of their ED visit (AOR=0.45 [0.22, 0.95]). In addition to these statistically significant variables, the patient's route of consumption was retained in the final model to control for its confounding effect (when removed the coefficient for "primary intoxicant illegal" changed by over 15%).

2.5 Discussion

In this evaluation of a recently implemented ED-based THN program, THN was offered to patients in approximately half of ED visits for opioid overdose. We sought to determine whether the present ED-based THN program was missing certain patients by identifying factors associated with being

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offered THN. We found that patients were more likely to be offered THN if they experienced a severe overdose (GCS of 3-8), or had consumed an illegal opioid. In contrast, patients who had an active opioid prescription at the time of their ED visit, who left the ED without treatment of before treatment completion, or who were admitted to the hospital were less likely to be offered a THN kit.

One explanation for these findings is that in the context of a busy ED, a clinician's decision to offer THN may be driven by their perceptions of which patients are most at risk for overdose death. For instance, ED staff may more readily offer THN to patients who have experienced a severe overdose, since they are easily recognized as being at risk for future overdose. Similarly, clinicians may perceive people who use illegal drugs as being more vulnerable for future overdose. These perceptions are likely shaped by both clinical experience and media reports, as it is true that in the Western Canadian provinces of Alberta and British Columbia, over 80% of accidental opioid overdose deaths involved illegally manufactured fentanyl in 2017.[26,32] Additionally, clinicians may perceive THN as predominately meant for people who use illegal drugs, since it was originally developed to serve this population.[4]

Our finding that patients who were taking prescription opioids were less likely to be offered THN is consistent with previous research. In a survey of Canadian ED physicians, it was found that while the large majority of participants (>90%) agreed or strongly agreed that patients with a history of emergency care for opioid overdose would benefit from THN programs, fewer physicians (69%) agreed that patients prescribed high doses of opioids would benefit.[20] Similarly, previous qualitative studies found that almost all ED staff who were interviewed agreed certain patients should receive THN—such as those who are have overdosed in the past, are opioid dependent, or who inject opioids.[24,33] However, other staff disagreed on whether it was appropriate, necessary, or realistic to offer THN to all patients prescribed opioids. [24,33] In some cases, this appeared be due to their perceived lower risk of overdose.[24,33]

Other contributing factors have been explored in studies of chronic pain patients receiving primary care. In one qualitative study, some physicians expressed reluctance to co-prescribe THN with opioids because they felt that THN should not be necessary if opioids are prescribed properly.[34] Others believed that co-prescribing THN may offend patients due to the stigma associated with substance use disorders and THN. [34] However, in contrast to these perceptions, a study which surveyed chronic non-cancer pain patients found that only 13% of patients said that that they would be offended if offered THN, and 60% thought it would be a good idea.[35] Further, the act of giving THN to patients prescribed opioids for chronic pain and providing overdose prevention education may itself help reduce future opioid-related ED visits. This is evidenced by a US study which found that chronic pain patients who received THN had 63% less ED-related visits at 12-months compared to those that did not receive THN.[36]

It was not surprising that patients who unexpectedly left the ED without treatment or before treatment completion were less likely to be offered THN. At the time of this study, ED staff typically waited until discharge to offer THN to patients. Therefore, patients who left the ED without disclosing their intent to leave may have been missed. Patients who have been treated for opioid overdose may be experiencing symptoms of withdrawal and be eager to leave the ED to address these symptoms. Consequently, they may be less willing to complete discharge paperwork or THN training.[24] These patients may be especially vulnerable to a subsequent overdose immediately following their ED visit, given the relatively short half-life of naloxone,[37] and the additional risk posed by consuming further doses of opioids after leaving the ED. Equipping these patients with THN (and offering opioid agonist treatment and other supports) is especially critical. Finally, our findings showed that ED patients who were admitted to the hospital were more likely to be missed. Further efforts are needed to expand THN distribution to at-risk hospital inpatients in this setting.

The majority (82%) of patients in our study who were offered a THN kit either accepted it or already possessed one, which confirms previous reports showing that ED-based naloxone distribution is

acceptable to patients. This THN acceptance rate was slightly higher than the 68% reported in a previous study by *Kestler et al,* in which THN was offered to patients who had reported illegal drug use, were prescribed a high dose of prescription opioids, were receiving opioid agonist therapy, or had any clinical presentation suggestive of opioid use.[21] The higher acceptance rate among our population may suggest that people who have recently experienced an opioid overdose are more accepting of THN than other THN-eligible patients.

2.5.1 Limitations

There are several limitations to this study that are inherent to retrospective chart reviews. Since medical records are created for clinical purposes, some information may not be charted consistently. In particular, we were unable to ensure that every instance of THN being offered was documented. Although we reviewed ED medication dispensation data to confirm cases in which THN was both offered and accepted by the patient, some cases in which THN was offered but declined may not have been charted. Therefore, the proportion of ED visits in which THN was offered may have been underestimated. Other variables were missing values for a significant percentage of ED visits, including consumption route (18.1%), pre-hospital GCS (14.9%), and primary intoxicant (12.8%). We attempted to account for the uncertainty created by missing data with multiple imputation.

Additionally, the data may not always be accurate for variables that were partially or fully based on patient self-report or clinician suspicion, such as the patient's primary intoxicant. Patients may have been reticent to disclose the complete details related to their substance use, or they may have consumed a different substance from what they believed. However, given that the aim of the study was to examine clinician behavior, measuring the clinicians' perception of the patients' opioid intoxicant is likely more useful than the actual intoxicant.

The data abstracters were not blinded to the purpose of the study. However, it is unlikely this affected the results significantly since there were no specific *a priori* hypotheses regarding which variables would be associated with THN being offered. Finally, because our sample was limited to a single hospital site, it is possible that our results may not generalize to other geographic locations.

2.6 Conclusions and recommendations

Our results indicate that implementation of an ED-based naloxone program and accompanying staff training does not necessarily guarantee that even patients presenting with opioid overdose will be offered THN. Clinicians may consciously or unconsciously rely on their own perceptions as to who is at risk and overlook certain patients, especially if they lack clarity as to who should be offered THN. To ensure optimal implementation of ED-based THN programs, ED staff should be provided with information on the importance of offering THN widely, and clear guidelines regarding which patients should receive THN. The policy should be made easily accessible and distributed through several communication methods (i.e., staff orientations, staff meetings, and electronic mail). Further, hospitals implementing ED-based THN programs should also ensure that the patients who require hospital admission after an overdose are able to receive a THN kit prior to discharge. THN programs should be expanded to include hospital units that commonly see patients with substance use problems, such as internal medicine, psychiatry, and the ICU, if not all inpatient units.[38]

Another way for ED-based THN programs to improve their coverage to at-risk patients is to avoid waiting until discharge to offer THN. Where possible, THN should be offered during the patient's initial assessment, to ensure they are not missed should they leave the ED unexpectedly. Additionally, hospitals should explore the use of Electronic Health Record pop-up alerts, which have been successfully used elsewhere to facilitate naloxone prescribing to at-risk patients.[38] Finally, THN program coverage

levels should be monitored on an ongoing basis, when feasible, by collecting and comparing

administrative records on patient diagnostic codes and naloxone dispensations.

At minimum, all patients presenting to an ED with an opioid overdose should be offered THN.

However, several other groups might also benefit from THN distribution and training in an ED setting. In

particular, the Center for Disease Control and Prevention recommends that THN be offered to patients

taking higher doses of prescription opioids (≥50 OME/day), patients with concurrent opioid and

benzodiazepine use, and patients with a history of a substance use disorder.[39] We suggest that in

addition to targeting people who use opioids, ED providers should consider offering THN to people who

use any illegal substance, including stimulants. People who use non-opioid illegal substances may be

exposed to opioids through contamination,[40] or may witness an opioid overdose among their peers.

Future evaluations are needed to examine the extent to which these different patients can be targeted,

and identify barriers and facilitators to dispensing THN to these groups from the ED.

2.7 References

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2.8 Figures, tables, and additional files

Figure 2.1 Study flow diagram showing identification of ED visits for inclusion, and the frequencies and percentages of ED visits in which take home naloxone was offered and accepted.
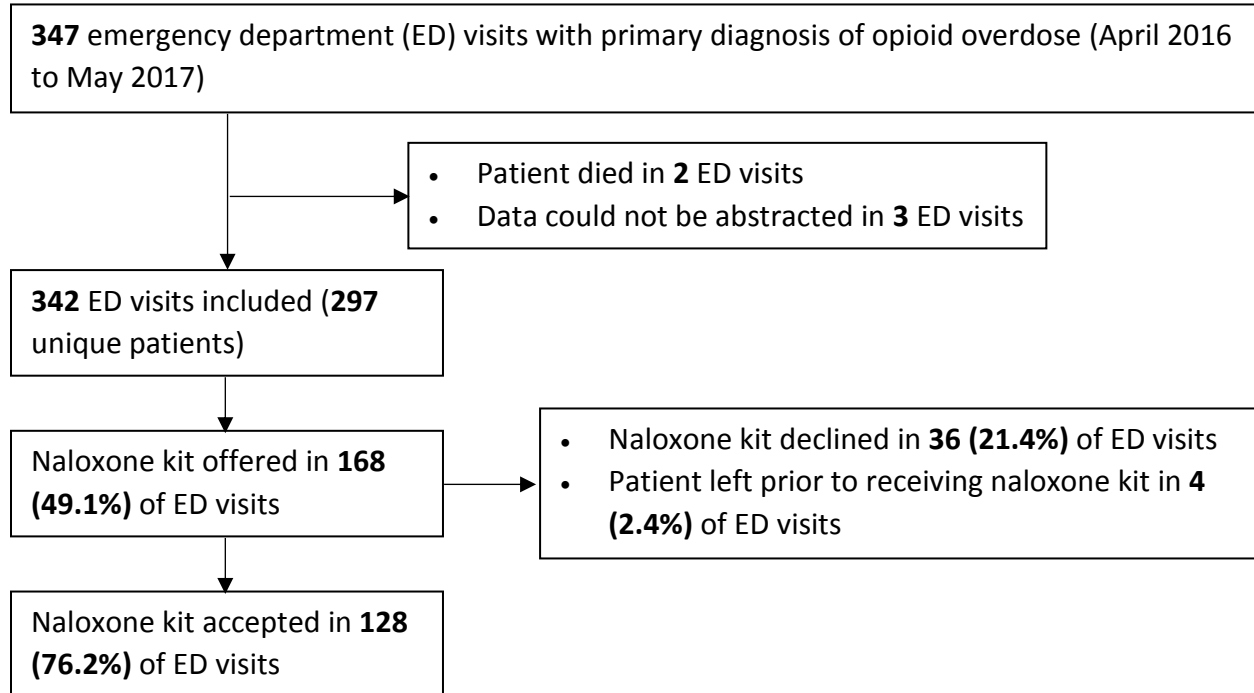
Table 2.1 Characteristics of ED visits for opioid overdose, and associations with take home naloxone kits offered

| Visit Characteristic (n=342)*** | Number of ED visits (%) | | | | |
	Total (n=342)	Offered THN (n=168)	Not offered THN (n=174)	Age-Sex Adjusted OR [95% CI]**	P-value
Patient characteristics					
Male sex	234 (68.4)	129 (76.8)	105 (60.3)	2.01 [1.23,3.30]	0.005*
Age (n=341)					
16-24	65 (19.1)	35 (21.0)	30 (17.2)	ref	0.004*
25-34	96 (28.2)	53 (31.7)	43 (24.7)	0.95 [0.48,1.88]	
35-44	81 (23.8)	47 (28.1)	34 (19.5)	1.13 [0.55,2.30]	
45-54	55 (16.1)	21 (12.6)	34 (19.5)	0.47 [0.22,1.04]	
+55	44 (12.9)	11 (6.6)	33 (19.0)	0.29 [0.12,0.69]	
Resident of inner city† (n=339)	102 (30.1)	50 (30.1)	52 (30.1)	1.11 [0.69, 1.80]	0.66
No fixed address (n=339)	23 (6.8)	12 (7.2)	11 (6.4)	1.11 [0.44,2.84]	0.82
Chronic pain	50 (14.6)	14 (8.3)	36 (20.7)	0.52 [0.25,1.08]	0.080*
Mental health disorder††	97 (28.4)	37 (22.0)	60 (34.5)	0.65 [0.39,1.06]	0.084*
Current prescription medications					
Opioid agonist therapy§	9 (2.6)	1 (0.6)	8 (4.6)	0.15 [0.03,0.86]	0.034*
Any active opioid prescription	82 (24.0)	22 (13.1)	60 (34.5)	0.41 [0.23,0.72]	0.002*
Prescribed high-dose opioids (≥50 OME)	53 (15.5)	11 (6.5)	42 (24.1)	0.31 [0.16,0.62]	0.001*
Overdose details					
Illegal opioid intoxicant (n=298)	186 (62.4)	126 (75.0)	27 (15.5)	6.42 [3.52,11.71]	<0.001*
Route of consumption (n=280)					
Oral and other¶	97 (34.6)	20 (11.9)	77 (44.3)	ref	<0.001*
Inhalation	77 (27.5)	48 (28.6)	29 (16.7)	5.03 [2.52,10.04]	
IV injection	106 (37.9)	70 (41.7)	36 (20.7)	6.01 [3.10,11.65]	
Overdosed in public (n=337)	102 (30.3)	40 (24.1)	62 (36.3)	0.59 [0.36,0.97]	0.039*
Overdose intentional (n=340)	28 (8.2)	6 (1.8)	22 (6.5)	0.28 [0.12,0.65]	0.003*
Overdose severity					
Glasgow Coma Scale Score (n=291)					
Severe (3-8)	210 (72.2)	127 (60.5)	83 (38.5)	4.16 [2.03,8.52]	<0.001*
Moderate (9-13)	27 (9.3)	6 (22.2)	21 (77.8)	1.37 [0.45,4.21]	
Mild (14-15)	54 (18.6)	11 (20.4)	43 (79.6)	ref	
Cardiac arrest	67 (19.6)	43 (25.6)	24 (13.8)	1.83 [1.04, 3.23]	0.036*
Respiratory arrest	111 (32.5)	72 (42.9)	39 (22.4)	2.23 [1.38,3.61]	0.001*
EMS & ED care					
Pre-hospital naloxone administered	225 (65.8)	132 (78.6)	93 (53.4)	2.51 [1.49,4.21]	0.001
ED naloxone administered	125 (36.5)	54 (32.1)	71 (40.8)	0.79 [0.50,1.24]	0.313
Required intubation	11 (3.2)	3 (1.8)	8 (4.6)	0.35 [0.10,1.22]	0.098*
Admitted to hospital	56 (16.4)	15 (8.9)	41 (23.6)	0.40 [0.21,0.76]	0.005*
Left against medical advice‡	34 (9.9)	14 (8.3)	20 (11.5)	0.64 [0.30,1.37]	0.25
Left without treatment/before treatment completion	29 (8.5)	6 (3.6)	23 (13.2)	0.17 [0.06,0.46]	0.001*
Time day at ED presentation					
0:01-8:00	94 (27.5)	47 (28.0)	47 (27.0)	ref	0.84
8:01-16:00	108 (31.6)	49 (29.2)	59 (33.9)	1.08 [0.60,1.93]	
16:01-24:00	140 (40.9)	72 (42.9)	68 (39.1)	1.17 [0.68,2.03]	
Time of day at discharge					
0:01-8:00	121 (35.4)	58 (34.5)	63 (36.2)	ref	0.36
8:01-16:00	94 (27.5)	53 (31.5)	41 (23.6)	1.39 [0.79,2.47]	
16:01-24:00	127 (37.1)	57 (33.9)	70 (40.2)	0.96 [0.56,1.64]	
Length of ED stay (median, IQR)	5.5 (3.3,9.2)	4.52 (2.7,7.6)	6.45 (3.9,11.0)	0.98 [0.95,1.01]	0.25

*** N=342 for all independent variables unless stated otherwise.

** Odds ratio of being offered take home naloxone for each independent variable, adjusted for and sex.

*Statistically significant at the level of 0.1 and thus eligible for inclusion in multivariable analysis

Table 2.2 Multivariable associations of patient and visit characteristics with offering of take home naloxone during ED visits for opioid overdose

Visit Characteristic	Adjusted OR [95% CI]**	P-value
Male sex	1.74 [1.96,3.15]	0.069
Age		
16-24	*ref*	0.52
25-34	0.73 [0.36,1.51]	
35-44	1.42 [0.64,3.16]	
45-54	0.80 [0.32,2.01]	
+55	0.99 [0.36,2.71]	
Active opioid prescription at time of ED visit	0.45 [0.22,0.95]	0.037*
Primary opioid intoxicant illegal	3.09 [1.32,7.24]	0.009*
Route of consumption		
Oral and other	*ref*	0.099
Inhalation	1.83 [0.76,4.42]	
IV injection	2.55 [1.07,6.08]	
Pre-hospital GCS		
Severe (3-8)	3.15 [1.46,6.79]	0.013*
Moderate (9-13)	1.97 [0.55,7.08]	
Mild (14-15)	*ref*	
Left without treatment/ before treatment completion	0.15 [0.05,0.42]	0.001*
Admitted to hospital	0.46 [0.22,0.99]	0.047*

* Statistically significant at the level of 0.05

** Odds ratio of being offered take home naloxone for each independent variable, adjusted for all other variables in the model

† Postal code overlaps Local Geographical Area of Edmonton East Wood, Includes T5B, T5G, T5H, T5J, T5K, T6W.

†† Anxiety disorder, Bipolar disorder, Major Depressive Disorder, Major Psychosis, Personality Disorder (Axis II), or Schizophrenia)

§ Methadone (liquid form, once daily ingestion, max period of 7 days), or Suboxone (once daily dosing, max period of 7 days).

¶ Oral and other routes includes oral (97%), rectal (1%), transdermal (1%), and Percutaneous endoscopic gastrostomy (1%).

‡ disclosed to the providers that they intended to leave and signed an AMA form.

‡‡ registered with triage and been assessed, but then left without warning or disclosing their intent to leave.

Appendix table 2.1 Measures of inter-rater relatability (% agreement and kappa statistic) for variables abstracted during the patient chart review

Variable	% Agreement	Kappa
Outcome- Was take home naloxone offered?	1	1
Age	1	1
Sex	1	1
Resident of inner city	1	1
No fixed address	1	1
Chronic pain	0.929	0.759
Mental health condition	0.9	0.79
Primary intoxicant	1	1
Primary intoxicant consumption route	0.957	0.93
Overdosed in public	0.97	0.925
Overdose Intention	0.986	0.934
Pre-hospital GCS	0.986	0.974
Cardiac arrest	1	1
Respiratory arrest	0.986	0.970
Pre-hospital naloxone administered	1	1
ED naloxone administered	1	1
Intubation	1	1
Admitted to hospital	1	1
Discharged against medical advice	1	1
Left without treatment, or prior to treatment completion	1	1
Time of day at presentation	1	1
Time of day at discharge	1	1
ED length of stay (quartiles)	0.929	0.845

Chapter 3: A comparison of naloxone administration between patients admitted to an Emergency Department for illegal and pharmaceutical opioid overdose: a retrospective chart review

3.2 Introduction

Canada continues to experience an overdose crisis.[1] The origins of this North American crisis have been well described. [2-7] Over the past two decades, the rising production and prescribing of pharmaceutical opioids (POs) led to iatrogenic opioid dependence in some patients exposed to opioids for acute and/or chronic pain management, and significantly increased diversion of POs into street drug markets.[2-5,7-11] This rising use and misuse of POs contributed to persistent increases in opioid-related deaths, Emergency Department (ED) visits, and substance use treatment admissions.[9,10,12-14] Moreover, the rising use of POs eventually corresponded with an increasing demand for heroin, which has increased since policymakers and prescribers began to recognize the harms associated with excessive PO use and limit their availability.[15-20]

In recent years, opioid-related harms have been further exacerbated by the proliferation of illegally manufactured synthetic opioids such as fentanyl and carfentanil in the street drug market.[21,22] Fentanyl is approximately 50-100 times stronger than morphine and 30-50 times stronger than heroin, and can rapidly induce life-threatening respiratory depression.[23,24] Because it can be reliably produced at low cost and transported in small volumes, fentanyl powder is often sold in street markets as a substitute or additive to heroin, or cut with other ingredients to produce powders and counterfeit prescription pills.[25-27] In Alberta and British Columbia, fentanyl has replaced heroin and POs as the most commonly detected opioid in substances seized by law enforcement,[28] and was implicated in 80-90% of opioid deaths in 2017-2018.[29,30] Similarly, a report of drug checking services in Vancouver between 2017 and 2018 found only 17.6% of samples that were expected to be heroin actually contained the expected substance, while 90.6% tested positive for fentanyl.[31]

Although few studies have described ED visits in communities with widespread illegally manufactured synthetic opioids, previous research suggests that heroin overdoses are often managed differently than POs, especially by Emergency Medical Services (EMS). [32] In particular, while EMS providers readily administer naloxone (opioid antagonist) in cases of heroin overdose, they reportedly under-administer naloxone in PO overdoses.[32-34] This discrepancy may occur in-part because the recognition of opioid overdoses is facilitated by certain social and environmental cues that are more common in cases of illegal drug use.[32-34] For instance, opioid overdose cases may be readily recognized when a young victim is found unconscious in a public location with evidence of injection drug use, but less apparent for older patients who overdose on opioids prescribed to them in their home. [32-34] However, it is unclear whether differences in naloxone administration between heroin and PO overdoses are predominately driven by environmental and social cues, or by actual differences in the patient's initial clinical presentation.

Additionally, the extent to which the administration of naloxone by EMS is related to naloxone administration and development of adverse outcomes in the hospital setting is unknown. Previous studies have shown that patients who overdose on POs more frequently require naloxone in the ED compared to heroin, and are more likely to require longer ED stays or hospitalization.[35] Whether these differences are related to pre-hospital naloxone administration has yet to be studied. It is plausible that patients who do not receive pre-hospital naloxone may experience prolonged respiratory depression, increasing the likelihood that they will require naloxone in the ED and experience other adverse outcomes.

We aimed to address these gaps in the literature by examining whether patients who overdosed using an illegal opioid such as heroin or illegally manufactured fentanyl, were more likely to receive naloxone from EMS compared to individuals who overdosed on POs (which may or may not have been prescribed). Additionally, we examine whether receiving pre-hospital naloxone from EMS or other

first responders affected the likelihood of requiring subsequent naloxone administration in the ED.

Finally, we sought to describe differences in adverse outcomes, including overdose-related

complications, ED length of stay, need for hospitalization, and death.

3.3 Methods

3.3.1 Setting

This retrospective chart review was conducted using medical records of ED visits from the Royal

Alexandra Hospital, which is located in the inner city of Edmonton, Alberta. This large, urban, tertiary

care center received 73,163 ED visits in 2016-2017,[36] and has the highest number of ED visits related to

opioids and other substances of misuse of all hospitals in the province.[37]

3.3.2 Case identification

We included all ED visits to the Royal Alexandra hospital between May 1st, 2016 and April 31st

2017 for which the primary diagnosis was opioid overdose. Cases were identified according to ICD-10

codes, as any of the following: T40.0-T40.4, and T40.6. We excluded cases if the hospital chart could not

be retrieved, or if the patient's primary opioid intoxicant was unknown. Our protocol received ethics

approval from the University of Alberta's Health Research Ethics Board.

3.3.3 Data Collection

All documentation from EMS, ED staff, and hospital inpatient care was subject to data

abstraction. The patient's primary opioid intoxicant and co-intoxicants were identified from blood and

urine toxicology tests if available. However, most cases were confirmed by patient self-report, or else

suspected by EMS or ED staff. Other variables extracted included patient demographics, medical and

psychiatric co-morbidities, overdose intention, overdose location, need for hospital admission, discharge approval status, overdose-related medical complications, length of ED stay, and Glasgow Coma Scale (GCS) score, which was measured both by EMS upon arrival and at ED triage. Naloxone administrations and other interventions provided by any personnel, including ED staff, inpatient unit staff, EMS, fire rescue services, and non-medical bystanders, were recorded. Additionally, patients' active opioid prescriptions were identified using data from the provincial Pharmaceutical Information Network, which tracks prescription medication dispensations. To establish inter-rater reliability of the abstraction protocol, a second reviewer independently reviewed a random subset of 20% of ED medical records. Percent agreement and kappa statistics were calculated and are included in appendix 1.

The patients' primary opioid intoxicant was categorized as either an illegal or pharmaceutical opioid. Illegal opioids included heroin, carfentanil, and illegally manufactured fentanyl. If a patient's primary opioid intoxicant was fentanyl, it was assumed to be illegally manufactured if the patient did not have an active prescription for fentanyl at the time of their ED visit. Heroin and fentanyl were categorized together as "illegal opioids," because typically in communities with illegally manufactured fentanyl in the street drug supply, most substances that are expected to be heroin are either contaminated with or entirely consist of fentanyl and other psychoactive drugs and buffing agents.[31,38]

"Pharmaceutical opioids" included fentanyl that was actively prescribed to the patient, and other pharmaceutical opioids (i.e. oxycodone, hydromorphone, codeine, methadone, tramadol, and morphine), regardless of whether they had been actively prescribed. Patients who consumed a PO that was not actively prescribed to them may have previously received a prescription for this PO but taken it outside of the intended prescription period, or obtained a PO that had been diverted from legal sources.

3.3.4 Data analyses

Analyses were performed using STATA 14.0 IC. Differences in categorical variables between illegal opioid overdoses and pharmaceutical overdoses were detected using Chi-squared and Fischer's exact tests, and continuous variables with Mann-U Whitney tests.

Separate multivariable analyses were conducted to identify factors associated with receiving naloxone from i) EMS and ii) ED personnel. Cases were excluded if the patient did not arrive at the ED via an ambulance, since they could not have received naloxone from EMS. The multivariable analyses were conducted using Generalized Estimating Equations (GEE) with logit link and exchangeable correlations structure to adjust standard errors, since a significant portion of ED visits were repeated visits and data were potentially correlated. Plausible associations were first screened in a series of bivariate analyses, with variables significant at the P=0.25 level entered into a multivariable model. Variables were retained in the final multivariable model if they were significant at the P=0.05 level, or if removing the variable caused a change in the coefficient of another significant variable by >20%. Additionally, the variables age, sex, initial GCS, previous naloxone administrations, and opioid intoxicant (illegal vs. PO) were included regardless of statistical significance. Missing data were imputed with multiple imputation using chained equations with 30 imputations. All variables in table 3.5 were included in the multiple imputation model.

3.4 Results

There were 347 visits to the ED in which the patient received a primary diagnosis of opioid overdose during the study period. Patient charts could not be retrieved for 3 visits, and 44 visits were excluded because the patient's primary opioid intoxicant could not be identified. The remaining 300 ED visits included for analysis were made by 260 unique patients, with 35 patients having either 2, 3 or 4 ED visits.

3.4.1 Primary opioid intoxicant

Patients' primary opioid intoxicant was confirmed by self-report in 273 (91.0%) visits, suspected by EMS in 12 (4.0%) visits, and suspected by ED staff in 13 (4.3%) visits. Blood and urine toxicology screen were only conducted in 2 (0.7%) visits, in which the patient died in hospital. The 5 most commonly identified primary opioid intoxicants were heroin (41.6%), fentanyl (21.0%), oxycodone (11.6%), morphine (7.7%), and hydromorphone (5.3%) (table 3.1). The patient had an active prescription for their opioid intoxicant on the day of their ED visit in 14.3% of cases, and in the past 180 days in 18.3% of cases (table 3.1). The patient's primary opioid intoxicant was considered an illegal opioid in 187 (62.3%) of ED visits and a pharmaceutical in 113 (37.7%) of ED visits (table 3.2)

3.4.2 Patient & overdose characteristics

Illegal opioid overdoses had a lower median patient age (34 vs. 45, P<0.001), and were more likely to involve males (73% vs. 58.4%, P=0.011) compared to PO overdoses (table 3.2). Illegal opioid intoxicants were also more likely to be injected (46% vs. 14.2%) or smoked (35.3% vs. 6.2%) compared to POs (P<0.001) (table 3.2). Of the 26 overdoses that were intentional, 19 (73.1%) involved POs compared to only 7 (26.9%) involving illegal opioids (P<0.001). PO overdose were also more likely to involve patients with chronic pain (27.4% vs. 7.5%, P<0.001) or mental health (42%.5 vs. 19.3%, P<0.001) comorbidities. Similarly, in 46% of cases of PO overdose, the patient had an active opioid prescription, compared to 12% of illegal opioid overdoses (P<0.001).

3.4.3 Level of consciousness & naloxone administration

Among the 261 ED visits in which the patient received EMS care, 82.8% of illegal opioid overdoses were unconscious (GCS 3-8) on EMS arrival, compared to 44.1% of PO overdoses (P<0.001) (table 3.3).

However, this difference was reversed at the ED triage, with less illegal opioid overdoses having a GCS between 3-8 than PO overdoses (3.6% vs. 16.3%, P<0.001) (table 3.3). Pre-hospital naloxone was administered more frequently in cases of illegal opioid overdose by EMS providers (71.7% vs. 38.1%, P<0.001), fire rescue services (3.7% vs. 0, P=0.05), and bystanders with naloxone kits (10.7% vs. 0.9%, P=0.001) (table 3.3). In contrast, PO overdoses were more likely to require naloxone in the ED (53.1% vs. 24.6%, P<0.001) (table 3.3).

3.4.4 Factors associated with EMS & ED naloxone administration

Results from the multivariable analysis show that patients who were unconscious upon EMS arrival (GCS 3-8) were more likely to receive naloxone from EMS, (AOR=29.9[11.2,79.6]), and from the ED (AOR=2.91[1.19, 7.09] (table 3.5). In contrast, patients who overdosed on an illegal primary opioid intoxicant were more likely to receive naloxone from EMS (AOR=2.79[1.03,7.54]), but less likely to receive naloxone in the ED (AOR=0.40[0.17,0.95]) (table 3.5). Patients were less likely to have received EMS naloxone if they previously received pre-hospital naloxone (from fire rescue services or a bystander with a naloxone kit, AOR=0.23[0.03,0.28]) (table 3.5). However, receiving pre-hospital naloxone via any route (EMS, fire rescue services and/or bystander) was not related to whether ED naloxone was administered (AOR=0.88[036,2.11]) (table 3.5). Finally, although route of consumption was not related to EMS naloxone administration, its effect on ED naloxone appeared to approach statistical significance (P=0.10). Specifically, patients who injected (AOR=0.39[0.15,1.02]) or smoked (AOR=0.34[0.13,0.97] their primary intoxicant were less likely to require naloxone in the ED than those who consumed their intoxicant orally (table 3.5).

3.4.5 Overdose complications & ED care

In cases of illegal opioid overdose, patients were more likely to experience cardiac arrest (28.3% vs. 7.1%, P<0.001) and respiratory arrest (42.8% vs. 20.4%, P<0.001) at some point while under EMS or

ED care compared to those with PO overdose (table 3.4). However, patients with PO overdoses had longer ED stays (mean length of stay 6.6 vs. 5.7 hours, P<0.001), and were much more likely be hospitalized (30.1% vs. 9.1%), P<0.001) (table 3.4).

3.5 Discussion

We identified several differences in the progression of ED visits for overdose involving illegal opioids (heroin & non-prescribed fentanyl) and POs. Overall, our results show that illegal opioid overdoses were more severe, but recovered relatively quickly. In contrast, PO overdoses were less severe initially but took longer to recover. Specifically, in ED visits for illegal opioid overdose, patients were more likely to be unconscious upon EMS arrival, and experienced more respiratory and cardiac arrests. By comparison, ED visits for PO overdose were less likely to be unconscious upon EMS arrival, yet more likely to be unconscious at ED triage, have longer length of stays, and require hospitalization. This difference in the progression of ED visits for PO and illegal opioid overdoses is also consistent with how naloxone was administered throughout the ED visit. Patients who overdosed on illegal opioids were more likely to receive pre-hospital naloxone from EMS, fire rescue services, and bystanders with naloxone kits, but patients who overdosed on a PO were more likely to require naloxone in the ED.

In our analysis of factors that impact whether EMS administered naloxone, we found that patients who overdosed on an illegal opioid intoxicant were more likely to receive naloxone from EMS even when controlling for potentially confounding variables such as level of consciousness, route of consumption, previous naloxone administrations, and patient age and sex. However, the discrepancies observed in naloxone administration from first responders between illegal opioid and PO overdoses did not appear to significantly impact overdose recovery in the ED. This is evidenced by the observation that naloxone administration from EMS or other first responders was not associated with whether naloxone was required in the ED.

Our finding that illegal opioid overdoses had lower GCS and more respiratory and cardiac arrests is likely due to the advent of illegally manufactured fentanyl in the illegal drug supply, which can cause respiratory depression much more rapidly than either POs or heroin.[4,24] Since patients who overdosed on an illegal opioid were more likely to be unconscious (GCS ≤8), it was not surprising that they were also more likely to receive naloxone from EMS, given that decreased consciousness is one of main physical signs used to identify opioid overdose.[39] However, our study showed that patients who overdosed on an illegal opioid were more likely to receive naloxone from EMS even after controlling for level of consciousness upon EMS arrival. This supports the hypothesis put forth by previous studies that EMS may more readily administer naloxone in cases of illegal opioid overdose, but potentially under-administer naloxone in cases of PO overse.[32-34] The less frequent administration of naloxone in cases of PO overdose is concerning, given that it could possibly result in prolonged respiratory depression and adverse outcomes for these patients.

Possible reasons for the observed discrepancy in EMS naloxone administration could be related to EMS training and guidelines, which may inadvertently emphasize the role of naloxone for heroin and illegally manufactured fentanyl overdose more than PO overdose.[32] Currently, guidelines for EMS often recommend the use of environmental cues (ie. drug paraphernalia, powders) to help identify opioid overdose.[39,40] While such cues may be helpful for the quick recognition of opioid overdose in some cases, it is possible that the conscious or unconscious use of these cues could lead to missed opportunities for early overdose reversal in cases of pharmaceutical opioid overdose, where such cues are often absent. Further research is needed to more fully understand the reasons behind the differential management of illegal and pharmaceutical opioid overdoses by EMS. If the discrepancy is related to the ease with which EMS recognized illegal opioid overdoses as oppose to clinical differences in patient presentations, EMS training programs should consider adjusting their training to put greater emphasis on the use of naloxone for both illegal and PO overdoses.

Although patients who overdosed on a PO were less likely to received naloxone from first responders (EMS, fire rescue, bystanders with THN kits), our study also showed that receiving naloxone from first responders did not impact whether naloxone was required in the ED. This suggests that the the lower frequency of naloxone administration to patients who overdosed on POs was not a factor driving the longer recovery observed in ED visits for PO overdose. Rather, requiring naloxone in the ED was associated with consuming a PO intoxicant, and somewhat associated with oral route of consumption. In general, opioids that are taken orally have a slower onset of action than if they are injected or inhaled.[41,42] Effect onset can be particularly gradual with POs, since many are formulated for controlled or extended release for the purpose of pain management.[43-45] Therefore, patients who consumed an oral PO may have experienced a delayed overdose onset that did not initially warrant naloxone from EMS, but subsequently required naloxone in the ED. It is also possible that since most POs have a longer duration of action than either heroin or fentanyl, patients who overdosed on a PO may have required repeated naloxone doses in the ED or a naloxone infusion in order to achieve sustained overdose reversal.[35,46,47]

Previous studies have suggested that the longer lasting effect of oral POs is responsible for the longer lengths of stay in the ED and more frequent hospitalizations in cases of PO overdose compared to heroin overdoses.[35] While this is likely the case in our study as well, there are also several other factors that may have contributed to the greater healthcare resource burden. For instance, patients who overdosed on a PO were older in age, were more likely to overdose intentionally, and had higher levels of chronic pain and mental health disorders.

Our finding that almost all instances of bystander administered naloxone occurred in cases of illegal opioid overdose is consistent with previous research showing that people who use heroin are more likely to be aware of, and use take-home naloxone kits.[48,49] Naloxone distribution programs have historically been targeted to people who use illegal opioids (i.e. heroin), but are increasingly being used

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to reduce harms among patients prescribed opioids.[50,51] Our results show that further efforts are

needed to provide take home naloxone kits to patients who are prescribed opioids. In addition to

providing a safety net in case of overdose, distributing naloxone kits and providing overdose prevention

training to patients prescribed opioids may actually result in behavioral changes that reduce the risk of

subsequent ED visits.[51]

Finally, our study is consistent with previous literature showing that patients who overdose on

heroin and fentanyl typically recover relatively quickly after naloxone is administered.[52-54] However,

patients who use illegal opioids are at high risk for future overdose mortality, given the erratic nature of

street opioids in communities with illegally manufactured fentanyl. Therefore, it is critically important to

use the ED as an opportunity to screen patients for opioid use disorder, provide interventions, and

facilitate referral to treatment programs. In particular, initiating at-risk patients on opioid agonist

treatment in the ED with direct connection to primary care has been shown to increase engagement in

addiction treatment and reduce illegal opioid use.[55]

3.5.1 Limitations

Because toxicology screens are not regularly conducted for overdose-related ED visits at our

hospital, we relied on patient self-report and clinician suspicions to identify opioid intoxicants.

Therefore, the patient's primary opioid intoxicant may have been misclassified in some cases. In

particular, some opioid intoxicants that were assumed to be illegally manufactured fentanyl may have

actually been diverted pharmaceutical fentanyl, whereas some intoxicants assumed to be

pharmaceutical opioids may have really been counterfeit pills made with illegally manufactured

fentanyl.

Additionally, since the information about the overdose scene available in this study was limited

to routinely collected administrative data, it is possible that other unobserved variables affected the

decision of EMS to administer naloxone. For instance, while we controlled for patient level of consciousness, we were not able to account for other physical signs used to identify opioid overdose, such as pupil size or breathing rate. Therefore, we were unable to determine with certainty whether naloxone was indicated based on the patient's physical presentation. Further, although we controlled for route of administration as gathered from medical records, we could not adjust for the actual presence of drug paraphernalia or physical characteristics indicative of injection drug use that may have been apparent to EMS responders at the overdose scene.

It is also important to note that the generalizability of this study is potentially limited due to its low sample size and a single hospital setting. Finally, while most variables collected had excellent inter-rater reliability, several co-intoxicant variables (benzodiazepines, methamphetamine, cocaine/crack) had low kappa-statistics as a result of questionable reliability and low event occurrence (appendix table 1).

3.6 Conclusions and recommendations

This study shows that patients who overdosed on pharmaceutical opioids were less likely to be rescued by a bystander with a naloxone kit, and less likely to receive naloxone from EMS providers compared to patients who overdosed on an illegal opioid. Although the impact of this discrepancy on overdose recovery seemed to be minimal in this study, the lower frequency of naloxone in cases of PO overdose is a concerning trend that should be addressed. In particular, further efforts are needed to provide patients who take prescription opioids with THN kits to help prevent future opioid overdose death. Additionally, given that several studies have now found a discrepancy in EMS naloxone administration between illegal and PO overdoses, further research is warranted to investigate the reasons why EMS decide to administer naloxone in some cases of opioid overdose but not others.[32-34]

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3.8 Tables, figures, & additional files

Table 3.1 Primary opioid intoxicants of patients during ED visits for opioid poisoning, and the number that were actively prescribed at the time of the visit and in the 180 days prior

Primary opioid intoxicant*	Total ED visits no. (%) N=300	Active prescription for primary intoxicant on date of ED visit no. (%)	Active prescription for primary intoxicant in 180 days before ED visit no. (%)
Heroin	125 (41.6)	-	-
Fentanyl	63 (21.0)	2 (3.2)	2 (3.2)
Oxycodone	35 (11.6)	10 (28.6)	14 (40.0)
Morphine	23 (7.7)	6 (26.1)	9 (39.1)
Hydromorphone	16 (5.3)	10 (62.5)	11 (68.8)
Codeine	14 (4.7)	7 (50.0)	11 (78.6)
Methadone	12 (4.0)	8 (66.7)	8 (66.7)
Tramadol	1 (0.3)	0	0
Carfentanil	1 (0.3)	-	-
Total	**300 (100)**	**43/300 (14.3)**	**55/300 (18.3)**

* Patients' primary opioid intoxicant was confirmed by self-report in 273 (91.0%) visits, suspected by EMS in 12 (4.0%) visits, and suspected by ED staff in 13 (4.3%) visits.

Table 3.2. Demographics, co-morbidities, co-intoxicants, and overdose details of ED patients admitted for opioid overdose, by use of illegal versus pharmaceutical opioid intoxicants

	No. (%) of ED visits			
	All ED visits (n=300)	Illegal (n=187)	Pharmaceutical (n=113)	P-value
Patient characteristics				
Age (mean ±SD) (n=299)	38.2 ±14.5	34.0 ±11.6	45.1 ±16.1	<0.001*
Male sex	202 (67.3)	136 (72.7)	66 (58.4)	0.010*
Location of Residence				
Downtown core‡	90 (30.0)	59 (31.6)	31 (27.4)	0.65
Outside downtown core	192 (64.0)	116 (62.0)	76 (67.3)	
No fixed address	18 (6.0)	12 (6.4)	6 (5.3)	
Overdose details				
Intentional overdose	26 (8.7)	7 (3.7)	19 (16.8)	<0.001*
Route of consumption (n=265)				
Injection	102 (34.0)	86 (46.0)	16 (14.2)	<0.001*
Smoking	73 (24.3)	66 (35.3)	7 (6.2)	
Oral	87 (29.0)	11 (6.4)	76 (69.0)	
Rectal	1 (0.3)	1 (0.5)	0	
Transdermal	1 (0.3)	0	1 (0.9)	
PEG‡‡	1 (0.3)	0	1 (0.9)	
Overdose location (n=298)				
Private residence	204 (68.0)	135 (72.2)	69 (61.1)	0.05*
Public	85 (28.5)	47 (25.1)	38 (33.6)	
Hotel	4 (1.3)	3 (1.6)	1 (0.1)	
Hospital/nursing home	3 (1.0)	0	3 (0.03)	
Prison	2 (0.7)	1 (0.5)	1 (0.1)	
Mode of arrival				
Ambulance (EMS)	262 (87.0)	169 (90.4)	92 (81.4)	0.03*
Private Vehicle	37 (12.3)	17 (9.1)	20 (17.7)	
Police	1 (0.3)	1 (0.5)	0	
Hospital rapid response team	1 (0.3)	0	1 (0.5)	
Current opioid prescriptions				
Active opioid prescription	74 (24.7)	22 (7.3)	52 (17.3)	<0.001*
Opioid agonist therapy†	9 (3.0)	9 (8.0)	0	<0.001*
Co-intoxicants				
Other opioids	30 (10.1)	17 (9.1)	13 (11.6)	0.50
Methamphetamine (speed, pint)	34 (11.4)	28 (15.1)	6 (5.4)	0.011*
Cocaine (crack)	15 (5.0)	11 (5.9)	4 (3.6)	0.426
Alcohol	62 (20.8)	35 (18.8)	27 (24.1)	0.28
Benzodiazepine	16 (5.4)	7 (3.8)	9 (8.0)	0.12
Cannabis	12 (4.0)	6 (3.2)	6 (5.4)	0.377
Co-morbidities				
Chronic pain	45 (15.0)	14 (7.5)	31 (27.4)	<0.001*
HIV	16 (5.3)	10 (5.3)	6 (5.3)	1.0
Hepatitis C	63 (21.0)	39 (20.9)	24 (21.2)	1.0
Mental health disorder††	84 (28.0)	36 (19.3)	48 (42.5)	<0.001*

* Significant at 0.05-level

‡ Downtown core residence includes patients with postal code that overlap with Local Geographical Area of Edmonton East Wood.

‡‡ Percutaneous endoscopic gastrostomy

† Methadone (liquid form, once daily, max prescription 7 days), or Suboxone (once daily, max prescription 7 days).

†† Anxiety disorder, Bipolar disorder, Depression, Major Psychosis, Personality Disorder(s) (Axis II Dx), or Schizophrenia

Table 3.3 Level of consciousness & naloxone administration in ED visits for opioid overdose, by use of illegal versus pharmaceutical opioid intoxicants

	No. (%) of ED visits			
	All ED visits (n=300)	Illegal (n=187)	Pharmaceutical (n=113)	P-value
GCS at EMS arrival (n=254)†				
Mild (GCS 14-15)	53 (20.9)	19 (11.6)	34 (37.8)	<0.001*
Moderate (GCS 9-13)	20 (7.9)	5 (3.0)	15 (16.7)	
Severe (GCS 3-8)	181 (71.3)	140 (85.4)	41 (45.6)	
GCS at ED triage				
Arrived with EMS in ambulance (n=261)				
Mild (14-15)	200 (76.6)	146 (86.4)	54 (58.7)	<0.001*
Moderate (9-13)	40 (15.3)	17 (10.1)	23 (25.0)	
Severe (3-8)	21 (8.0)	6 (3.6)	15 (16.3)	
Arrived in private vehicle (n=38)				
Mild (14-15)	23 (59.0)	8 (44.4)	15 (71.4)	0.06
Moderate (9-13)	9 (23.1)	4 (22.2)	5 (23.8)	
Severe (3-8)	7 (17.9)	6 (33.3)	1 (4.8)	
Pre-hospital naloxone				
Any pre-hospital naloxone (n=299)‡	197 (65.7)	151 (80.7)	46 (40.7)	<0.001*
Bystander administered naloxone	21 (7.0)	20 (10.7)	1 (0.9)	0.001*
Fire rescue naloxone	7 (2.3)	7 (3.7)	0	0.05*
Other first-responder naloxone‡‡	3 (1.0)	1 (0.5)	2 (1.8)	1.0
EMS Naloxone	177 (59.0)	134 (71.7)	43 (38.1)	<0.001*
Pre-hospital naloxone Dose (n=295)				
Median, interquartile range	0.8, 0-1	0.8, 0.4-1.2	0, 0-0.8	0.004*
0 mg	103 (34.9)	37 (20.1)	66 (59.5)	
≤0.4 mg	33 (11.2)	24 (13.0)	9 (8.1)	
0.41-1.20 mg	113 (38.3)	89 (48.4)	24 (21.6)	
1.21-2.0 mg	37 (12.5)	27 (14.7)	10 (9.0)	
>2.0 mg	9 (3.1)	7 (3.8)	2 (1.8)	
ED naloxone (n=300)				
Any ED naloxone	106 (35.3)	46 (24.6)	60 (53.1)	<0.001*
ED naloxone route				
Intravenous Bolus	96 (32.0)	41 (21.9)	55 (48.7)	<0.001*
Intravenous drip	27 (9.0)	10 (5.3)	17 (15.0)	0.006*
Intramuscular	8 (2.7)	6 (3.2)	2 (1.8)	0.45
ED naloxone dose				
Median, interquartile range	0, 0-0.4	0, 0-0	0.2, 0-1	<0.001*
0 mg	194 (64.7)	141 (75.4)	53 (46.9)	
≤0.4 mg	39 (13.0)	18 (9.6)	21 (18.6)	
0.41-1.20 mg	32 (10.7)	15 (8.0)	17 (15.0)	
1.21-2.0 mg	13 (4.3)	7 (3.7)	6 (5.3)	
>2.0 mg	22 (7.3)	6 (3.2)	16 (14.2)	
Total Naloxone				
Any pre-hospital or ED naloxone (n=299)	244 (81.3)	164 (87.7)	80 (71.4)	0.001*
Total Naloxone dose (n=296)				
Median, interquartile range	0.8, 0.4-1.6	0.8, 0.4-1.5	0.75, 0-1.8	0.064
0 mg	55 (18.6)	23 (12.5)	32 (28.6)	
≤0.4 mg	44 (14.9)	25 (13.6)	19 (17.0)	
0.41-1.20 mg	109 (36.8)	84 (45.7)	25 (22.3)	

1.21-2.0 mg	48 (16.2)	33 (17.9)	15 (13.4)
>2.0 mg	40 (13.5)	19 (10.3)	21 (18.8)

* Significant at 0.05-level

† Pre-hospital Glasgow Coma Scale (GCS) score only available for patients transported to ED by EMS

‡ Patient may have received pre-hospital naloxone from more multiple sources

‡‡Naloxone was administered by healthcare provider at site other than Royal Alexandra Hospital

Table 3.4 Overdose complications, non-naloxone interventions, and ED care summary of ED visits for opioid poisoning, comparing ED visits with illegal and legal opioid intoxicants

	No. (%) of ED visits			
	All ED visits (n=300)	Illegal (n=187)	Pharmaceutical (n=113)	P-value
Overdose complications				
Acute kidney injury	9 (3.0	4 (2.1)	5 (4.4)	0.31
Acute withdrawal symptoms	4 (1.3)	2 (1.1)	2 (1.8)	0.63
Anoxic brain injury	6 (2.0)	4 (2.1)	2 (1.8)	0.83
Aspiration pneumonia	17 (5.7)	9 (4.8)	8 (7.1)	0.41
Cardiac arrest	61 (20.3)	53 (28.3)	8 (7.1)	<0.001*
Hypothermia	2 (0.7)	1 (0.5)	1 (0.5)	1.0
Respiratory arrest	103 (34.3)	80 (42.8)	23 (20.4)	<0.001*
Rhabdomyolysis	7 (2.3)	3 (1.6)	4 (3.5)	0.43
Seizures	1 (0.3)	1 (0.5)	0	1.0
Non-naloxone ED interventions				
Intubation	11 (3.7)	5 (2.7)	6 (5.3)	0.34
Mechanical ventilation	11 (3.7)	5 (2.7)	6 (5.3)	0.34
GI decontamination	8 (2.7)	4 (2.1)	4 (3.5)	0.48
ED care summary				
ED length of stay (hours)				<0.001*
Range	0.2-30.4	(0.2,30.4)	(0.3-26.0)	
Mean ±SD	6.5 ±4.7	5.7 ±4.4	7.7 ±5.1	
Median (IQR)	5.2 (3.2,8.9)	4.5 (2.8,7.6)	6.4 (3.9,10.7)	
Disposition				<0.001*
Admitted to hospital	52 (17.4)	18 (9.1)	34 (30.1)	
Discharged/left from ED	248 (82.7)	169 (90.4)	79 (69.9)	
Discharge status				0.72
Discharged with approval	240 (80.0)	151 (80.7)	89 (78.8)	
Left against medical advice	31 (10.3)	18 (9.6)	13 (11.5)	
Left prior to completing treatment	5 (1.7)	2 (1.1)	3 (2.7)	
Left without treatment	22 (7.3)	15 (8.0)	7 (6.2)	
Died in hospital	2 (0.7)	1 (0.5)	1 (0.9)	
Unit of inpatient admission				
Medicine	37 (12.3)	11 (5.9)	26 (23.0)	<0.001*
Intensive care unit	10 (3.3)	4 (2.1)	6 (5.3)	0.19
Psychiatry	2 (0.7)	2 (1.1)	0	-
Nephrology	1 (0.3)	0	1 (0.9)	-
Inpatient length of stay (days)				0.49
Range	0-233.0	0-46.8	0-233.0	
Average ±SD	11.6 ±34	9.5 ±12.4	12.6 ±40.7	
Median (IQR)	3.0 (1.5,10.3)	4.0 (0.99,14.9)	2.7 (1.5,9.5)	
Referrals¶				
ARCH team§	53 (17.7)	43 (23.0)	10 (8.8)	0.002*
Mental health support team	3 (1.0)	2 (1.1)	1 (0.9)	1.0
Opioid agonist treatment center	4 (1.3)	4 (2.1)	0	0.30
Hospital social work	38 (12.7)	28 (15.0)	10 (8.8)	0.12
Psychiatry	24 (8.0)	8 (4.3)	16 (14.2)	0.002*

* Significant at 0.05-level

¶ Referrals to additional medical services may have been received in the ED or on an inpatient unit

§ Addictions Recovery and Community Health- an in-hospital addiction medicine consultation service

Table 3.5 Bivariate and multivariable factors associated with receiving naloxone from Emergency Medical Service & emergency department providers, during emergency department visits for opioid overdose (N=261)§

	Outcome			
	Received EMS naloxone		Received ED naloxone	
	Unadjusted OR [95% CI]	Adjusted OR [95% CI]	Unadjusted OR [95% CI]	Adjusted OR [95% CI]
Pre-hospital GCS				
Mild (GCS 14-15)	*ref*	*ref*	*ref*	*ref*
Moderate (GCS 9-13)	2.76 [0.91,8.37]†	3.37 [1.00,11.3]	2.48 [0.87,7.09]†	2.40 [0.79,7.31]
Severe (GCS 3-8)	34.0 [14.6,79.5]**	29.9 [10.8,78.4]**	1.19 [0.61,2.31]	2.92 [1.19,7.18]*
Patient Characteristics				
Male sex	2.80 [1.59,4.96]**	1.98 [0.96,4.09]	1.34 [0.76,2.37]	1.67 [0.83,3.35]
Age (per year older)	0.98 [0.96,0.99]*	1.02 [0.99,1.06]	1.03 [1.01,1.05]*	1.01 [0.99,1.04]
Location of Residence				
Downtown core	0.84 [0.47,1.49]	-	1.00 [0.56,1.79]	-
No fixed address	1.45 [0.44,4.78]	-	1.58 [0.55,4.48]	-
Chronic Pain	0.85 [0.41,1.76]	-	2.14 [1.05,4.37]*	-
Overdose details				
Intentional overdose	2.08 [0.82,5.29]†	-	0.47 [0.20,1.13]†	-
Overdosed in public	0.67 [0.37,1.22]†	-	0.95 [0.53,1.70]	-
Route of consumption				
Oral and other	*ref*	*ref*	*ref*	*ref*
Inhalation	3.87 [1.95,7.69]**	1.39 [0.40,4.77]	0.21 [0.10,0.46]**	0.34 [0.13,0.97]¶
Injection	3.60 [1.82,7.10]**	1.39 [0.43,4.50]	0.27 [0.14,0.52]**	0.39 [0.15,1.02]¶
Substance use details				
Illegal opioid intoxicant	4.43 [2.53,7.73]**	2.79 [1.03,7.54]*	0.25 [0.14,0.43]**	0.39 [0.17,0.94]*
Active opioid prescription	0.53 [0.30,0.94]*	-	2.05 [1.12,3.74]*	-
Prior naloxone received				
Received naloxone prior to EMS ‡	0.23 [0.09,0.57]*	0.09 [0.03,0.27]**	-	-
Received any pre-hospital naloxone ‡‡	-	-	0.74 [0.41,1.33]†	0.86 [0.36,2.07]

§ (n=261) includes patients who arrived via ambulance only

**P-value <0.001

*P-value <0.05

†P-value <0.25 in unadjusted bivariate analysis, and therefore considered for inclusion in multivariate analysis

‡ Naloxone from bystander with naloxone kit, fire rescue services, or other first responder

‡‡ Naloxone from Emergency Medical Services (EMS), bystander with naloxone kit, fire rescue services, or other first responder

¶ Variable not significant overall (P=0.10)

Appendix table 3.1 Measures of inter-rater relatability (% agreement and kappa statistic) for variables extracted in the patient chart review

Variable	% Agreement	Kappa
Patient characteristics		
Age	1	1
Sex	1	1
Residence	1	1
Chronic pain	0.93	0.76
Mental health disorder	0.89	0.76
HIV	0.99	0
Hepatitis C	0.90	0.29
Overdose characteristics		
Primary opioid intoxicant	1	1
Primary intoxicant consumption route	0.97	0.94
Opioid co-intoxicant	0.91	0.62
Alcohol co-intoxicant	0.93	0.91
Methamphetamine co-intoxicant	0.90	0.49
Cocaine/crack co-intoxicant	0.97	0
Benzodiazepine co-intoxicant	0.94	-0.022
Overdose location	0.97	0.94
Overdose Intention	0.986	0.934
Mode of arrival	1	1
Glasgow Coma Scale & naloxone administered		
GCS at EMS arrival	0.986	0.974
GCS at ED arrival	0.986	0.925
Any pre-hospital naloxone	1	1
Pre-hospital naloxone dose	1	1
Bystander naloxone	1	1
Naloxone present, but not used	1	1
Fire rescue services naloxone	1	1
EMS naloxone	1	1
Other pre-hospital naloxone	1	1
ED naloxone	1	1
ED naloxone dose	1	1
Intravenous bolus	1	1
Intravenous drip	1	1
Intramuscular	1	1
Total naloxone	1	1
Total naloxone dose	1	1
Overdose complication & ED care		
Acute kidney injury	1	1
Acute withdrawal symptoms	1	1
Anoxic brain injury	1	1
Aspiration pneumonia	1	1
Cardiac arrest	1	1
Hypothermia	1	1
Respiratory arrest	0.986	0.970
Rhabdomyolysis	1	1
Seizures	1	1
Intubation	1	1
Mechanical ventilation	1	1
GI decontamination	1	1

ED length of stay (categorized into quartiles)	0.89	0.85
Length of inpatient stay (categorized into quartiles)	1	1
Disposition	1	1
Discharge status	1	1
Unit of inpatient admission	1	1
Referrals		
ARCH team	0.97	0.87
Mental health support team	1	1
Opioid agonist treatment center	0.99	0.66
Hospital social work	1	1
Psychiatry	1	0.96

Chapter 4: Discussion and conclusions

4.1 Summary

Both studies in this thesis reveal differential health-care system treatment of patients who overdose on illegal opioids relative to pharmaceutical opioids. The first study aimed to evaluate the implementation of the ED-based THN program at the Royal Alexandra Hospital. We found that just under half of patients who visited the ED for an opioid overdose were offered THN by ED staff. This is concerning, because individuals who visit the ED for an opioid overdose are at high risk for future overdose death. We found that patients were more likely to be offered THN if they overdosed on an illegal opioid, or if they had a severe overdose, as measured by their GCS score when EMS arrived at the overdose scene. In contrast, patients were less likely to be offered THN if they had an active prescription for opioids, if they left the ED unexpectedly without disclosing their intent to leave, or if they had been admitted to the hospital.

The purpose of the second study in this thesis was to compare the treatment and recovery of patients who visited the ED for an illegal opioid overdose relative to those who overdosed on a pharmaceutical opioid. We found that EMS were more likely to administer naloxone to patients who overdosed on an illegal opioid compared to a pharmaceutical opioid. This difference was independent from the patient's initial GCS, the route through which they administered the opioid intoxicant, the patient's age and sex, and whether the patient had previously received naloxone from a non-medical bystander or another first responder. Additionally, patients were much more likely to have received naloxone if they had a severe GCS score upon EMS arrival (≤ 8), and were less likely to have received naloxone if they had previously received it from a bystander with naloxone or fire rescue personnel.

We also assessed whether patients who did not receive naloxone from EMS or another first responder were more likely to subsequently require naloxone from ED staff. It seems plausible that

patients who do not received adequate pre-hospital naloxone would be more likely to require it in the ED. However, our analysis showed that receiving naloxone in he ED was not related to whether naloxone was previously administered by EMS or any other first responder. Rather, we found that patients were more likely to receive naloxone in the ED if they were initially unconscious upon EMS arrival, if they overdosed on a PO, or if they consumed their primary opioid intoxicant orally.

We identified several other differences in the characteristics and outcomes of ED visits for illegal opioid overdose compared to pharmaceutical opioid overdoses. For instance, illegal opioid overdoses were more likely to involve males and younger patients. Additionally, fire rescue naloxone was only administered in cases of illegal opioid overdose, and almost all instances of THN administration by bystanders were in cases of illegal opioid overdose. Illegal opioid overdoses were more likely to result in respiratory and cardiac arrest at some point while under EMS or ED care. However, while illegal opioid overdoses were more likely be unconscious upon EMS arrival GCS (≤8), they were more likely to have regained consciousness (GCS 14-15) when they were assessed at the ED triage.

As mentioned earlier, patients with pharmaceutical opioid overdose were more likely to receive naloxone in the ED despite receiving it less frequently from EMS. Pharmaceutical opioid overdoses also more frequently required naloxone infusions, had longer stays in the ED, and were more likely to be hospitalized. Overall, illegal opioids overdoses were more severe but recovered more quickly. In contrast, pharmaceutical opioid overdoses were initially less severe but took longer to recover and required a higher burden of health care resources.

4.2 Contextualizing the present findings within the extant literature

Previous evaluations of the ED-based THN programs have described challenges in providing THN to all at-risk patients. For instance, Drainoni *et al* (2016)[1] found that only 8% of ED patients considered at risk for overdose based on opioid overdose, misuse, or dependence diagnoses received a THN kit. This

is much lower than the proportion of patients in our study that were offered THN (~50%), which is likely because our study only included patients who visited the ED for an opioid overdose. This narrow subset is perhaps the "lowest-hanging fruit" for ED-based THN programs, in the sense that they are at the highest risk for future overdose mortality and should be easily identifiable. The relatively high rate of THN coverage in this population is consistent with the views of the ED staff interviewed by Drainoni *et al* (2016),[1] who generally agreed that patients with a history of opioid overdose should be offered THN.

Our ED-based THN program evaluation also revealed that the majority of patients (82%) either accepted a THN kit when offered or stated that they already possessed a kit. This is slightly higher than the 68% acceptance rate previously reported by *Kestler et al.* (2017),[2] who conducted a trial of an ED-based THN program in which THN kits were offered to patients who reported illegal drug use, were prescribed a high dose of prescription opioids, were receiving opioid agonist therapy, or had any clinical presentation suggestive of opioid use. The higher acceptance of THN among our population suggests that patients who have recently overdosed on an opioid may be especially receptive to THN.

Our findings that patients who overdosed on an illegal opioid were more likely to be offered a THN kits while patients who were prescribed an opioid were less likely to be offered THN are consistent with previous studies which have examined willingness of ED staff to provide THN. For instance, in a study in which ED physicians were surveyed, LaCroix *et al.* (2018) found that more than 90% of respondents strongly agreed that patients with a history of ED care for opioid overdose would benefit from THN, but only 69% agreed that patients prescribed high doses would benefit.[3]

Additionally, in qualitative group interviews with ED providers conducted by Drainoni *et al.* (2016), several participants described reasons why they would be less likely to offer THN to patients prescribed opioids. For instance, at least one participant seemed to explain the issue as a problem of not knowing which patients to offer THN. That is, while they stated that "you can't miss" someone who

visits the ED for an overdose, in their perception it was less clear whether older patients on chronic narcotics should receive THN. The same participant also described being unsure of whether they should offer THN to patients with a history of overdose, but who were visiting the ED for an unrelated reason. Overall, there was a general consensus among participants of confusion regarding who is the "right" patient to offer THN.

In the same study, another participant admitted that they more easily remember to offer THN to patients who inject drugs, which is typically more common with illegal drugs. For this patient, the idea of offering THN was simply more salient when treating patients for anything related to IV drug use. Other participants in this study reported that they did not think providing THN to all patients prescribed an opioid was realistic or feasible, and that they should instead focus on the highest risk populations. Similar attitudes were expressed by ED physicians and pharmacists interviewed in a study by Holland *et al* (2019).[4] Specifically, some participants were reluctant to provide THN to people using prescription opioids for pain because they perceived them as having a low risk of overdose.

Further insight into attitudinal barriers related to providing THN to patients prescribed opioids comes from a qualitative study of primary care physicians.[5] In this study, some physicians expressed concern that chronic pain patients taking prescription opioids would be offended if they were offered THN because of the stigma attached to THN and substance use. Other physicians perceived a conflict between simultaneously prescribing opioids while providing THN. They expressed that if physicians are doing their jobs properly they should prescribe opioids in appropriate doses, thereby making THN unnecessary.

Our evaluation of the ED-based THN program at the Royal Alexandra also found that THN was less likely to be offered to patients who left the ED without treatment or before treatment completion. This is likely because staff typically waited until patient discharge before offering THN, so if the patient

left unexpectedly without disclosing their intent to leave then they would likely be missed. This finding is consistent with the qualitative study by *Drainoni et al* (2016),[1] in which many ED staff identified a lack of clarity on the best time to distribute THN. Moreover, several nurses and physicians in this study stated that discharge may not be an ideal time to offer THN, since patients are often eager to leave the ED and are not willing to wait until discharge.

Finally, the first study found that patients who were admitted to the hospital were less likely to be offered THN, indicating a need to establish a reliable pathway to provide hospital inpatients with THN access. Hospital inpatient units are increasingly being recognized as an important setting to make THN kits available.[6]

The findings from the first study related to which patients were more likely to be offered THN are consistent with the results of the second study regarding differences in THN administration to patients by bystanders with naloxone kits. Specifically, the second study in this thesis showed that almost all instances of THN administration by a bystander occurred in cases of illegal opioid overdose (20/21; 95%). This finding is consistent with a study of illicit drug users in Vancouver, which found that injection heroin use was associated with the possession of a THN kit.[7] Similarly, a study of individuals seeking inpatient opioid detoxification services found that while 17% of people who used heroin had reported using THN to reverse an overdose in the past, none of the individuals who used other opioids had done so.[8] Taken together, it appears that THN programs are mainly reaching individuals who use illegal opioids as opposed to pharmaceutical opioids.

The second study in this thesis strengthened existing evidence that EMS are less likely to administer naloxone to patients who have overdosed on a pharmaceutical opioid. Our study detected a difference in EMS naloxone administration between illegal and pharmaceutical opioid overdoses even after controlling for various patient characteristics, including their initial level of consciousness. Thus,

even among patients for who naloxone administration was probably indicated because they were unconscious (GCS ≤ 8), patients were less likely to received naloxone from EMS if they consumed a pharmaceutical opioid. Although previous studies have found similar differences in naloxone administration between heroin and pharmaceutical opioid overdose, these studies were not able to control for initial differences in the patient's overdose presentation as we did. Specifically, while *Levy et al.* (2016)[9] and *Sumner et al.* (2016)[10] showed that decedents who overdosed with heroin were more likely to have had naloxone administered by EMS, they were not able to rule out the possibility that naloxone was actually more indicated for they patients based on their physical presentation. In contrast, *Banta-Green et al.* (2017)[11] showed that individuals who overdosed on heroin were more likely to receive EMS naloxone than those who overdosed on a pharmaceutical opioid despite having a very similar clinical presentation in terms of GCS and respiration rate. However, this study was mainly descriptive in nature and did not control for other potentially confounding factors such as patient characteristics, overdose location, or route of opioid consumption.

Additionally, these previous studies were all conducted prior to the advent of illegally manufactured fentanyl. In communities with fentanyl contaminating the street drug supply, I would not expect patients who overdosed on an illegal opioid to have a similar overdose severity as those who overdosed on a pharmaceutical opioid. Indeed, our study found that illegal opioid overdoses more frequently had a more severe GCS upon EMS arrival, and were more likely to experience respiratory or cardiac arrest at some point while under EMS or ED care. Since initial GCS is an important criteria that EMS use to decide whether to administer naloxone, it was critical for our study to control for GCS in order to properly compare EMS naloxone administration between illegal and pharmaceutical opioid overdoses.

In general, the second study of this thesis showed that patients who overdosed on an illegal opioid recovered more quickly despite having more severe symptoms initially. This pattern is consistent

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with findings by Morizio *et al.* (2017),[12] who showed that patients who overdose on a pharmaceutical opioid are more likely than those who overdose on heroin to require naloxone in the ED, require naloxone infusions, have longer stays in the ED, and be admitted to the hospital.[12] It is plausible that these differences may be in-part attributable to discrepancies in naloxone administration. However, our study shows that this explanation is unlikely, since ED naloxone administration was unrelated to whether naloxone was previously administered by EMS or other first responders.

An alternative explanation was offered by M*orizio et al.* (2017),[12] who attributed the higher burden of ED care required by pharmaceutical opioid overdoses to the longer pharmacological half-life of many oral POs, particularly those with extended release formulations.[12] The longer half-life of many pharmaceutical opioids when consumed orally increases the likelihood that respiratory depression will persist, and require additional doses of naloxone, naloxone infusion, or hospitalization.[12] Additionally, extended-release PO formulations have a very gradual onset of effect when taken orally.[13,14] Therefore, patients who overdosed on POs may have experienced worsening overdose symptoms during their ED stay.

Similar to previous studies of heroin overdose, a recent study from Vancouver showed that the large majority of ED visits related to illegally manufactured fentanyl are uncomplicated, and rarely require repeated naloxone doses in the ED or admission to hospital.[15] Fentanyl has a similar half-life as heroin, although it has a short duration of effect.[16] The effect of fentanyl lasts between 30-60 minutes when injected, compared to 4-5 hours for heroin. [12] This shorter action is attributable to its high lipophilicity, which allows it to rapidly enter and exit the central nervous system.[12] Taken together, these observations provide an explanation as to why the patients in our study that overdosed on an illegal opioid (heroin & fentanyl) recovered more quickly than patients who overdosed on POs, and were less likely to require ED naloxone or hospitalization.

4.3 General implications

Taken together, both studies in this thesis indicate that further efforts are needed to provide THN to patients prescribed opioids. While the first study showed that ED staff were less likely to offer THN in the ED, the second study showed that THN kits were rarely used to reverse overdoses involving a pharmaceutical opioid. One possible reason for this difference is reluctance among ED and primary care physicians to extend THN coverage to patients prescribed opioids. Efforts are needed to educate ED and primary care providers on the benefits of providing patients who use prescription opioids with THN. Specifically, a study of chronic pain patients receiving primary care in the US showed that those who received THN and overdose prevention training subsequently had a 63% lower rates of ED visits within the next year.[17] This study suggests that THN dispensing and overdose education may lead patients who use prescription opioids to modify their opioid consumption in ways that lowered their risk. Further, a study which surveyed chronic non-cancer pain patients found that only 13% of patients said that they would be offended, and 60% thought offering THN would be a good idea.[18] This finding may help to allay the concerns of some physicians that patients prescribed opioids would be offended if they were offered THN.

4.3.1 Implications of study #1

Our evaluation of the ED-based THN program at the Royal Alexandra Hospital showed that even among patients who have visited the ED for an opioid overdose, certain patients that may be less likely to be offered THN than others. It appears that in the context of a busy ED, clinicians readily offer THN to patients who use illegal opioids or experience a severe overdose, but may miss patients who are prescribed opioids. While illegal opioids carry a higher risk of overdose in communities with illegally manufactured fentanyl, it is important to note that all patients in our study experienced an opioid

overdose. Therefore, all patients in our population were at high risk for subsequent overdose and ideally should have received a THN kit to help prevent future mortality.

In addition to showing areas for program improvement in the ED, our study also showed that further efforts are needed to establish naloxone distribution in hospital inpatient units. Hospitals may consider targeting departments frequently visited by people who use drugs such as internal medicine, the ICU, and psychiatry.[19]

Previous literature suggests that ED staff may be unsure of which patients are eligible to receive THN. Thus, hospital ED's should provide clinicians with clear guidelines as to which patients should be targeted. The Center for Disease Control released guidelines for prescribing opioids to chronic pain patients that included recommendations to provide THN to patients with a history of overdose, a history of substance use disorder, higher opioid dosages (≥50 OME/day), or concurrent benzodiazepine use.[20] In the context of the ED, clinicians should also consider offering THN when patients present with conditions indirectly related to substance use, such as endocarditis or skin abscesses.

Guidelines for providing THN should also clarify when THN and training should be offered. ED staff in previous studies have expressed a lack of clarity in this area, and have acknowledged that waiting until patient discharge is not ideal, since patients who use opioids are often eager to leave and unwilling to participate.[1,4] Further, our study showed that patients who leave the ED without treatment or before treatment completion were less likely to be offered THN. To avoid missing patients who leave unexpectedly, THN should ideally be offered at the initial assessment if possible. Indeed, patients who are experiencing opioid withdrawal may be highly motivated to leave the ED and address their symptoms through further opioid use. These patients may be especially vulnerable to a subsequent overdose immediately following their ED visit, given the relatively short half-life of naloxone,[21] and the

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additional risk posed by consuming further doses of opioids after leaving the ED. Equipping these patients with THN (and offering opioid agonist treatment and other supports) is especially critical.

Previous literature has consistently pointed to lack of staff training and education as barriers to optimizing the implementation of THN in the ED programs.[1,3,4,22] ED training should emphasize the importance of providing THN to individuals at high risk of overdose, noting that previous studies have shown that at least 9% of people who use drugs who are given THN will use it to reverse an overdose within 3-months, and 25% use it within one-year.[23,24] THN programs policies, information, and training modules ought to be made easily accessible and distributed through several communication methods (i.e., staff orientations, staff meetings, and electronic mail).

4.3.2 Implications of study #2

The second study of this thesis has potential implications for the training and education of EMS providers. Guidelines for EMS often recommend using circumstantial evidence of drug use (ie drug paraphernalia, track marks) to help identify opioid overdose in addition to more objective criteria, such as GCS, breaths per minute, and miotic pupils.[25,26] This aspect of training may inadvertently emphasize the role of naloxone for illegal opioid overdoses compared to pharmaceutical opioid overdoses. Given that several studies have found that EMS are less likely to administer naloxone in cases of overdose caused by pharmaceutical opioids compared to illegal opioids, further research is warranted to understand the process by which EMS providers decided to administer naloxone in cases of illegal and pharmaceutical opioid overdose. [9-11] If it is determined that the discrepancy in naloxone treatment is based on ease of recognition by EMS providers rather than the patient's clinical presentation, EMS training programs should take steps to emphasize the role of naloxone in reversing overdoses cause by both illegal and pharmaceutical opioid overdose.

In recent years, the rise of illegally manufactured fentanyl has created a highly erratic and toxic street drug supply, in which people who use illegal drugs may unknowingly consume a potentially fatal opioid dose. Our study showed that it is rare for patients who use illegal opioids to be hospitalized following an ED visit for overdose. Therefore, the ED may be one of the only windows of opportunity to engage these high risk patients in ways that will help prevent future overdose death. In particular, EDs must attempt to stabilize patients by initiating opioid agonist therapy, and facilitating their connection into primary care and social services.

4.3.3 Directions for future research

Future research on ED- based THN programs should examine barriers and facilitators to providing THN to other at-risk patients besides those who visited the ED for an opioid overdose. Such at-risk groups might include patients who have a history of substance use or who use prescription opioids, but have visited the ED for an issue other than overdose. This area of research is well-suited to mixed method approaches, in which interviews are conducted with ED providers to gain detailed understanding as to why certain patients are more likely to be offered THN than others. Further research and evaluation is also needed to understand how to optimize overdose response training for patients in the context of a busy ED with limited time and resources.

Finally, research is needed to fully understand factors that may influence EMS decisions to administer naloxone. In particular, qualitative interviews would be helpful to more deeply understand reasons why EMS may decide not to administer naloxone to patients with altered mental status. Additionally, future quantitative research would ideally use data that is systematically collected prospectively. For instance, a standardized questionnaire could be designed for EMS providers that would more fully capture the patient's physical presentation and other overdose scene characteristics.

Such information could be used to more comprehensively evaluate whether naloxone is administered when objectively indicated.

4.4 Strengths and limitations

Both studies contained in this thesis have several strengths. The first study in this thesis helps fill a clear gap in the literature on ED-based THN programs. Previous studies in this area have examined ED staff willingness to provide THN and patient acceptance. However, while some ED staff interviewed in qualitative studies have reported difficulty identifying the "right" patient to offer THN in the ED, there had been no previous research on the extent to which ED staff can identify at-risk ED patients and offer them THN. Our study addresses this gap by showing that even among a high risk population of patients, there are certain patient groups that are less likely to be offered THN by ED staff. Furthermore, while previous studies on ED-based THN programs have been conducted in the context of a research trial in which paid research assistants offered THN in the ED,[2] our study evaluates the implementation of a THN program in a real-world ED setting. Studies that evaluate real-world program implementation are valuable because there are many practical considerations that may affect novel interventions in hospital EDs, such as workflow logistics, lack of time, and confusion about the roles of different staff.

The second study in this thesis also makes a significant contribution to the literature related to how overdoses caused by different types of opioids are differentially managed by EMS and ED providers. Although previous studies have shown that EMS are more likely to administer naloxone to patients who overdose on heroin compared to those that overdose on pharmaceutical opioids, the extent to which this difference is based on differences in physical signs of the patient versus environmental and social cues in the overdose scene is unclear. Furthermore, the differential management of illegal and pharmaceutical overdoses had not yet been replicated in the context of a community with illegally manufactured fentanyl in the street drug supply. With the advent of illegally manufactured fentanyl, it is

highly likely that overdoses caused by illegal street opioids will have more severe presentations than those caused by pharmaceutical opioids. Our study strengthens the existing literature because it assessed whether the patient's opioid intoxicant was associated with EMS naloxone administration while explicitly controlling for the patients overdose severity (as measured by GCS).

Further, this study is the first to examine whether the differential naloxone administration by EMS may have significant clinical consequences for overdose recovery in the ED. While previous studies have shown that patients who overdose on pharmaceutical opioids are more likely to require ED naloxone administrations, whether this difference is related to prehospital naloxone administration had not been previously studied.

The studies contained in this thesis also have several limitations that are important to note. Both studies used data that were collected through a retrospective chart review, which inherently has several limitations. In particular, since the data were collected for medical purposes, certain information may have been charted inconsistently. For instance, in our evaluation of whether THN was offered to patients that visited the ED for opioid overdose, it is possible that some instances in which THN was offered were not recorded in ED nursing or physician notes. If the patient accepted and received the THN kit, this instance of THN being offered would have been captured by the hospital's electronic system that tracks medication dispensation in the ED (Pyxis). However, if the patient was offered a kit but declined it, this instance of THN being offered may have been missed by the chart review. Due to these potential misclassification errors in the study outcome, it is possible our study underestimated the proportion of patients who visited the ED for overdose who were offered THN.

Additionally, it is possible that the patient's primary opioid intoxicant may have been misclassified for some cases, which would have affected both studies. The patient's primary opioid intoxicant was most commonly determined through patient self-report, although in some cases it was

based on the suspicion of EMS or ED staff. Thus, in some cases the patient may have consumed a different opioid from what they believed, or the suspicions of the EMS and Ed staff many have been incorrect.

Categorizing patients who reported consuming fentanyl as a primary opioid intoxicant was particularly vulnerable to misclassification error, since fentanyl can either be a pharmaceutical or an illegal drug depending on the source. To reduce possible misclassification errors, we used the pharmaceutical information network data to help categorized patients who reported consuming fentanyl. Specifically, a patient who reported consuming fentanyl was considered to have consumed pharmaceutical fentanyl if they had an active prescription for fentanyl, otherwise their opioid intoxicant was assumed to be illegally manufactured fentanyl. However, it is possible that some patients who were grouped into the "illegal opioid" category may have actually consumed pharmaceutical fentanyl that had been diverted from legal sources. Similarly, patients who thought they consuming a diverted pharmaceutical such as OxyContin may have unknowingly consumed counterfeit opioid pills containing illegally manufactured fentanyl.

Although the patient's self-report or suspected primary opioid intoxicant may not accurately reflect the opioid that was actually consumed in all cases, it is likely an accurate representation of the clinician's perceptions. For both studies in this thesis, the clinician's perception of whether the patient's intoxicant was pharmaceutical or illegal was likely more relevant that the actual opioid intoxicant. For instance, the first study was related to the clinicians' decision as to who should be offered a THN kit, which is likely to be influenced by the clinician's perception of the patient's opioid intoxicant. The same can be said of EMS providers' decision to administer naloxone to overdose patients, although in most situations EMS must rely on a combination of the patient's physical presentation and environmental cues, as they often would not have the benefit of knowing the patient's self-reported opioid intoxicant.

Several variables used in both studies in this thesis had a significant proportion of missing values, including the primary opioid intoxicant, the route of opioid consumption, and the patient's initial GCS upon EMS arrival. We used multiple imputation techniques to account for the uncertainty created by this missing data in all regression models. Multiple imputation has been used previously in combination with Generalized Estimated Equations (GEE), and has the benefit of only requiring the Missing at Random (MAR) assumption, which is less restrictive than the usual GEE assumption of Missing Completely at Random (MCAR).[27] The MAR assumption requires that the probability of missingness depends on either the outcome or the observed covariates, as opposed to the MCAR requirement of completely random missingness.[27]

Other variables collected in the retrospective chart review were limited by their inter-rater reliability. Inter-rater reliability was assessed by calculating kappa statistics and percent agreement for all included variables, which are available in the appendix tables of chapters 3 & 4. Specific variables with poor reliability as measured by the kappa statistic included HIV, hepatitis C, methamphetamine co-intoxicant, cocaine/crack co-intoxicant, and benzodiazepine co-intoxicant. Although these variables typically had a high percent agreement, a combination of low event rates and poor reliability resulted in low kappa score. These low kappa scores factored into my decision not to include them in any regression models, although they are included in the chapter 3 result tables for descriptive purposes.

Another limitation of the first study that is related to the nature of retrospective chart review data is that there were several potentially important variables that were not captured in the medical records. For instance, whether THN was offered may have been related to patient ethnicity, overdose history, whether patients were diagnosed with a substance use disorder, or how long patients have been using drugs for. These characteristics were either not available in the medical records or were missing in too many cases to be useful.

Similarly, the main limitation of the second study included in this thesis is that our retrospective chart review did not capture all variables that have previously been shown to be associated with receiving EMS naloxone. [9-11] For instance, previous studies have shown that EMS naloxone administration is associated with the patient's breathing rate, ethnicity, pupil miosis, whether the overdose was witnessed, whether the patient had a substance use disorder, and whether drug paraphernalia were present at the overdose scene.[9-11] In particular, I suspect that the patient's breathing rate and pupil size would be significantly related to EMS naloxone administration, since these are two of the three main physical criteria that EMS use to recognize opioid overdoses.[25,26]

The data used in this thesis were collected through a convenience sample of all ED visits for opioid overdose at one hospital over 13 months. When the data was collected, there were no preconceived notions about how large of a sample size was needed to attain a certain level of statistical power, since there were no *a prioiri* hypotheses for the analysis of the first study. While the second study was more hypothesis-driven, it was conducted as a secondary analysis of the data after it had already been collected for the first study. Given that the data had already been collected, I mainly used the "rule of 10" for logistic regression to guide the number of covariates I included in the multivariable analyses.[28] Specifically, I sought to ensure that for every covariate I included in a model, there were a least 10 event occurrences in the outcome variable.

For the first study, there were 168 events (THN kits offered) among the 342 ED visits, which according to the "rule of ten" meant that I could include ~16 covariates in a multivariate model without the risk of overfitting. This sample size proved to be more than adequate for the purposes of this study, as I included 13 variables in the final multivariable model.

However, the sample size was more constraining in the second study, especially since I restricted the multivariable analysis to cases in which the patient's primary opioid intoxicant was known

and the patient arrived at the ED via EMS (n=261). The two outcomes included in the multivariable

analyses in this study were i) not receiving naloxone from EMS (n=84/261) and ii) receiving naloxone

from the ED (n=82/261). These event occurrence proportions allowed me to fit approximately 8

covariates in the final models for each of these outcomes. However, if the sample size had been larger it

is possible that the greater power would have led to the detection of other significant associations.

Further, the small sample size precluded the examination of other outcomes of interest using

multivariable analyses that had lower event rates, such as hospitalization (n=43/261).

Finally, it is important to note that the generalizability of this thesis is potentially limited since it

only included data from ED visits at one hospital site. However, given that the Royal Alexandra Hospital

deals with a large burden of ED visits related to opioids and other substance misuse, it provides for an

ideal setting to study overdose presentations and harm reduction interventions such as THN

distribution.

4.4 Conclusions

The first study in this thesis evaluated the implementation of the THN program in the ED of the

Royal Alexandra Hospital. We found that even among the highest risk patients who visit the ED, those

who have overdosed on an opioid, certain patients are more likely that other to be offered THN. It is

possible that ED staff may have difficulties identifying the "right" patients alternatively, ED clinicians

may be reluctant to offer THN to certain patients. Hospital EDs should provide education and training to

ED staff regarding the importance of providing at risk ED patients with THN, as well as clear guidelines

identifying which patients should be offered THN. Additionally, there appears to be several logistical

barriers to offering THN to all eligible patients. Patients may be missed if they leave the ED

unexpectedly, or if they are admitted as an inpatient to the hospital. Staff training should outline when

THN and overdose education should take place, and establish a reliable pathway to provide at-risk

hospital inpatients with access to THN. Future research can expand on this study by examining barriers

and facilitators to offering THN to patients outside the narrow population included in our study, such as

patients who did not present to the ED for overdose but who have a history of substance use disorder or

opioid dependence, are taking prescription opioids, or present with symptoms suggestive of substance

use.

The second study adds to literature showing that THN is less frequently administered in cases of

pharmaceutical opioid overdose. Given the benefits to individuals who use prescription opioids that THN

and overdose education has been shown to provide, further efforts are needed to extend THN access to

individuals who use prescription opioids for pain management. These efforts may involve interventions

in both hospital ED and primary care settings.

This study also strengthens existing evidence showing that individuals who overdose with a

pharmaceutical opioid are less likely to be administered naloxone from EMS relative to those who

overdose with an illegal opioid. This is potentially problematic, as timely naloxone administration is key

to prevent overdose complications and death. However, our study also provides evidence suggesting

that the higher burden of ED care typically required by patients who overdose on pharmaceutical

opioids is not related to the lack of pre-hospital naloxone received by these patients. Future research

should further examine why EMS might not administer naloxone to patients found unconscious.

4.5 References

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