ILLICIT PRESCRIPTION OPIOID INJECTION: PREVALENCE, CHARACTERISTICS, AND HEALTH OUTCOMES AMONG PEOPLE WHO INJECT DRUGS IN VANCOUVER, CANADA

by

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ABSTRACT

Background: The use of prescription opioid (PO) painkillers has increased substantially in Canada and the United States over the previous two decades, bringing widespread public health concern related to non-medical PO use and overdose. Meanwhile, the injection of POs has become common among illicit drug-using populations. This thesis sought to outline the health outcomes associated with injecting POs; evaluate the impact of PO injection on non-fatal overdose; and identify the characteristics associated with PO injection among HIV-positive individuals who use injection drugs (IDU).

Methods: A systematic search was undertaken to identify studies that assessed associations between PO injection and various health outcomes. Data-driven studies used longitudinal measures from the Vancouver Injection Drug User Study (VIDUS) or the AIDS Care Cohort to Evaluate Exposure to Survival Services (ACCESS). Generalized estimating equations (GEEs) were used to estimate the effect of PO injection (with and without concurrent heroin use) on non-fatal overdose (study 1) and to identify exposures and clinical characteristics independently associated with PO injection among HIV-positive IDU (study 2).

Results: Among 31 articles included in a systematic review, several health outcomes were identified in relation to PO injection. Between December 2005 and May 2014, study 1 followed 1660 IDU, of whom a median of 24.5% reported recent PO injection. In a multivariable GEE analysis, injecting heroin or both POs and heroin, but not PO alone, significantly increased the odds of overdosing compared to injecting non-opioids. Between December 2005 and November 2013, study 2 followed 634 HIV-positive IDU. In a multivariable GEE analysis, periods of PO injection were positively associated with Caucasian ethnicity, heroin injection and drug dealing, and negatively associated with older age and methadone maintenance treatment.

Conclusions: Findings of this research highlight a constellation of social and drug-related vulnerabilities associated with injecting POs, emphasizing the importance of considering PO injection in current harm reduction strategies. These results further strengthen the rationale for expanding several harm reduction-based interventions (e.g., supervised injection sites, take-home naloxone, methadone maintenance treatment and alternatives), and integrating them into current health care treatment for IDU.
PREFACE

Work for this thesis was conducted using data from two US National Institutes of Health (NIH)-funded ongoing prospective studies of people who inject drugs from Vancouver’s Downtown Eastside: The Vancouver Injection Drug Users Study (VIDUS) and the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), led by Drs. Thomas Kerr, Kanna Hayashi, and M-J Milloy. All data collection, entry, coding, and cleaning was previously completed by staff at the BC Centre for Excellence in HIV/AIDS. These studies have been approved by the University of British Columbia/Providence Health Care Ethics Board (VIDUS: H05 – 50234; ACCESS: H05 - 50233)

With the guidance and assistance of my supervising committee (Dr. Thomas Kerr, Dr. Jane Buxton, Dr. M-J Milloy), I conceptualized the research designs (Chapter 3 & 4) and systematic review (Chapter 2). I worked closely with statisticians from the BC Centre for Excellence in HIV/AIDS to develop a data analysis plan, which was carried out by them using SAS and R. I created all tables and figures using Microsoft Word or Microsoft Excel.

A version of Chapter 2 has been submitted for publication: Lake, SL & Kennedy, MC. “Health outcomes associated with illicit prescription opioid injection: A systematic review” (Under Review).

Co-author Mary Clare Kennedy (SPPH PhD student) contributed to this work by independently screening full-text articles, and confirming the accuracy of final article data and quality scores.

Versions of Chapters 2 and 3 are currently undergoing co-author revision, and will be submitted for publication in the upcoming months. Findings from Chapter 4 of this thesis will be presented in poster form at the 8th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention. July 19-22, 2015. Vancouver, Canada.
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**ACCESS:** AIDS Care Cohort to evaluate Exposure to Survival Services  
**AIDS:** Acquired immunodeficiency syndrome  
**AOR:** Adjusted odds ratio  
**ASI:** Addiction Severity Index  
**BC:** British Columbia  
**c/mL:** Copies per milliliter  
**CD4:** Cluster of differentiation 4  
**CESD:** Center for Epidemiologic Studies Depression Scale  
**CI:** Confidence interval  
**DSM:** Depression Severity Manual  
**DTES:** Downtown Eastside  
**FDA:** Federal drug administration  
**GHQ:** General Health Questionnaire  
**GEE:** Generalized estimating equation  
**ICD:** International Classifications of Disease  
**IQR:** Interquartile range  
**IDU:** People who inject drugs (abbreviated according to alternative term “injection drug user”)  
**(HA)ART:** (Highly Active) antiretroviral therapy  
**HBV:** Hepatitis B virus  
**HCV:** Hepatitis C virus  
**HIV:** Human immunodeficiency virus  
**MAP:** Maudsley Addiction Profile  
**MeSH:** Medical Subject Heading  
**OST:** Opioid substitution therapy  
**OTI:** Opioid Treatment Index  
**PO:** Prescription opioid  
**QIC:** Quasi-Akaike Information Criterion  
**RNA:** Ribonucleic acid  
**SDS:** Severity of Dependence Scale  
**SIF:** Safe injection facility  
**TasP:** Treatment as Prevention
**THN:** Take-home naloxone

**US:** United States

**VIDUS:** Vancouver Injection Drug Users Study

**VL:** Viral load
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DEDICATION

To the memory of Thaddeus: my cousin, my best friend.
1. STUDY BACKGROUND, RATIONALE, AND OBJECTIVES

1.1. BACKGROUND

1.1.1. Prescription Opioids

Centuries of medical practice have relied on opioids for their analgesic qualities (1). Originally isolated from the opium poppy (*Papaver somniferum*), opiates are part of the opioid class of chemicals that can interact with opioid receptors to not only block pain signals from entering the brain (2), but also produce feelings of euphoria and reduced emotional distress (3). As such, their therapeutic record is accompanied by an extensive history of use for non-medical (i.e. euphoric) purposes (1, 4). Because opioids are also respiratory depressants, they carry the potential to lead to death in the event of an overdose (5). Efforts to synthesize a safer yet equally efficacious analgesics have resulted in a myriad of pharmaceutical compounds, including diacetylmorphine (heroin), that could mimic the effect of natural opiates (e.g. morphine) by binding to the same neurologic receptors (1, 4). While heroin is now primarily manufactured for illicit use, many other opioids have been developed and are manufactured by pharmaceutical companies for therapeutic use; however, little progress has been made in developing a safe (i.e. cannot be used illicitly), yet medically effective opioid (4). In order to regulate the use of these potentially dangerous therapeutic opioids, these drugs have been classified under schedule I in the Controlled Drugs and Substances Act (6) and are part of a controlled prescription program, making them prescription opioids (POs).
1.1.2. Prescription Opioid Epidemic in North America

Fuelled by the introduction of OxyContin® in 1995 (an extended-release form of the pharmaceutical opioid oxycodone) and the heavy marketing that accompanied it (7, 8)), an explosion of PO use has occurred over the previous two decades since (7, 9-11). This phenomenon is most prevalent in Canada and the United States (US), where 80% of the world’s opioid supply is consumed (12). While OxyContin may have been a major contributor to the rise in PO use, prescriptions for several other opioids including hydromorphone (Dilaudid, Vicodin), morphine, methadone, meperidine (Demerol), buprenorphine, fentanyl, and codeine have also increased substantially (13). By 2005, the most prescribed drug in the US was hydrocodone/acetaminophen (e.g., Vicodin), reaching 63 million prescriptions (14). This trend has been echoed throughout Canada, where per-capita consumption of POs more than tripled between 2001 and 2009 (15). Currently, Canada’s PO consumption is amongst the highest in the world (10).

The societal effects of such a drastic spike in opioid use are far-reaching. Accompanying the increasing trend of PO prescribing, there has been a change in the landscape of opioid use characterized by increasing rates of non-medical PO use and dependence (16-18). In Canada, while heroin remains the main opioid used in Vancouver and Montreal, illicit PO use is estimated to be more common than heroin use in other major cities including Edmonton, Toronto, Quebec City, Fredericton, and Saint John (18). In Toronto between 2000 and 2004, the proportion of detoxification admissions for oxycodone increased from 3.8% to 55.4%, while heroin admissions remained stable and under 20% (19). Various accounts depict illicit PO use as a so-called gateway to higher-risk drug use, such as heroin injection (20-22). In a large study of patients entering substance abuse treatment for heroin use/dependence in the US, three-quarters of those who initiated non-medical opioid use between 2000
and 2010 were introduced to POs (medically or non-medically) before heroin (23). Youth and young adults appear to be especially vulnerable to non-medical PO use (24, 25). There has been a substantial increase in PO use among Canadian youth since the early 2000’s (26), where POs are now the third most frequently used substance after alcohol and cannabis among high school students in Ontario (27) and British Columbia (28). In 2013, an estimated 11% of adolescents in British Columbia tried prescription pills (including opioids) without a doctor’s consent (29). Furthermore, PO use appears to be correlated with other illicit drug use among youth. For example, US high school seniors who report non-medical PO use have over twenty times the odds of using other illicit drugs (30). Finally, illicit PO use has enormous societal costs: in 2007, for example, illicit PO use and dependence was estimated to have cost the US over $55 billion, including $25 billion in healthcare expenditures (31).

By far the most compelling indication of the detrimental societal impacts of PO use to date is the ongoing surge in opioid-related deaths across the United States and Canada (32). Data from the US National Vital Statistics System revealed a 62% increase in drug toxicity deaths between 1999 and 2004, where PO-attributable deaths increased by more than 350% in some rural areas, while heroin-related deaths remained relatively stable (33). In Canada, deaths attributable to POs are estimated to have increased proportionally in parallel with US rates (34). Between 2006 and 2008, opioids were responsible for over half of drug-related deaths in Ontario, with oxycodone contributing to roughly one-third of these deaths (35). Comparing deaths from POs to other injury-related deaths contextualizes the severity of the epidemic: not only do PO-related overdoses outnumber those resulting from heroin and cocaine combined in the US, they have even surpassed the rate of deaths from motor vehicle accidents in some states (11, 36).
1.1.3. Prescription Opioids and People who Inject Drugs

Prescription Opioid Injection: Prevalence and Trends

POs are easily diverted to illicit drug markets (37, 38). The illicit injection of POs has been reported among groups of people who inject drugs (IDU) in many settings, including people in Australia (39), New Zealand (40), Europe (41), Asia (42), and – to a much greater degree – the US (43, 44) and Canada (45, 46).

In North America, while rates of illicit PO injection have soared in particular among groups of IDU in rural communities who have lower access to other opioids (i.e. heroin (43)), rates are also increasing in large urban drug centers despite high and stable supplies of heroin. For example, in Vancouver’s Downtown Eastside (DTES) neighbourhood between 2006 and 2010, drug users reported increases in the immediate availability of aspirin/codeine, hydromorphone, morphine, oxycodone, acetaminophen/codeine, while they reported steady and high availability of heroin, crack, cocaine, and crystal methamphetamine (47). A decade of descriptive research from Vancouver has also demonstrated that while the prevalence of daily heroin injection among people who use illicit drugs decreased between 1997 and 2007, the rate of PO injection increased from approximately 8% to approximately 31% over the same time period (48). The illicit PO market has affected other large urban IDU populations even more dramatically; for example, three-quarters of those from a Montreal sample of IDU reported injecting POs in 2009 (45).

People who Inject Drugs

It is estimated that more than four million Canadians have a history of using injection drugs, while – at the most recent estimate (2004) – approximately 269,000 currently inject drugs (49). IDU are highly marginalized and vulnerable populations affected by a constellation of social and structural-level determinants of poor health,
including high rates of poverty and homelessness (50-52), violence (53, 54), crime (55), criminalization and stigmatization (56), and incarceration (52, 57, 58). Survivors of traumatic life events, including childhood physical and sexual abuse are highly represented among IDU (59-61). Mental illness (50, 62), and suicide/suicidal ideation (63, 64) are also frequent within these populations. Additionally, IDU experience a high level of injection-related morbidity from soft tissue infection (65, 66), drug overdose (67, 68), and transmissible disease (e.g., Hepatitis C Virus [HCV], and Human Immunodeficiency Virus [HIV] (69, 70)).

With the risk of acquiring HIV being almost 50-fold for IDU compared to people who do not inject drugs (71), discussions of health issues affecting IDU cannot take place without an emphasis on HIV/AIDS. In 2011, of the estimated 71,300 people in Canada living with HIV/AIDS, roughly 12,000 (16.9%) had a history of injecting drugs (71), and according to the most recent surveillance estimates, approximately 11% of IDU in Canada are living with HIV/AIDS (52). HIV-related morbidity and mortality is generally poorer for IDU compared to non-IDU HIV-positive individuals (72). Even in regions where access to highly active antiretroviral therapy (HAART) is made universally available to HIV-positive IDU (e.g., British Columbia (73)), many will encounter significant social and structural-level barriers to access (74). Among those who do start treatment, a significant portion will experience sub-optimal treatment outcomes, such as incomplete viral suppression (i.e. failing to have an undetectable level of HIV RNA in the blood (75, 76)). Ultimately, this contributes to ongoing HIV transmissibility (73), increased likelihood of progression to AIDS (77), and a diminished quality of life (78) for many HIV-positive IDU.

IDU are consistently at a significantly increased risk of death compared to the general population (79, 80). In Vancouver, between 1996 and 2000, accidental overdoses accounted for almost half of deaths among HIV-negative IDU and a quarter
of deaths among HIV-positive IDU (81). Furthermore, in HIV-positive IDU, HIV/AIDS accounted for another third of deaths (81). Despite significantly decreased AIDS-related deaths paralleling recent clinical and policy advancements in HIV treatment (82), HIV positivity remains a strong predictor of all-cause mortality among IDU in Vancouver (83). A recent meta-analysis concluded that AIDS and drug overdose are the top two killers of IDU worldwide (79). Understandably, injection-related disease transmission – particularly HIV/AIDS – and drug overdose remain two of the most critical health issues facing IDU.

**Prescription Opioid Injection: Known Associations and Knowledge Gaps**

The emergence of the PO epidemic has led to a myriad of research characterizing non-medical PO use. However, since the effects of PO use are so widespread among the general population, most efforts have been concentrated on determining factors related to risk of initiating non-medical PO use, and transitioning into PO dependency among people who may have been previously naïve to illicit drugs (84), e.g. youth (85-87), older adults (88, 89), and pain patients (90-92)). However, research into illicit PO use has been slower to progress among high-intensity poly-drug using populations, including IDU.

Only recently has PO use been characterized among illicit drug users in terms of socio-demographic and behavioural factors. This research has demonstrated that illicit drug using populations, including IDU, who use POs may constitute a higher risk sub-sample of their respective populations. In addition to increased rates of homelessness (93) and reports of generally poorer physical (94) and mental health (95, 96), IDU and other illicit drug users who use POs are often more likely to engage in other high-risk behaviours, including syringe sharing (93, 97, 98), unsafe sex (97), higher frequency injection drug use (93, 98), hazardous alcohol consumption (94), and
polydrug use (93, 98). Despite the ongoing burden of HIV/AIDS among IDU, unique characteristics, including clinical outcomes, of HIV-positive IDU who inject POs appear to be missing from the literature.

1.2. RATIONALE

While co-occurring environmental and behavioural patterns associated with PO use have been identified among IDU, little research has identified harms potentially associated with PO use among IDU – and specifically those linked with injecting POs, such as transmissible disease, injection-related infections, and overdose. While a small but growing number of studies are evaluating PO-associated risk for infectious disease acquisition (45, 99, 100), PO-associated risk for overdose warrants closer investigation. A solid research base confirms a high level of correlation between PO use and overdose in the general population (101-106), but there remains a critical need to evaluate how the injection of POs by long-term illicit drug-using populations shapes their risk of overdose. The lack of knowledge surrounding PO injection as it relates to both overdose and HIV-specific characteristics is concerning, given that overdose and AIDS are at the root of a significant portion of IDU morbidity and mortality worldwide.

1.3. FRAMEWORK

Traditional public health interventions to prevent drug-related harms, including disease transmission and overdose, have typically operated from individualistic frameworks, such as the health belief model (107). These frameworks assume that, given the proper knowledge, individuals will rationally and
autonomously change their behaviours in order to prevent specific harms (108). However, these types of frameworks have been criticized for focusing too hard on individualistic choices while overlooking the impact of a host of physical, social, economic, and policy influences at the macro- and micro-levels that interact to create barriers against engaging in healthier behaviours (108-111). For example, in order to prevent overdose, IDU are often instructed to gauge drug potency by testing a portion of their drug before injecting (108). However, this instruction assumes that IDU are in ideal environment to comply. In reality, IDU face various environmental influences at the micro level, such as high rates of homelessness, which are influenced by economic and policy influences at the macro-level, such as insufficient revenue to expand low-income housing. These exposures at varying levels and/or environment types may interact to create barriers to positive behavioural change. Homeless or marginally-housed IDU may be forced to inject in public, where they risk confrontation with law enforcement or other IDU (112-114). As a result, the injection may be rushed, and the overdose prevention step of drug sampling (i.e. testing a small amount of the drug before injecting the full amount) bypassed in rushing the injection (114, 115).

The Risk environment framework, first proposed in 2002 by Rhodes (116) considers how these various physical, social, economic, and policy influences interact with each other to shape the risk of harm among IDU. This framework serves as the basis for many structural public health interventions targeted at reducing drug-related harm through creating ‘safer’ environments (117), such as supervised injection sites (115). The present research will use Rhodes’ framework to frame discussions of PO injection and its correlates, outcomes, and implications for policy.
1.4. STUDY SETTING AND SAMPLE

The current research seeks to explore characteristics and quantify health outcomes associated with injecting POs, and to contextualize these relationships in the broader risk environment. This research was undertaken as part of two larger ongoing research projects of people who inject drugs from Vancouver’s DTES neighbourhood.

1.4.1. Study Setting

The DTES – often referred to as the “poorest urban postal code” in the nation (118) – is home to 18,000 residents (118, 119), between 6000 and 10,000 of which are estimated to inject drugs (120). It is estimated that about 70% of people who use drugs on the DTES are homeless or marginally housed (119). In addition, many homeless and low-income residents from other neighbourhoods visit the DTES for its support services (119). In the 1990’s, rates of HIV in this neighbourhood were epidemic (121, 122). While various structural interventions have helped reduce transmission significantly since then, high rates of infectious disease remain a key characteristic of the DTES. The neighbourhood also suffers from a high level of crime and violence (119). While mental health is likely underestimated due to under-diagnosis, roughly one in five DTES residents are believed to be living with some form of mental illness (119). Sex workers and people living with disabilities also contribute to the landscape of the DTES (119). Many residents on the DTES suffer from a combination of the above-listed vulnerabilities.

1.4.2. Study Sample

In the midst of unprecedented rates of new HIV infections and overdose fatalities among IDU on the DTES (122, 123), the Vancouver Injection Drug Users
Study (VIDUS) was started in 1996 to study the epidemiology of various harms within the community, including patterns of overdose and HIV transmission, and associated risk factors (48, 120). Since its creation, data from this ongoing study has informed the rationale for numerous public health interventions, such as Insite (Vancouver’s supervised injection site (124)). VIDUS is an ongoing prospective cohort study of IDU recruited through extensive street outreach and snowball sampling methods. Eligibility criteria at enrolment includes being aged 18 or older, residing in the greater Vancouver area, having injected illicit drugs in the previous 30 days, and providing written informed consent. At baseline (enrolment), and every six months, participants complete an extensive interviewer-administered questionnaire related to health, substance use, and other behavioural factors and undergo a clinical examination, including testing for HIV and HCV anti-bodies (124). Study nurses also provide basic medical care and referrals to external health care providers if needed.

In 2005, all HIV-positive participants were offered participation in a new study called the AIDS Care Cohort to Evaluate Exposure to Survival Services (ACCESS (48)). Since the incidence of HIV among IDU in Vancouver has decreased dramatically since the mid 1990s (48), in order to increase the sample size, eligibility criteria for ACCESS was extended to include people who used an illicit drug other than cannabis (i.e. by injection or non-injection) in the previous 30 days. Beyond HIV seropositivity and illicit drug use, all other eligibility criteria for ACCESS are identical to VIDUS. Participants from both studies undergo the same interview process and respond to the same interview questionnaire; however, ACCESS participants are also interviewed about health issues related to their HIV/AIDS and provide blood samples for serologic analysis of HIV/AIDS (rather than testing for HIV sero-status) with extensive clinical follow-up. Participants from both studies receive a $30 honorarium.
for each study visit. Both studies have received ethical approval by the Providence Health Care/University of British Columbia Research Ethics Board.

1.5. OBJECTIVES

The objectives of this thesis are three-fold:

1. **To systematically review the current literature base to identify existing epidemiological studies examining physical and mental health outcomes associated with illicit injection of POs.** Chapter 2 will systematically summarize the existing evidence for specific health outcomes related to PO injection, including infectious disease acquisition, overdose, and mental illness. Based on findings, this chapter will identify critical inconsistencies and gaps in the current literature base, and outline areas for future research.

2. **To evaluate how PO injection affects risk for non-fatal overdose among IDU in Vancouver's DTES.** Using 8.5 years’ worth of data, Chapter 3 will employ generalized estimating equations (GEEs) to analyze the correlations between non-fatal overdose and: a) PO injection exclusive of heroin injection; b) heroin injection exclusive of PO injection; and c) both PO and heroin injection at each study follow-up stage. The aim of this study is to characterize the independent effect of PO injection, both exclusive and in conjunction with heroin, on overdose within high-risk poly-substance users. PO injection has been associated with overdose among less experienced samples of drug users (e.g. young people who use POs (125)); the current cohorts consist of experienced and older drug users. Given that POs are consistent in their purity and dosage compared to other commonly-used
illicit drugs (126), it is hypothesized that PO injection alone will not serve as an independent risk factor for overdose among this sample of IDU. However, it is also hypothesized that people who inject both POs and heroin will be, on average, higher risk drug users who will exhibit an increased risk for non-fatal overdose.

3. **To characterize PO injection among HIV-positive IDU in the context of universal access to HAART.** Chapter 4 will examine the prevalence of PO injection among HIV-positive IDU, and determine factors associated with injecting POs, including HIV clinical outcomes. Over the same study period as chapter 3, GEEs will be used to determine factors significantly associated with injecting POs. As active injection drug use and various associated micro-social vulnerabilities (e.g., homelessness) have been shown to negatively impact exposure to and uptake of ART, even in regions where ART is available at no cost (74), and particularly as previous research has characterized PO injectors as higher risk drug users, it is hypothesized that ART exposure will be less likely alongside periods of PO injection.

This thesis is divided into five chapters: Chapter 1 presents an introductory section to contextualize the three research manuscripts that follow; Chapter 2 provides findings from a systematic review of the known physical and mental health outcomes associated with injecting POs; Chapter 3 is an original research study investigating the risk of overdose associated with injecting POs; Chapter 4 provides a second data-driven research study examining associations between PO injection and several socio-demographic, structural, behavioural, and clinical characteristics among HIV-positive
IDU; and Chapter 5 provides a synthesis and discussion of all findings, in the context of the current knowledge base surrounding PO use.
2. HEALTH OUTCOMES ASSOCIATED WITH ILLICIT PRESCRIPTION OPIOID INJECTION: A SYSTEMATIC REVIEW

2.1. INTRODUCTION

Opioids account for the highest illicit drug-related burden of disease globally (127). Over the previous decade, opioid consumption has risen dramatically due to the increasing availability of prescription opioids (POs) (128-130). Consuming the vast majority of the world’s PO supply (131), and concurrently suffering increasing rates of non-medical PO use and dependence (132), as well as an epidemic of PO-related overdose deaths (133), North America has felt the brunt of this phenomenon.

POs are licitly manufactured and used for the primary purpose of pain relief; however, some POs, such as methadone and buprenorphine, are also commonly used in the treatment of opioid dependence (134). Producing pharmacological properties comparable to heroin (either naturally occurring – e.g. morphine, or synthetically manufactured – e.g. oxycodone (128)), POs are commonly diverted from clinical sources for re-sale in illicit drug markets (37). The increasing availability of POs in North America has been accompanied by increasing rates of illicit injection of various POs in many areas (17, 44, 45). In addition, PO injection has been observed among drug-using populations from other regions, including Australia (135), Europe (41), and Asia (42). As such, potential effects related to the illicit injection of POs are garnering scientific attention.

1 A version of this chapter has been submitted for publication: Lake, SL & Kennedy, MC. “Health outcomes associated with illicit prescription opioid injection: A systematic review” (Under Review)
While existing reviews have thoroughly summarized findings of observational research related to other illicit drugs (136-138), PO use – and particularly PO injection – introduces an emerging area for the synthesis of epidemiological findings. Not only might the use of POs by injection give rise to a distinct set of health effects compared to its oral or intranasal routes of administration, key differences existing between POs and other illicitly used drugs may further yield unique health outcomes. For example, unlike heroin, which often fluctuates in purity and content (126), the manufacturing of POs by pharmaceutical companies virtually eliminates dosage and purity inconsistencies, which could lead to a reduced risk for overdose. On the other hand, the addition of filler agents (e.g., talc, starch, cellulose) in various oral prescription drugs poses a major concern for injection-induced complications, such as endocarditis (139, 140). Furthermore, the steps required in preparing a PO for injection, which often include crushing and dissolving the drug from pill or capsule form rather than an easily soluble powder (141) may present additional pathways for injection-related skin complications (e.g. abscesses) and transmissible diseases (e.g. HCV infection (142)).

The objective of the current study, therefore, was to systematically identify, evaluate and synthesize the most current research considering the potential harms associated with illicit PO injection. From a clinical perspective, there is a need to identify harmful outcomes associated with injecting POs in order to increase practitioner awareness of the increasing role that POs may play in their patients’ health profiles. Furthermore, researchers require the most up-to-date knowledge of the evidence base surrounding PO injection in order to identify critical areas for future study. Finally, knowledge of the full scope of health outcomes related to PO injection is needed in order to build evidence in support of prevention and harm reduction programs that are inclusive of people who inject POs.
2.2 METHODS

2.2.1. Search Strategy

After consultation with a librarian specializing in health literature databases, a comprehensive search strategy was developed to identify original research articles, conference proceedings, and dissertations that were potentially related to the research question. Nine electronic databases were searched: PubMed, Ovid Medline®, EMBASE, Journals@Ovid, CINAHL, PsycInfo, Web of Science® Core Collection, CAB Direct, and ERIC. Search keywords included ‘prescription opioid’ and common variants, ‘injection’ and synonyms, and ‘injection drug user’ and common variants. Opioid MeSH terms were included wherever possible. Search filters or additional search terms were used wherever possible to limit results to epidemiological study methodologies. Additionally, search alerts were set up until February 1, 2015 to identify potentially relevant studies that were indexed after the original search. Furthermore, various conference abstract collections and article reference lists were hand-searched to identify potentially relevant studies not captured by the search strategy. The search was restricted to studies that were published in the English language, and since concerns related to PO injection parallel the increase in PO availability that begun in the early 1990’s (7), the search was further limited to records published from 1990 onwards. All database searches were conducted in December 2014.

2.2.2. Inclusion Criteria

Studies that were considered for inclusion were those published in a peer-reviewed scientific journal, dissertation database, or academic conference proceeding. Grey literature, review articles, commentaries or letters, case reports, or case-series
were not included. As outcomes associated with PO injection were the main focus, studies reporting strictly descriptive results (i.e. those which did not include a measure of association) were not included. In order to keep results as comparable as possible without severely limiting scope, eligibility criteria included studies of adults and/or young adults, but not adolescents. Therefore, studies where the mean or median age of the sample was below 18 years were excluded. If separate publications with duplicate or overlapping results were found, the publication with the most complete information (e.g., research manuscript rather than a conference abstract) was retained.

Studies were marked as potentially relevant if they contained a well-defined group of people who inject drugs (i.e. a portion of the sample, if not the full sample, needed to be injecting drugs). Furthermore, a variable clearly indicating PO injection (rather than PO use) was required in the statistical analysis. Exposure groups that included PO amongst a host of other drugs (e.g., some but not all participants in the exposure group injected POs) were not considered relevant for this analysis. In order to maximize the scope and results of this review, any PO type(s) under study were considered acceptable. Relevant outcomes were those directly causing physical or psychological harm, and were confirmed as such through the World Health Organization (WHO) International Classification of Diseases (ICD)-10 (143). Behaviours or events that can moderate harm, e.g., syringe sharing or incarceration, were not considered health outcomes.

2.2.3. Screening Process

All records were imported into Endnote X7. The primary reviewer (S.L.) manually deleted any duplicate records that were not automatically deleted by the software. Articles were screened in two stages. First, the primary author (S.L.)
screened all titles and/or abstracts. Studies that clearly did not meet eligibility criteria were deleted. Records for which abstract eligibility was unclear moved on to the second screening stage where both reviewers (S.L. and M.C.K.) independently screened the full-text versions of these remaining articles. Studies were either marked as ‘potentially relevant’ or ‘not relevant’ by each author. Each reviewer sorted the excluded records into folders marked with reasons for deletion. Both reviewers compared their respective classifications and discussed discrepancies until an agreement was reached.

2.2.4. Data Extraction and Analysis

Study-specific information, including author, publication date, country, study design, sample characteristics, exposure and outcome measurements, and statistical findings, were extracted from each study into a Microsoft® Excel spreadsheet. The standardized chart was completed S.L. and independently reviewed for accuracy by M.C.K.

2.2.5. Quality Assessment

A modified version of the Downs & Black checklist for the reporting of health care studies (144), a valid and reliable quality assessment tool for observational research (144), was used to assess the methodological quality of each study. Through this version of the checklist, studies could score a maximum of 18 points, representing the highest methodological quality. Studies were assessed for quality by S.L. and checked independently for accuracy by M.C.K. Any scoring discrepancies between reviewers were discussed until a consensus was reached.
2.3. RESULTS

2.3.1. Literature Search

Database searching resulted in 2,833 records, and hand-searching yielded an additional 17 potentially relevant studies. After automatic (n = 409) and manual (n = 81) duplicate removal, 2,113 records were eliminated in the first round based on title and/or abstract information, while the remaining 247 records went on to the full-text screening round, which led to the exclusion of another 214 records. A high level of agreement was reached through independent author screening (κ = 0.94). Figure 2.1 presents a detailed account of the screening process, including reasons for deletion of full-text articles. Two additional records were removed for missing information after unsuccessful attempts to contact study authors. At the final stage, the review included 31 relevant peer-reviewed studies published between 1996 and 2015 (median: 2008). Key information from each study, including main findings, was extracted into Table 2.2 displayed at the end of this chapter.

2.3.2. Quality Assessment

Modified Downs & Black scores were generally quite high with a median score of 14 (interquartile range [IQR]: 13-15). Scores for the category ‘external validity’ were consistently low, as none of the retrieved records demonstrated complete sample representativeness.
2.3.3. Summary of Included Studies

Almost half (n = 14, 45.2%) of included studies were undertaken in the United States and Canada, followed by Australia (n = 7, 22.6%), India and Nepal (n = 5, 16.1%), and France and Estonia (n = 5, 16.1%). The majority of studies (n = 24, 77.4%)
employed a cross-sectional design. The remaining studies used prospective cohort (n = 6, 19.4%), and case-control (n = 1, 3.2%) designs. The median sample size was 365 (IQR: 203 – 720). All studies assessed PO injection through self-report; however, the length of recall ranged from one month to lifetime, and the type of PO assessed also varied greatly across studies. Table 2.1 summarizes the types of POs and outcomes considered, separated by geographic region. Most North American studies examined pain pill-type opioids (e.g. oxycodone, hydromorphone, hydrocodone [n = 10, 71.4%]). Australian studies focused heavily on POs often used for opioid substitution therapy (OST) (e.g. buprenorphine and methadone [n = 6, 85.7%]). All French studies focused on buprenorphine, while fentanyl was the PO of interest in the study from Estonia. All studies from India evaluated harms related to injection of dextropropoxyphene (a weak opioid analgesic usually available in combination with acetaminophen and dicyclomine (145), which is off the market in North America and Europe (146, 147)). The sole study from Nepal examined outcomes related to the injection of buprenorphine-benzodiazepine-antihistamine cocktails. Consideration for covariate or confounding measures in the included studies varied from strong to inexistent; just over half (n = 18) explored a potential association between PO injection and a relevant outcome with a multivariable model.

The included studies considered a range of health outcomes but were heavily represented in certain topic areas. The outcomes investigated most often fell under the ICD-10 classification ‘Infectious and Parasitic Diseases’, with 16 (51.6%) studies examining viral hepatitis (HCV and Hepatitis B Virus [HBV]), and/or Human Immunodeficiency Virus (HIV) infection. Following infectious diseases were 13 (41.9%) studies examining ‘Injuries and Poisoning’ – i.e., drug overdose. Outcomes related to ‘Mental or Behavioural Disorders’ (n = 8, 25.8%) and ‘Diseases of the Skin
and Subcutaneous Tissue' (n = 6 each, 19.4%) were also common. A few studies (n=2, 6.9%) examined general health indicators, and are classified as ‘Other’.
Table 2.1. Summary of considered prescription opioids and outcomes, by geographic region

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\(^a\) Includes hydrocodone, oxycodone, hydromorphone
\(^b\) Includes buprenorphine and methadone
\(^c\) Includes fentanyl, pentazocine (Talwin), dextropropoxyphene (proxyvon)
\(^d\) HIV, Hepatitis C virus (HCV), Hepatitis B virus (HBV)
\(^e\) Abscesses, blocked veins, oedema, bruising/scarring
\(^f\) Includes pain and general physical health measures
2.3.4. Infectious Diseases

*Hepatitis C Virus*

The study of infectious disease outcomes occurred across all geographic regions. HCV was the most common outcome of interest in this category, and collected the most compelling evidence for an association with PO injection of all the outcomes considered. North American studies almost consistently found links between HCV infection and PO injection. For example, PO (pain pill-type opioids and methadone) injection was a strong and independent risk factor for HCV seropositivity (148) in a study of nearly 400 rural American IDU. This cross-sectional association was confirmed in other North American samples of drug users (44, 149), including young adults (100, 150). There were two prospective cohort studies that considered this outcome: Bruneau and colleagues found that those who exclusively injected POs had almost three times the odds of HCV seroconversion compared to non-PO injectors (45). Conversely, Hadland and colleagues concluded that PO injection was not a significant predictor of HCV conversion in a cohort of young drug users, despite a strong baseline association with HCV seropositivity (99).

In Australia, Aitken and colleagues did not find significantly different rates of HCV for buprenorphine injectors compared to non-injectors (151), but Iversen and colleagues analyzed data from over 15,000 IDU and found that among less experienced injectors (≤ 4 years), those who injected methadone or buprenorphine and other POs had significantly increased odds of HCV seropositivity, and this association was stronger among women (152). By contrast, the three studies that examined dextropropoxyphene/dicyclomine (‘proxyvon’) injection compared to heroin injection in India found a negative association between proxyvon injection and HCV seropositivity (153-155).
Hepatitis B Virus

Evidence for an association with HBV was weak. Of the two studies that considered HBV (44, 149), Wylie and colleagues found an unadjusted association between PO injection and being HBV-positive – but this was only true for Talwin [pentazocine]/Ritalin injection and not morphine injection (149). The other study that considered HBV did not observe an association with injecting pain pill-type opioids (44). In both cases, type of HBV (i.e. acute vs. chronic) was not made explicit.

Human Immunodeficiency Virus

Based on the included studies, there is no consistent trend in the association between PO injection and HIV infection. Only one study found a significant and positive association in this area, where reporting fentanyl as one’s main injection drug (as opposed to amphetamine) was an independent risk factor for HIV seropositivity in Estonian IDU (156). In other studies, PO injection actually appeared to be protective of HIV; for example, Obadia and colleagues observed significantly lower rates of HIV for exclusive buprenorphine injectors compared to other injectors (157), and Mahanta and colleagues noted that exclusive proxyvon injectors had significantly lower odds of HIV seropositivity compared to heroin injectors (155). Results from the two remaining studies were non-significant (149, 158). The sole study of HIV-positive IDUs did not find significant differences in indicators of disease progression related to injecting buprenorphine (159).

2.3.5. Injuries and Poisonings

Studies of overdose were especially common in North America and Australia. In North America, half (n = 3) of the overdose studies found a significant and positive association with PO injection: two studies from Vancouver (160, 161) demonstrated
that recent morphine injection was a significant predictor of recent non-fatal overdose among IDU; however, this association was only present among women in the latter study (161). A study of rural American drug users found a marginally significant positive association between injection of methadone and pain pill-type opioids and number of lifetime overdoses (162). Silva and colleagues found that among a cross-sectional sample of PO-using (morphine and pain pill-type opioids) young adults, those with a lifetime history of overdose reported PO injection at a significantly higher rate than those who did not; however, in a multivariable model, PO injection was not found to be an significant predictor of overdose (125). Similarly, two other cross-sectional North American studies did not observe an independent association between PO injection and non-fatal overdose (163, 164).

Of the four Australian studies that considered overdose, three were primarily concerned with methadone injection (165-167). In all three studies, methadone injection was positively associated with lifetime overdose; however, all results were reported at the bivariant-level only. Degenhardt and colleagues compared those who inject morphine with other IDU but did not observe a significant difference in overdose rates between groups (168). Only one study from India investigated non-fatal overdose, and found that PO (buprenorphine, dextropropoxyphene, pentazocine) injectors were as likely as heroin injectors to have experienced a lifetime overdose (169). On the other hand, the sole Estonian study found that injecting fentanyl was significantly and positively associated with lifetime overdose (156).

2.3.6. Diseases of the Skin and Subcutaneous Tissue

A few studies sought to evaluate risk for various injection-related cutaneous and subcutaneous problems, such as abscesses, cellulitis, thrombosis, and oedema. No studies out of North America were identified in this area, while four were identified
from Australia (165, 167, 168, 170) and one each from France (171) and India (169). Three studies (50%) recorded a significant positive association in this category – one among injectors of dextropropoxyphene, pentazocine, or buprenorphine (169), and two among injectors of methadone (165, 167). In the first case, PO injection was associated with blocked veins and abscesses, and in both methadone studies, abscesses, infections, thrombosis, and bruising/scarring of injection sites were more common among methadone injectors; however, one of these studies reported a bivariable estimate only (165). In a case-control study comparing IDU with ‘puffy hand syndrome’ (a type of oedema exclusive to IDU (172)) to those without, Andrezs and colleagues demonstrated that buprenorphine injection was not a significant risk factor (171). Similarly, Jenkinson and colleagues did not find significantly different rates of injection-related health problems (which included abscesses, scarring/bruising, thrombosis in addition to overdose) for buprenorphine injectors, compared to heroin injectors (170). The only morphine study in this category did not find a link between morphine injection and injection-site harms (168).

2.3.7. Mental and Behavioural Disorders

General Mental Health

The majority of studies in this category (n = 3, 75%) observed a correlation between PO injection and poor mental health. Lankenau and colleagues found that among their cross-sectional sample of young adults who use POs illicitly, significantly more injectors than non-injectors had a history of psychiatric institutionalization (150). Among Nepalese IDU, those who injected buprenorphine cocktails intensively had, on average, a higher mean Maudsley Addiction Profile (MAP) (173) mental health score than cocktail non-injectors, indicating poorer mental health outcomes (158). While one study did not observe a higher mean psychiatric score (using the Addiction
Severity Index (174) among PO injectors (44), another used the General Health Questionnaire (175) to identify significantly more methadone injectors than other IDU experiencing psychological distress and meeting diagnostic criteria for psychopathology (167).

Depression and Suicide

Studies monitoring buprenorphine injection among IDU on buprenorphine maintenance treatment found depression (159) and suicide attempts/ideation (176) to be independently and positively associated with buprenorphine injection.

Substance Dependence

With the exception of one buprenorphine study (176), research examining substance dependence identified a significant and positive association with PO injection at the bivariable level: Surratt and colleagues concluded that PO users who met DSM-IV criteria for past-year substance dependence had roughly four times the odds of being injectors (177), and two Australian studies (166, 167) found that methadone injectors were significantly more dependent on heroin than non-methadone-injecting IDU, according to the Severity of Dependence Scale (178).

2.3.8. Other Outcomes

Two studies included measures for general health status. Ojha and colleagues observed statistically similar MAP physical health scores across levels of buprenorphine cocktail exposure, but did find that reporting ‘serious health problems’ increased significantly with each subsequent buprenorphine cocktail injection exposure level (none, moderate, intensive (158)). Darke and colleagues
demonstrated significantly poorer general health for methadone injectors compared with other IDU (167), according to the Opioid Treatment Index (179).

2.4. DISCUSSION

The present review identified 31 articles that evaluated associations between the injection of one or multiple types of POs and various physical and mental health outcomes. POs under consideration varied across region of study, where pain pill-type opioids and morphine were most often considered in North American research; OST-type opioids were more common in Australian and French research; and dextropropoxyphene was exclusive to studies from India. Other opioids included fentanyl; Talwin/Ritalin cocktails; and buprenorphine, antihistamine, benzodiazepine cocktails. Outcomes considered in the relevant research included infectious disease, overdose, injection-related health problems, and general mental and physical health.

All North American cross-sectional HCV studies, and one of two prospective cohort studies, identified a positive association between HCV and PO injection. It is becoming clear that PO-using IDU frequently engage in other high-risk behaviours, such as syringe sharing, even compared to their non-PO injecting counterparts (93, 180), which is likely to be contributing to this positive association. In addition, as many POs are designed for oral use, their injection may require additional steps (e.g., crushing, dissolving, and filtering) and unique paraphernalia, which may increase HCV risk (142). For example, the residue (‘wash’) that remains on the filter is often kept for future injection and may be shared between users (46, 141), revealing a potentially new transmission risk pathway between users. In fact, all studies that considered pain pill-type opioids recorded high rates of HCV infection among young adult PO injectors (99, 100, 150, 152). These results closely parallel descriptive reports
of high rates of oxycodone and other PO use (injection and non-injection) among newly infected youth across the US (181). However, the only study to longitudinally examine HCV acquisition among young users resulted in a null finding (99). The authors of this study note, however, that the majority of PO injectors engaged in other injection drug use in this setting, which likely attenuated the adjusted estimate. Independent associations found in others studies may be partially explained by unmeasured behaviours unique to certain types of PO injection, described above. In India, where IDU mainly inject heroin or proxyvon (dextropropoxyphene/dicyclomine), proxyvon appears to be protective of HCV and HIV compared to heroin (153-155). Authors of these studies note that proxyvon capsules tend to be injected by one user each – unlike heroin, which may be split between various users who are likely to share injection paraphernalia. Weak evidence for an association with HBV may have been confounded by differing availability of HBV immunization across settings. With the exception of one study (156), there was no apparent HIV risk associated with injecting PO. HIV incidence rates among IDU have been substantially reduced in many regions over the previous decade (182, 183), demanding a higher level of statistical power to detect incidence risk factors. Furthermore, since illicit PO use is a relatively new trend among IDU, many PO injectors (HIV-positive and negative) will have histories of non-PO injection drug use, likely tempering associations with prevalent HIV in non-longitudinal studies. High-powered prospective studies and research involving young and inexperienced IDU may address this gap. Finally, only one study that examined progression of HIV in relation to PO (buprenorphine) injection was identified (159). As non-medical PO use is common among HIV patients (184, 185), ongoing research is needed to identify how PO injection affects the clinical risk profile of HIV-positive IDU.
The findings for an association between PO injection and non-fatal overdose are equivocal. Inconsistent findings might be reflective of the diverse list of POs under consideration for this category. For example, Talu and colleagues found that people who had experienced an overdose had roughly three times the odds of reporting fentanyl as their primary injection drug, rather than amphetamine (156). As fentanyl is one of the strongest POs available (50 to 100 times stronger than morphine (186)), and is often responsible for spikes in overdose deaths within street drug using populations (187-189), this finding is not surprising. Prescription fentanyl is also unique from other types of POs in that it is contained within a slow-release patch rather than an oral medication. Diverted fentanyl sold as a portion of this patch (190) means users are unaware of the amount of drug they are consuming - a commonly reported issue in overdoses involving other illicitly-used drugs (191). In terms of overdoses related to OST-type opioids, several studies found higher rates of overdose among injectors (165-167). Drugs used for OST are often designed to metabolize slowly (192), which may create a higher risk for overdose if other substances, including non-opioid drugs, are used while slow-acting opioids are in the circulatory system. However, it should be noted that the findings from these three OST-type opioid studies were all cross-sectional and bivariable. More rigorous investigation in this area will be helpful, especially as the list of drugs used to treat opioid dependence continues to grow.

Only one study of pain pill-type opioids observed an increased risk of overdose associated with injection (162), which was surprisingly small in light of the current overdose epidemic related to POs – and especially oxycodone – in North America (193, 194). Null findings in this area may be explained through differential high-risk lifestyle patterns for people who inject POs, such as homelessness (195) and engagement in other intensive drug use (45). Controlling for these types of factors may have sufficiently attenuated the association with overdose in some studies;
however, the possibility that engagement in PO injection actually increases risk for these exposures cannot be ruled out. Secondly, people may engage in PO use for specific non-euphoric purposes, including self-“treatment” of physical or emotional pain (94, 196, 197) and opioid withdrawal and addiction (i.e. to ‘stay clean’ (198, 199)). In IDU samples, perhaps some of those who inject POs are a comparatively lower risk population for these reasons. Third, spikes in overdose among IDU are sometimes related to the circulation of unusually potent drugs (111); people with long-term drug injecting experience may be less likely to overdose with POs simply due to their regulated dosing, purity, and composition. In fact, qualitative research has discussed how the consistent nature of POs influences preference for POs among street-based drug users (46). Despite the growing popularity of pain pill-type opioid among IDU, especially in North America, no studies were identified that used longitudinal methods to examine the relationship between the injection of pain pill-type opioids and overdose, revealing an important area of research required to strengthen the evidence base in this area.

Clinical case-based research has documented several severe skin and subcutaneous problems arising from PO tablet – particularly buprenorphine – injection (65, 200). However, the implications of these studies could not be fully supported by the epidemiological studies included in the present review, as only one buprenorphine study (33.3%) recorded a positive independent association between buprenorphine injection and injection-related complications (169). However, it appears that methadone injection is associated with increased injection-related health problems including abscesses, infections, and thrombosis. This might be a result of injecting the highly viscous methadone syrup, or from injecting a high volume of the diluted product, which can reach up to 20 mL per injection (167). A significant drawback to five of the six included studies is the self-reported nature of injection-
related harms, including infections, injection-site scarring, and thrombosis (sometimes measured through proxies such as ‘difficulty injecting’). Studies that can validate these complications through clinical consultation are an important addition to understanding the effect of PO injection on various injection site-related health issues. Finally, there was a surprising lack of research related to injection-related infections arising from injection of pain pill-type opioids, which will be essential in understanding implications exclusive to PO injection in Western regions, where the injection of various types of opioids is more prevalent.

PO injectors appear to elicit poorer mental health. Aside from two studies demonstrating increased odds of buprenorphine injection among depressed (159) and suicidal (176) drug users, few studies that examined specific types of mental illness in relation to PO injection were identified. As nationally representative cross-sectional research in the United States has demonstrated associations between non-medical PO use and mental health and behavioural disorders, such as social phobia, generalized anxiety disorder, and panic disorder (201, 202), exploring these outcomes among PO injectors is an important next step for future research.

In all outcome categories, findings should be taken with caution, particularly as cross-sectional studies were over-represented, thus it is possible that the outcome(s) of interest occurred prior to, or independent of, the exposure(s) of interest in many cases. Clearly, there is a need for more prospective study designs that are able to distinguish temporality between measures in order to strengthen the current evidence base. Just under one-half (42%) of findings were confirmed at the bivariable level but unexplored at the multivariable level, thus eliminating the ability to conclude independence of association; studies considering a range of demographic, socio-environmental, and behavioural confounders are critical. Furthermore, due to the hard-to-reach nature of the involved populations of interest, the external validity of
the included studies suffered. While it is not possible to achieve full representativeness among IDU samples, national health and drug use surveys (e.g., National Survey of Drug Use and Health in the United States (203)) could update injection drug-related questions to include PO injection in order to monitor transitions to PO injecting, and compare POs and other illicit drugs in terms of various health indicators on a geographically representative household-based level.

The findings of this study contain additional limitations for consideration. As the goal was to include sources exhibiting high methodological quality, non-peer-reviewed records were not included, thus some potentially helpful resources (e.g. reports by government agencies or academic research groups, fact sheets, and policy documents) may have been overlooked in this review. Additionally, it is possible that some potentially relevant peer-reviewed records may not have been captured in this review, despite extensive searching and screening efforts. As there is a high level of subjectivity involved in selecting articles for inclusion, this review aimed to minimize any selection biases through enlisting two independent authors for screening articles, extracting data (with a standardized form), and assessing article quality (with a validated checklist for rating methodological rigor). Finally, in order to narrow the scope of potentially relevant studies, this review did not examine harms of non-injection routes of PO; however, it is acknowledged that non-injection PO use is also common among IDU (204) and other high-risk drug users (95), and research should continue to investigate harms related to all forms of PO use, and specifically differences in outcomes related to administration route, in these populations.

Based on the included articles, people who inject POs appear to be at risk of poorer general physical and mental health as well as an increased risk of HCV (with the exception of dextropropoxyphene injection among Indian IDU). Those who inject POs – including young adults – appear to be highly susceptible to HCV seropositivity,
but it is unclear whether PO injection independently predicts seroconversion to HCV. There was inconsistency in findings of associations with other infectious diseases, overdose, and cutaneous and subcutaneous conditions. For some outcomes, certain POs appear to be more strongly linked than others (e.g. methadone and skin infection; fentanyl and overdose). However, the current evidence regarding health outcomes associated with injecting POs is both inconsistent and incomplete in various methodologies and topics, including a lack of longitudinal studies of PO injection as a risk factor for overdose (especially for pain pill-type opioids), cutaneous and subcutaneous complications, and specific mental health outcomes. Few studies were identified that investigated progression of HIV/AIDS among those who inject POs. High-quality research should aim to fill these knowledge gaps. As PO injection remains popular among IDU, and those who inject POs appear to be a high risk population in terms of substance use behaviours and physical and mental health outcomes, interventions aimed at reducing injection-related harm should ensure inclusivity of people who inject POs.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
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<tr>
<td>Aitken 2008, Australia (151)</td>
<td>Cross-sectional</td>
<td>N = 316 current IDU recruited through street outreach¹</td>
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<td>Buprenorphine injection in the previous three months</td>
<td>Hepatitis C virus (HCV)</td>
<td>Prevalence of HCV antibody was not significantly different for people who injected buprenorphine compared to other IDU.</td>
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<tr>
<td>Ambekar 2015, India (169)</td>
<td>Cross-sectional</td>
<td>902 male drug users recruited from harm reduction drop-in centres; mean age = 33.4 years</td>
<td>14</td>
<td>Primary drug of injection (buprenorphine, pentazocine, dextropropoxyphene vs. heroin)</td>
<td>Abscess, blocked vein, overdose (lifetime)¹</td>
<td>Primary PO injectors were more likely to report abscesses (ARR = 1.40 [1.06-1.85]) and blocked veins (ARR = 2.51 [1.89-3.35]) than primary heroin users, but not significantly more likely to have experienced an overdose (p&gt;0.05).</td>
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<tr>
<td>Andresz 2006, France (171)</td>
<td>Case-control</td>
<td>33 cases and 33 controls recruited from OST centres; mean age = 34 years</td>
<td>15</td>
<td>Lifetime buprenorphine injection; years of buprenorphine injection¹</td>
<td>Puffy hand syndrome (oedema)</td>
<td>Cases were not significantly more likely than controls to have injected buprenorphine (n = 23 (69.7%) vs. 19 (59.4%), p&gt;0.05), or to have longer mean duration of buprenorphine injection (4.5 years vs. 3.7 years, p&gt;0.05).</td>
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<tr>
<td>Bruneau 2012, Canada (43)</td>
<td>Cohort (St. Luc cohort)</td>
<td>246 HCV-negative IDU recruited through street outreach; mean age = 34.5 years</td>
<td>15</td>
<td>PO injection (hydrocodone, oxycodone, others) in the previous month</td>
<td>HCV</td>
<td>PO injection was independently and positively associated with HCV seroconversion (AHR = 1.87 [1.16-3.03]). Those who reported injection PO but not heroin had significantly increased odds of seroconverting compared to those who did not (AHR = 2.88 [1.52-5.45]). Those who injected both PO and heroin did not have increased odds of HCV seroconversion.</td>
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<tr>
<td>Carrieri 2003, France (159)</td>
<td>Cohort (Manif 2000 cohort)</td>
<td>114 HIV-positive IDU on buprenorphine maintenance treatment; mean age = 33.6 years</td>
<td>14</td>
<td>Buprenorphine injection in the previous six months</td>
<td>Depression (CESD score); HIV disease progression (CD4+ cell count, HIV-1 RNA detectability, clinical stage)</td>
<td>Periods of depression were significantly and positively associated with periods of buprenorphine injection (ARR: 1.04 [1.01-1.06]) over the study period. HIV-related clinical outcomes did not differ significantly according to buprenorphine injection status.</td>
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<tr>
<td>Study</td>
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<td>Chelleng 2008,</td>
<td>Cross-sectional</td>
<td>143 IDU recruited from drop-in centers, treatment centers, counselling settings; mean age = 24.7 years</td>
<td>15</td>
<td>Proxyvon injection in the previous six months</td>
<td>HCV</td>
<td>Compared to those who injected heroin but not Proxyvon, people who exclusively injected Proxyvon had significantly lower odds of being HCV positive (AOR = 0.08 [0.02-0.37]).</td>
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<td>India (153)</td>
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<td>Darke 1996,</td>
<td>Cross-sectional</td>
<td>312 heroin injectors recruited through street outreach; mean age = 28.8 years</td>
<td>13</td>
<td>Methadone injection in the previous six months (vs. other IDU)</td>
<td>General health status (OTI score); lifetime abscesses and infections; thrombosis; heroin overdose (lifetime and previous six months); psychological functioning (GHQ score); current heroin dependence (SDS score)¹</td>
<td>Methadone injectors had significantly poorer general health (OTI score: 18.0 vs. 15.5), increased psychological distress (GHQ score: 10.2 vs. 7.8), and met diagnostic criteria for psychopathology (67% vs. 54%), all p&lt;0.05. Methadone injection was positively associated with abscesses and infections (OR = 2.40 [1.30-3.30]), thrombosis (OR = 2.2 [1.1-4.6]), lifetime overdose (OR = 2.2 [1.4-3.5]), recent overdose (OR = 2.5 [1.4-4.6]), and heroin dependence (AOR = 1.07 [1.01-1.13]).</td>
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<td>Australia (167)</td>
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<td>Darke 2002,</td>
<td>Cross-sectional (IDRS)</td>
<td>788 IDU recruited through street outreach; mean age = 28.6 years</td>
<td>11</td>
<td>Methadone injection in the previous six months (vs. benzodiazepine and other)</td>
<td>Heroin overdose (lifetime and previous six months); Current injection site harms (abscesses/ infections/ bruising/scarring)¹</td>
<td>Rate of lifetime overdose was higher for methadone injectors compared to other IDU (72% vs. 45%, p&lt;0.05), but not rate of recent overdoses (17% vs. 15%, p&gt;0.05). Methadone injectors reported significantly more injection-site problems than other IDU (p&lt;0.05).</td>
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<td>Australia (165)</td>
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<td>Das 2007,</td>
<td>Cross-sectional</td>
<td>221 IDU (only 2 women); median age = 26 years</td>
<td>12</td>
<td>Current drug injection (Proxyvon vs. heroin)</td>
<td>HCV</td>
<td>Prevalence of HCV was significantly lower among exclusively proxyvon injectors compared to exclusively heroin injectors (n=27 [23.9%] vs. 5 [45.4%], p&lt;0.05).</td>
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<td>India (154)</td>
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<td>Degenhardt 2006, Australia (168)</td>
<td>Cross-sectional (IDRS)</td>
<td>795 IDU recruited through street outreach; mean age = 33.8 years</td>
<td>12</td>
<td>Current morphine injectors (vs. exclusively heroin injectors)</td>
<td>Current (previous month) injection site harms (abscesses/infections/, bruising/scarring); lifetime overdose</td>
<td>Recent morphine injection was not significantly associated with injection site harms at the multivariable level. Morphine injectors were as likely as heroin injectors to have experienced a lifetime heroin overdose (p&gt;0.05).</td>
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<tr>
<td>Fischer 2004, Canada (163)</td>
<td>Cross-sectional (OPICAN study)</td>
<td>651 untreated opiate users from 5 cities, recruited through street outreach; mean age = 34.8 years</td>
<td>15</td>
<td>Hydromorphone injection in the previous six months</td>
<td>Overdose in the previous six months</td>
<td>Those who injected hydromorphone were not significantly more likely to report an overdose compared to those who did not inject hydromorphone, at the multivariable level.</td>
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<tr>
<td>Hadland 2014, Canada (99)</td>
<td>Cohort (At-Risk Youth Study)</td>
<td>940 street youth recruited through street outreach; mean age = 21.7 years</td>
<td>15</td>
<td>PO injection (morphine, oxycodone, hydromorphone, meripidine, fentanyl, methadone) in the previous six months</td>
<td>HCV</td>
<td>PO injection was significantly and positively associated with HCV seropositivity at baseline (OR = 8.69 [5.01-15.1]), but was not significantly associated with HCV seroconversion in the multivariable longitudinal model.</td>
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<tr>
<td>Havens 2007, USA (44)</td>
<td>Cross-sectional</td>
<td>184 PO users recruited through street outreach; median age = 30 years</td>
<td>12</td>
<td>PO injection (oxycodone, methadone, hydrocodone) in the previous month</td>
<td>HCV and HBV status; psychiatric assessment (ASI composite score)</td>
<td>Significantly more people who inject POs self-reported HCV compared to those who did not inject POs (n=9 [14.8%] vs. 2 [1.7%], p&lt;0.05). PO injectors and non-injectors did not differ in HBV prevalence (n=4 [6.6%] vs. 2 [1.7%], p&gt;0.05); Mean psychiatric score did not significantly differ between PO injectors and non-injectors (0.27 vs. 0.26, p&gt;0.05).</td>
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<tr>
<td>Havens 2011, USA (162)</td>
<td>Cross-sectional (SNAP study)</td>
<td>400 rural drug users recruited through street outreach; median age = 31 years</td>
<td>15</td>
<td>Lifetime PO injection (oxycodone, methadone, hydrocodone)</td>
<td>Number of lifetime overdoses</td>
<td>Lifetime PO injection was marginally significantly and positively associated with number of non-fatal overdoses (AIRR = 1.58 [1.01-2.49]).</td>
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<td>Study</td>
<td>Study design</td>
<td>Participants characteristics</td>
<td>Score</td>
<td>Exposure(^1)</td>
<td>Outcome(s)</td>
<td>Main Findings</td>
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<tr>
<td>Havens 2013, USA (148)</td>
<td>Cross-sectional (SNAP study)</td>
<td>392 rural IDU recruited through street outreach; median age = 31 years</td>
<td>15</td>
<td>Lifetime PO injection (oxycodone, methadone, hydrocodone)</td>
<td>HCV</td>
<td>PO injection was significantly and positively associated with HCV seropositivity (AOR = 2.22 [1.13-4.35]).</td>
</tr>
<tr>
<td>Humeniuk 2003, Australia (166)</td>
<td>Cross-sectional</td>
<td>365 heroin users recruited through street outreach; mean age = 28.9 years</td>
<td>11</td>
<td>Methadone injection in the previous six months</td>
<td>Number of heroin overdoses(^1); Heroin dependence (Severity of Dependence Scale (SDS))</td>
<td>Current methadone injectors reported a marginally significantly higher mean (1.8 vs. 1.4) and median (1 vs. 0) number of lifetime heroin overdoses than those who did not inject methadone (both (p&lt;0.05)). Methadone injectors were significantly more dependent on heroin than non-injectors (mean SDS score =8.9 vs. 6.4, (p&lt;0.05)).</td>
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<tr>
<td>Iversen 2010, Australia (152)</td>
<td>Series of cross-sectionals</td>
<td>15,852 IDU recruited from Needle and Syringe Program (NSP) sites; mean age = 31 years</td>
<td>16</td>
<td>Drug last injected (methadone/buprenorphine, other POs, heroin, or other vs. methamphetamine)</td>
<td>HCV</td>
<td>Among inexperienced ((\leq)4 years) IDU, women who injected methadone or buprenorphine (AOR = 4.78 [2.63-8.70]) and other POs (AOR = 2.20 [1.24-3.90]) had significantly increased odds of HCV seropositivity. Among men in this group, injection of both methadone/buprenorphine (AOR = 3.06 [1.58-5.92]) and other POs (AOR = 1.77 [1.03-3.04]) were significantly but less strongly associated with HCV seropositivity.</td>
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<tr>
<td>Jenkins 2011, USA (164)</td>
<td>Cross-sectional</td>
<td>447 opioid users recruited from NSPs; median age = 38 years</td>
<td>15</td>
<td>Methadone and other PO injection in the previous year</td>
<td>Opioid overdose in the previous year(^1)</td>
<td>Neither methadone nor PO injection were significantly associated with non-fatal overdose (both (p&gt;0.05)).</td>
</tr>
<tr>
<td>Jenkinson 2005, Australia (170)</td>
<td>Cross-sectional (Illicit Drug Reporting System)</td>
<td>156 IDU recruited through street outreach; mean age = 30 years</td>
<td>12</td>
<td>Buprenorphine injection in the previous six months</td>
<td>Past month injection-related health problems (overdose, abscesses, scarring/bruising, thrombosis)(^1)</td>
<td>Injection-related health problems were more common among buprenorphine injectors at the bivariable level ((p&lt;0.05)), but not the multivariable level.</td>
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<tr>
<td>Study</td>
<td>Study design</td>
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<td>Score</td>
<td>Exposure&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>Kerr 2007, Canada</td>
<td>Cohort (VIDUS &amp; ACCESS)</td>
<td>1587 IDU recruited through street outreach; median age = 33.4 years</td>
<td>15</td>
<td>Morphine injection in the previous six months</td>
<td>Overdose in the previous six months&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Morphine injection was significantly associated with non-fatal overdose in bivariable analyses, but did not remain significant in the multivariable model (p&gt;0.05).</td>
</tr>
<tr>
<td>Lankenau 2015, USA</td>
<td>Cross-sectional</td>
<td>162 PO-using young IDU, recruited through street outreach; mean age = 21.4</td>
<td>14</td>
<td>Lifetime PO (prescription pain pills) injection</td>
<td>HCV status&lt;sup&gt;1&lt;/sup&gt;; psychiatric institution ever&lt;sup&gt;1&lt;/sup&gt;</td>
<td>HCV-positive IDU were significantly more likely to report lifetime injection of POs (AIRR = 2.69 [1.07-6.78]); PO injectors reported a marginally significantly higher rate of psychiatric institutionalization (IRR 1.24 [1.01-1.50]).</td>
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<tr>
<td>Mahanta 2009, India</td>
<td>Cross-sectional</td>
<td>398 IDU recruited from drop-in centers; median age = 26 years</td>
<td>11</td>
<td>Type of drug(s) injected in the previous six months (Proxyvon only, heroin only, and both)</td>
<td>HIV, HCV</td>
<td>Compared to those who only injected heroin, those who injected Proxyvon only had significantly lower odds of being HIV positive (AOR = 0.27 [0.10-0.71]) HCV positive (AOR = 0.42 [0.24-0.71]), and HIV/HCV co-infected (AOR = 0.23 [1.10-0.5]).</td>
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<tr>
<td>Obadia 2001, France</td>
<td>Cross-sectional</td>
<td>343 IDU recruited from harm reduction sites; median age = 30</td>
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<td>Drug(s) injected in the previous six months (only buprenorphine vs. other)</td>
<td>HIV status&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Buprenorphine injectors experienced significantly lower rates of HIV (AOR = 0.63 [0.41-0.94]).</td>
</tr>
<tr>
<td>Ojha 2014, Nepal</td>
<td>Cross-sectional</td>
<td>300 IDU from treatment facilities; mean age = 28.7 years</td>
<td>10</td>
<td>Injection of buprenorphine cocktail (buprenorphine, benzodiazepine, antihistamine) in the previous month (intensive, moderate, no use)</td>
<td>HIV, HCV, co-infection, physical and mental health problems&lt;sup&gt;1&lt;/sup&gt;, serious health problems&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Prevalence of mental health problems were higher for intensive cocktail injectors compared to non-injectors (mean MAP score 2.0 vs. 1.7, p&lt;0.05); physical health problems, HIV, HCV did not differ across groups (all p&gt;0.05); rate of HIV/HCV co-infection increased with injection intensity (47.7% for intensive, 31.4% for moderate, 18.6% for none [p&lt;0.05]); 23.2% intensive injectors reported ‘serious health problems’ vs. 4.7% of non-injectors (p&lt;0.05).</td>
</tr>
<tr>
<td>Study</td>
<td>Study design</td>
<td>Participants characteristics</td>
<td>Score</td>
<td>Exposure</td>
<td>Outcome(s)</td>
<td>Main Findings</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>Pabayo 2013, Canada (161)</td>
<td>Cohort (VIDUS &amp; ACCESS)</td>
<td>1931 IDU recruited through street outreach; 96.4% above age 20</td>
<td>16</td>
<td>Morphine injection in the previous six months</td>
<td>Overdose in the previous six months&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Morphine injection not a significant predictor of overdose for men (AOR = 1.04 [0.81-1.35]), but was for women (AOR = 1.81 [1.24-2.64]).</td>
</tr>
<tr>
<td>Roux 2008, France (176)</td>
<td>Cohort</td>
<td>111 patients on buprenorphine maintenance treatment; mean age = 38.0 years</td>
<td>15</td>
<td>Buprenorphine injection in the previous month</td>
<td>lifetime overdose at baseline&lt;sup&gt;1&lt;/sup&gt;, lifetime suicide attempt or ideation at baseline&lt;sup&gt;1&lt;/sup&gt;, past year alcohol dependence (CAGE), substance dependence (heroin, cocaine, poly-drug)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Overdose and history of suicide attempt/ideation were significantly associated with buprenorphine injection at the bivariable level. In multivariable analysis, suicide attempt/ideation remained significantly associated with buprenorphine injection (AOR = 2.6 [1.2-5.7]). Buprenorphine injection was not significantly associated with any measure of substance dependence.</td>
</tr>
<tr>
<td>Silva 2013, USA (125)</td>
<td>Cross-sectional</td>
<td>596 young adults who use prescription drugs illicitly, recruited through street outreach; mean age = 20.9 years</td>
<td>15</td>
<td>Lifetime PO (oxycodone, hydromorphone, morphine, hydrocodone, other) injection</td>
<td>Lifetime overdose&lt;sup&gt;1&lt;/sup&gt;</td>
<td>PO injection was associated with overdose in bivariable analyses (OR = 3.68 [2.45-5.53]), but did not remain significant in the final multivariable model.</td>
</tr>
<tr>
<td>Surratt 2011, USA (177)</td>
<td>Cross-sectional</td>
<td>791 PO users recruited through street outreach and treatment facilities; mean age = 34.5 years.</td>
<td>14</td>
<td>PO injection (hydrocodone, hydromorphone, oxycodone, morphine, methadone, codeine) in the previous three months</td>
<td>Past-year substance dependence (DSM-IV)</td>
<td>PO injection was significantly associated with increased odds of substance dependence (OR = 4.04 [1.23-13.3]).</td>
</tr>
<tr>
<td>Talu 2010, Estonia (156)</td>
<td>Cross-sectional</td>
<td>350 IDU recruited through street outreach; mean age = 23.9 years</td>
<td>12</td>
<td>Main injection drug (Fentanyl vs. amphetamine)</td>
<td>HIV and lifetime overdose&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Primary fentanyl injection was associated with increased odds of testing positive for HIV (AOR = 2.89 [1.55-5.39]) and lifetime overdose (AOR = 3.02 [1.65-5.54]).</td>
</tr>
<tr>
<td>Study</td>
<td>Study design</td>
<td>Participants characteristics</td>
<td>Score</td>
<td>Exposure(^1)</td>
<td>Outcome(s)</td>
<td>Main Findings</td>
</tr>
<tr>
<td>---------------</td>
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<td>------------------------------------------------------------------------------</td>
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<td>----------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Wylie 2006, Canada (147)</td>
<td>Cross-sectional</td>
<td>369 IDU recruited through street outreach.</td>
<td>16</td>
<td>Talwin/Ritalin injection and morphine injection in the previous six months</td>
<td>HIV, HCV, HBV</td>
<td>Talwin/ritalin injection was associated with higher odds of HCV (OR = 3.1 [1.9-4.9]) and HBV (OR = 3.1 [1.9-4.9]), but not HIV (OR=1.3 [0.6-3.1]). Morphine injection was not associated with any outcome (all p&gt;0.05).</td>
</tr>
<tr>
<td>Zibbell 2014, USA (100)</td>
<td>Cross-sectional</td>
<td>123 rural young adult IDU</td>
<td>15</td>
<td>PO injection (oxymorphone, oxycodone, hydromorphone, morphine, hydrocodone) in the previous six months</td>
<td>HCV</td>
<td>PO injection was independently associated with HCV positivity (AOR = 5.53 [1.92-15.91]).</td>
</tr>
</tbody>
</table>

\(^1\)Self-reported
3. THE EFFECT OF PRESCRIPTION OPIOID INJECTION ON NON-FATAL OVERDOSE AMONG PEOPLE WHO INJECT DRUGS

3.1. INTRODUCTION

An epidemic of opioid-related overdose deaths in North America has followed substantial increases in the use of prescription opioids (POs (32, 102, 130)). The use of diverted POs among high-risk substance-using populations, including people who inject drugs (IDU), has also increased (45, 205). While alarmingly high rates of PO injection have been documented in rural areas where access to a range of illicit drugs may be limited (44), accounts from urban drug centers have also demonstrated that despite high accessibility to other injectable opioids (i.e., heroin), PO injection has increased in prevalence (47). While the association between PO use and accidental overdose in the general public has been well-established (101, 106, 206), the impact of PO use on overdose among long-term drug users, such as IDU, is not known.

Overdose is a leading cause of morbidity and mortality among IDU (207-209). Non-fatal overdoses are also of concern due to how frequently they are experienced by IDU: roughly 30-45% of IDU have experienced at least one overdose in their lifetime (67, 160, 162, 210, 211), and as many as 20% report overdosing in the previous year (211). The potential health implications of non-fatal overdose are substantial and include peripheral neuropathy, temporary limb paralysis, stroke, hypoxia and brain injury, renal failure, and seizures (209, 212). Furthermore, those who have survived an

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2 A version of this chapter will be submitted for publication: Lake S, Hayashi K, Buxton, J, Milloy MJ, Dong H, Montaner J, and Kerr T. The effect of prescription opioid injection on non-fatal overdose among people who inject drugs in a Canadian setting
overdose are at a heightened risk for future overdose (213, 214), including fatal overdose (215). Finally, non-fatal overdoses are among the most common reasons IDU visit the emergency department (216), posing a major financial burden on the health care system.

Past research has identified a significant positive association between PO use (i.e., oral, intranasal, or injection) and non-fatal overdose (217), and has also found that among PO-using young adults, overdose is more likely to be experienced by those who inject POs (125). However, studies that have explored PO injection as a potential risk factor for overdose among experienced IDU are scarce. While many IDU have long-term experience with heroin injection, the harms associated with PO injection may be perceived as comparatively less threatening; despite similarities in pharmacological effect (2), key differences in the composition and preparation of these two types of drugs may produce different overdose risks. For example, whereas POs are manufactured for licit use and maintain consistent doses and purities, these characteristics may be unpredictable in heroin due to its roots in unregulated illicit drug market (218). In turn, the consistent nature of POs could result in a reduced likelihood of overdose among experienced opioid users who inject them.

As PO injection becomes more prevalent among high-risk drug using populations, understanding the effect of PO injection among IDU is critical to overdose prevention efforts. The present study therefore aims to investigate the effect of PO injection on non-fatal overdose among IDU.
3.2. METHODS

3.2.1. Study Sample

This study included participants from the VIDUS and ACCESS ongoing prospective cohorts, described in detail in Chapter 1, section 5.2. The present analysis was restricted to participants who completed a baseline questionnaire and at least one follow-up questionnaire between December 2005 and May 2014, and who reported active (i.e., previous six month) injection drug use.

3.2.2. Measures

For this analysis, the outcome of interest was self-reported non-fatal overdose in the previous six months. Consistent with previous work on non-fatal overdose in this cohort (160), participants who responded ‘yes’ to the question “In the previous six months, have you overdosed by accident (i.e. where you had a negative reaction from using too much drugs)?”, were considered recent overdose survivors. PO injection was assessed through the question: “In the last six months, which of the following drugs did you inject?”, to which participants were provided a list and pictures of common POs. The list underwent yearly modifications in order to reflect up-to-date trends in the types of illicit POs used. The most recent questionnaire included oxycodone (OxyNeo, OxyContin, Percocet), hydromorphone (Dilaudid), morphine, meperidine (Demerol), methadone, fentanyl, and pentazocine (Talwin). Participants were also given the option of specifying other POs that were not on the list. The primary exposure variable was then separated into four categories: no opioid injection (reference category); PO injection exclusive of heroin injection (category 2); heroin use exclusive of POs (category 3); and co-occurring heroin and POs (category 4).
Based on previously established associations with non-fatal overdose, various potential sociodemographic and substance use-related confounders were examined. Sociodemographic confounders were: age (per year older); gender (male vs. female); ethnicity (Caucasian vs. other); recent homelessness (yes vs. no); and recent incarceration (yes vs. no). Behavioural/drug-related characteristics were: binge drug use (yes vs. no); injecting in public (yes vs. no); requiring help injecting (yes vs. no); enrolled in a methadone maintenance program (yes vs. no); heavy alcohol use, defined as >14 drinks per week or >4 drinks on one occasion for men, and >7 drinks per week or >3 drinks on one occasion for women (219), yes vs. no; cocaine injection (yes vs. no); methamphetamine use (yes vs. no); benzodiazepine use (yes vs. no); crack smoking (yes vs. no); and non-injection PO use (yes vs. no). All behavioural and substance use-related characteristics as well as recent incarceration and recent homelessness refer to events or behaviours in the previous six months.

3.2.3. Analysis

First, the bivariable relationships between each independent variable and non-fatal overdose were examined using generalized estimating equations (GEEs) with logit link for correlated data (220). This method uses an exchangeable correlation structure to provide standard errors adjusted by multiple observations per individual (i.e., data from each participant’s follow-up visits), and was chosen due to the repeated binary outcome measure for each participant. This method has been used successfully in previous overdose studies (213, 221). Next, we built a full multivariable GEE model that included all variables significantly associated with the outcome at \( p<0.10 \) in the bivariable model. Using a conservative stepwise backward selection approach, a series of reduced models were fitted to compare the coefficient value associated with the main explanatory variable in the full model to its corresponding
value in each of the reduced models, and the secondary variable associated with the smallest relative change was dropped. This iterative process continued until the minimum change exceeded 5%. All analyses were performed in SAS software version 9.3 (SAS Institute Inc., Cary, NC). All $p$-values are two-sided.

3.3. RESULTS

Between December 2005 and May 2014, a total of 2000 people provided informed consent and were enrolled in this study. Of these, 214 (10.7%) participants were excluded for not completing a minimum of one baseline and one follow-up questionnaire. A further 126 (7.1%) participants did not inject drugs over the study period and were excluded. Thus, the final analytic sample consisted of 1660 IDU, including 559 (33.7%) women, who contributed a total of 10,909 observations. The median number of follow up visits was 5 (interquartile range [IQR]: 2 – 10). The baseline median age of the sample was 42.1 years (IQR: 35.5 – 48.0).

The proportion of IDU reporting recent injection of POs during the previous six months ranged from 16.3% to 35.1% (median: 24.5%), with rates peaking between June and November 2007. Figure 3.1 presents a visual summary of the proportion of participants reporting PO injection at each follow-up study period over the entire study period. Heroin was the most commonly injected opioid, with 30.1% – 49.3% (median: 40.5%) of IDU reporting exclusive heroin injection in the previous six months and 10.9% - 29.7% (median: 19.4%) reporting injection of both heroin and POs. A small proportion of IDU (2.7% - 6.6%, median: 5.4%) injected POs exclusive of heroin at each follow-up. At the most recent follow-up (December 2013 – May 2014), morphine and hydromorphone were by far the most frequently injected POs (Figure 3.2). Median prevalence of overdose at each follow-up period was 6.0% (IQR: 4.9% –
7.1%), with the highest rate being reported at 8.8% between December 2012 and May 2013. By the end of the study period, a total of 413 (24.9%) individuals experienced a total of 670 non-fatal overdoses. Table 1 summarizes sample baseline characteristics of the sample, stratified by opioid injection status.

Figure 3.1. Percent of VIDUS and ACCESS participants reporting PO injection in the previous six months at each study follow-up period, December 2005 – May 2014
In the multivariable GEE analysis (table 3.2, figure 3.3), exclusive PO injection was not independently associated with overdose (adjusted odds ratio [AOR]: 1.17, 95% confidence interval [CI]: 0.74 – 1.86); however, participants who injected heroin but not POs had significantly increased odds of overdosing (AOR: 1.72, 95% CI: 1.31 – 2.27), and those who injected both heroin and POs exhibited the highest odds of overdosing (AOR: 2.46, 95% CI: 1.83 – 3.30), compared to those who did not recently inject an opioid. Other factors positively associated with non-fatal overdose in the multivariable model included incarceration (AOR: 1.73, 95%CI: 1.40 – 2.13), public injecting (AOR: 1.46, 95% CI: 1.20 – 1.79), requiring help injecting (AOR: 1.51, 95% CI: 1.22 – 1.88), heavy alcohol use (AOR: 1.30, 95% CI: 1.04 – 1.62), and non-injection PO use (AOR: 1.44, 95% CI: 1.14 – 1.84). Methadone maintenance treatment was negatively associated with overdose (AOR: 0.72, 95% CI: 0.59 – 0.86).
Figure 3.3. Odds ratio estimate of association with non-fatal overdose, by opioid injection status (n = 1660), adjusted for incarceration, public injecting, assisted injecting, methadone maintenance treatment, heavy alcohol use, and PO non-injection.

3.4. DISCUSSION

Over the study period, approximately one-quarter of participants reported recent injection of POs, which is comparatively lower than the roughly one-half (93) and three-quarters (45) of IDU who report injecting POs from other studies in Canada. These comparatively lower PO injection rates may reflect the presence of a local, well-established heroin market (48). Similar rates of PO injection could only be identified in
studies of PO users (i.e. IDU and non-IDU) rather than IDU (44, 222). A detailed
discussion of the change in prevalence over the study period will be provided in
Chapter 5. The past six month prevalence of non-fatal overdose (median: 4.2%) is also
low compared with drug-using populations in other settings (163, 223).

A handful of studies have examined the relationship between PO injection and
non-fatal overdose among IDU, including two that found no association (163, 164) and
one that found a moderately significant association (162); however, this appears to be
the first study of non-fatal overdose that considers the unique effect of PO injection in
comparison to heroin injection, as well as the combined impact of both heroin and PO
injection. In doing so, a small proportion (3 – 7%) of people who injected POs but not
heroin was identified, while a consistently large proportion (30 – 50%) who injected
heroin but not POs, and a relatively variable moderate-to-large sized proportion (11 –
30%) who injected both types of opioids were identified. These findings are interesting
in light of widespread concern related to opioid overdoses in the general population,
as PO-related overdoses are a leading cause of injury-related death in the North
America (224, 225). It appears that exclusive PO injection may not pose a major threat
for overdose, compared to IDU who do not inject opioids. This finding might be
partially explained by simply the avoidance of heroin, which is known to undergo
potency fluctuations and composition inconsistencies (126, 226, 227), in favour of POs,
which provide a consistent and reliable dose and composition. In fact, there have been
several documented periods of overdoses (fatal and non-fatal) in the study region
being linked with unusually highly potent and/or tainted heroin (228). However, it
has been argued that opioid concentration alone may only play a minor – and
sometimes insignificant – role in predicting overdose (229, 230). The small group of
PO-only-using IDU in this study might also differ from concurrent PO and heroin
users in various ways that comparatively minimize risk for overdose. For example,
since heroin is readily available in this setting, people who inject POs may have a preference for POs for a specific purpose, such as self-management of pain or as a means of reducing use of heroin ("self-treating" opioid dependence or withdrawal) – both of which have been previously documented among people who use POs illicitly (196, 204, 231, 232). Furthermore, qualitative exploration in this environment has revealed a small subset of IDU who choose to inject POs rather than heroin as a sort of harm reduction method, as the consistent purity and dosage of POs allows for the ability to more accurately monitor drug intake (Kerr T 2015, personal communication, May 27). As research continues to characterize motives for engaging in non-medical PO use among more generalized populations (197, 233, 234), future qualitative studies may be needed to help to uncover motive-specific PO use among IDU.

Despite the absence of an association between exclusive PO use and overdose when compared with non-opioid-using IDU, the majority of those who injected POs in this study also reported injecting heroin, and these individuals are at a much greater risk of overdose. An earlier study amongst these two cohorts noted a significant and positive relationship between PO use (i.e. injection and non-injection) and overdose (217). Based on the results of the current study, which controlled for non-injection PO use, some underlying trends in this previously noted association were identified; namely, those who are injecting POs in addition to heroin during the same period may have accounted for the bulk of this previous group’s risk for overdose. Those who administrated POs by non-injection routes may have also contributed to this risk; as shown in table 3.2, non-injection PO use was considered as a secondary independent variable, and was significantly associated with overdose. One possible explanation for this finding is the recent local emergence of counterfeit tablets branded as OxyContin, which actually contain illicitly manufactured fentanyl (235). Some users who prefer to swallow or snort oxycodone may be inadvertently
ingesting fentanyl, which is a much more potent opioid (236). IDU who use both types of opioids may be those who predominantly use heroin but will use POs when more easily available, as has been documented through qualitative exploration (237). Based on previous work characterizing PO-using IDU, these individuals might also be more likely to engage in higher-risk drug use (45, 93, 98, 238). This interpretation is also in line with descriptive trends observed at baseline in the present study (Table 3.1). Finally, the strong association with non-overdose identified among this sub-sample of poly-opioid users is consistent with reports pointing to the detection of other illicit substances in a large portion of PO-attributable overdose deaths (135, 193, 239).

There may be interacting micro-environmental factors operating in the broader risk environment of IDU that modify susceptibility to overdose among PO users. For example, qualitative research has described the long process of injecting a PO, which often involves transforming a pill into a liquid, and requiring multiple consecutive injections in order to consume the entire dose (141). As such, this process tends to involve more time and paraphernalia than readily injectable drugs, such as heroin or cocaine. In public spaces, where many IDU are forced to inject, rushing the preparation and injection steps required for POs may lead to a differential risk for overdose. Some studies have also documented increased physical injection site-related problems among PO injectors (e.g. scarring, bruising, thrombosis, collapsed veins (165, 167, 169)). Experiencing such problems can lead to having difficulty injecting, and potentially seeking injection help from a fellow IDU, which is a well-known risk for overdose in the current setting (160, 240). Qualitative research that can identify the contextual determinants of PO use will be useful in the future to understand how risk might be modified by social and structural factors.

The findings of the present study suggest several implications for policy and programming aimed at reducing harms among people who use illicit drugs, including
strengthening the rationale for scaling-up the distribution of naloxone – an opioid antagonist that can effectively reverse an opioid overdose (241, 242). Since illicit PO use remains prevalent among IDU in this setting, increasing awareness of take-home naloxone among PO-using IDU, especially those who also use heroin, is crucial for preventing fatal overdose. Providing training for such programs is an opportunity to connect opioid users with community services, and to empower them to make a difference in their community (243, 244). Partnerships between community-based organizations, health care providers, and particularly governing health bodies are needed to enable naloxone programs reach their full life-saving potential. Second, considering the complexities of preparing a PO for injection, supervised injection sites (SIFs) are critical to minimizing the harms that other environments may present. The current findings support the continued use and expansion, of such facilities to ensure that people who inject POs – especially those who also inject heroin – are being served.

As will be explored in further depth in Chapter 5, section 3, the injection of POs appears to be inevitable in spite of various so-called abuse-deterrent formulas (245, 246), and the de-listing of certain POs in the province (e.g. OxyContin) may actually foster dangerous drug transitions (e.g. from primarily injecting PO to primarily injecting heroin (247)). With this in mind, research should continue to explore strategies that minimize the harm associated with injecting POs (e.g., exploring single-use syringe filters, such as Sterifilt® (140)) in order to facilitate safer injection of the substance, and to reduce transitions to more dangerous opioid injection. Finally, the prescribing of opioids as a substitution treatment shows promise in its ability to reduce overdoses. While various studies (including the present study; AOR: 0.72, \( p<0.05 \)) demonstrate the protective effect opioid substitution treatment (OST) has on overdose (160, 248-250), traditionally prescribed OST (e.g., methadone) fails for a
significant portion of severely addicted individuals (251, 252). In recent years, several randomized controlled trials have shown the prescribing of injectable diacetylmorphine (prescription heroin) to be a safe alternative treatment to methadone for these individuals (253-256). Notably, injectable diacetylmorphine appears to be significantly more effective than methadone in reducing co-occurring illicit drug use for some IDU (253, 254), which could prove beneficial in reducing overdose, pending medically supervised treatment.

This study is subject to some limitations. Those that are shared by the current study and the following study (Chapter 4) will be discussed in the thesis conclusion (Chapter 5, section 4.2). However, there were also certain limitations specific to this study. First, this study used a broad definition of overdose, which may have introduced bias to the outcome measure; however, this broad definition of overdose is considered advantageous in the current setting, where poly-drug use is common. This study was unable to capture data related to fatal overdoses, and may have missed any non-fatal overdoses associated with loss-to-follow-up (e.g., an overdose leading to an extended hospital stay). While the majority of diverted POs are regulated pharmaceuticals (37, 257), there may have been cases where an illicitly-manufactured PO was injected (e.g., illicit fentanyl). It is acknowledged that in building the main independent variable, participants who injected ‘speedballs’ (i.e. heroin and cocaine) or ‘goofballs’ (i.e. heroin and methamphetamine) may have been misclassified into the ‘PO only’ or reference groups. However, based on the poly-substance-using nature surrounding the injection of heroin cocktails, it is estimated that only a small number of participants may have been misclassified as non-heroin injectors by the independent variable. The current study was not able to identify these cases. Finally, although a strength of this study was the ability to examine associations at various points over a long period of time, it was not possible to determine the timing of each
event within each six-month period (e.g., whether an overdose occurred before, after, or during the reported PO injection events).

In conclusion, the present study demonstrated that, after controlling for co-occurring non-opioid illicit drug use, people who inject POs and heroin and those who inject heroin but not POs are both at a significantly increased risk of overdose, with the latter group exhibiting the highest risk. Those who injected POs but not heroin were not at an increased risk of overdose compared with non-opioid users. These findings highlight the importance of reaching people who inject POs - particularly those who also inject heroin – with the scale-up of proven structural-level overdose prevention programs, including addiction treatment and harm reduction. Finally, given the ongoing and widespread injection of POs within IDU populations, harm reduction interventions that consider the unique differences between POs and heroin (e.g., sterile paraphernalia for PO injection preparation) should continue to be explored.
Table 3.1. Descriptive characteristics of 1660 IDU in Vancouver at baseline, stratified by opioid injection status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (%)</th>
<th>Opioid Injection* (n = 488)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 1660)</td>
<td>PO Only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n = 51)</td>
</tr>
<tr>
<td><strong>Socio-demographic factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Med, IQR)</td>
<td>42.1</td>
<td>41.7</td>
</tr>
<tr>
<td>Male</td>
<td>1101 (66.3)</td>
<td>35 (68.6)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>992 (59.8)</td>
<td>33 (64.7)</td>
</tr>
<tr>
<td>Homeless†</td>
<td>564 (34.0)</td>
<td>15 (29.4)</td>
</tr>
<tr>
<td>Incarcerated†</td>
<td>282 (17.0)</td>
<td>5 (9.8)</td>
</tr>
<tr>
<td><strong>Substance use-related factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binge drug use†</td>
<td>673 (40.5)</td>
<td>21 (41.2)</td>
</tr>
<tr>
<td>Injected in public†</td>
<td>617 (37.2)</td>
<td>12 (23.5)</td>
</tr>
<tr>
<td>Needed help injecting†</td>
<td>396 (23.9)</td>
<td>13 (25.5)</td>
</tr>
<tr>
<td>MMT¥</td>
<td>710 (42.8)</td>
<td>18 (35.3)</td>
</tr>
<tr>
<td>Heavy alcohol use†</td>
<td>271 (16.3)</td>
<td>6 (11.8)</td>
</tr>
<tr>
<td>Any cocaine injection†</td>
<td>859 (51.7)</td>
<td>15 (29.4)</td>
</tr>
<tr>
<td>Any crystal meth use†</td>
<td>397 (23.9)</td>
<td>17 (33.3)</td>
</tr>
<tr>
<td>Any benzo use†</td>
<td>28 (1.7)</td>
<td>3 (5.9)</td>
</tr>
<tr>
<td>Any crack smoking†</td>
<td>1303 (78.5)</td>
<td>35 (68.6)</td>
</tr>
<tr>
<td>Any PO non-injection†</td>
<td>110 (6.6)</td>
<td>5 (9.8)</td>
</tr>
<tr>
<td>Non-fatal overdose†</td>
<td>113 (6.8)</td>
<td>2 (3.9)</td>
</tr>
</tbody>
</table>

† Denotes events in the previous 6 months

¥ MMT = Methadone maintenance treatment
Table 3.2. Bivariable and multivariable GEEs of factors associated with recent non-fatal overdose among 1660 IDU from Vancouver, Canada

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio (95% CI)</th>
<th>Unadjusted</th>
<th>p-value</th>
<th>Adjusted</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of opioid injected</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.00</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PO only</td>
<td>1.34 (0.86 - 2.09)</td>
<td>0.190</td>
<td>1.17 (0.74 - 1.86)</td>
<td>0.505</td>
<td></td>
</tr>
<tr>
<td>Heroin only</td>
<td>1.92 (1.48 - 2.48)</td>
<td>&lt;0.001</td>
<td>1.72 (1.31 - 2.27)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Both PO and heroin</td>
<td>3.40 (2.60 - 4.43)</td>
<td>&lt;0.001</td>
<td>2.46 (1.83 - 3.30)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Per year older</td>
<td>0.99 (0.98 - 1.00)</td>
<td>0.110</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Male</td>
<td>1.03 (0.83 - 1.28)</td>
<td>0.800</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
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<td></td>
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<td>Other</td>
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<td>Caucasian</td>
<td>1.13 (0.91 - 1.41)</td>
<td>0.277</td>
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<td><strong>Homeless</strong></td>
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<td></td>
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</tr>
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<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Yes</td>
<td>1.64 (1.36 - 1.97)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td><strong>Incarcerated</strong></td>
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<td></td>
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</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>2.20 (1.78 - 2.71)</td>
<td>&lt;0.001</td>
<td>1.73 (1.40 - 2.13)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Binge drug use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>1.00</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>1.42 (1.20 - 1.67)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Injected in public</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>2.07 (1.72 - 2.50)</td>
<td>&lt;0.001</td>
<td>1.46 (1.20 - 1.79)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Needed help injecting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>1.79 (1.46 - 2.18)</td>
<td>&lt;0.001</td>
<td>1.51 (1.22 - 1.88)</td>
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<tr>
<td>Characteristic</td>
<td>Unadjusted</td>
<td>p-value</td>
<td>Adjusted</td>
<td>p-value</td>
<td></td>
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<tr>
<td>--------------------------------</td>
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<td></td>
</tr>
<tr>
<td><strong>Methadone program</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>0.67 (0.56 - 0.80)</td>
<td>&lt;0.001</td>
<td>0.72 (0.59 - 0.86)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Heavy alcohol use</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.32 (1.07 - 1.63)</td>
<td>0.010</td>
<td>1.30 (1.04 - 1.62)</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td><strong>Cocaine Injection</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>No</td>
<td>1.00</td>
<td></td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.10 (0.92 - 1.31)</td>
<td>0.310</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Crystal meth use</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.82 (1.50 - 2.21)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Benzodiazepine use</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.32 (0.79 - 2.21)</td>
<td>0.292</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Crack smoking</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.13 (0.93 - 1.37)</td>
<td>0.220</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>PO non-injection</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.89 (1.50 - 2.39)</td>
<td>&lt;0.001</td>
<td>1.44 (1.14 - 1.84)</td>
<td>0.003</td>
<td></td>
</tr>
</tbody>
</table>

<sup>v</sup> GEE: Generalized Estimating Equation, <sup>g</sup> 95% CI = 95% Confidence Interval, <sup>c</sup> In the previous six months
4. PRESCRIPTION OPIOID INJECTION AMONG HIV-POSITIVE PEOPLE WHO INJECT DRUGS IN VANCOUVER, CANADA

4.1. INTRODUCTION

The prescribing of opioids (POs) for non-cancer pain has increased substantially in the United States and Canada over the previous decade (258, 259), including among people living with HIV/AIDS (260). As discussed in previous chapters, this surge in PO use has coincided with higher levels of PO-related morbidity and mortality, including PO-attributed overdoses, in the general population (32, 104, 106). Meanwhile, among high-intensity substance-using populations, such as IDU, PO use has been linked with injection-related infections, including outbreaks of viral hepatitis among young, inexperienced injectors (100, 181), and, most recently, an outbreak of HIV in the US state of Indiana (261). A growing number of studies have revealed that people who inject POs are often more likely than their non-PO-using peers to engage in risky substance use behaviours (e.g., syringe sharing (93, 99)).

People living with HIV/AIDS commonly report suffering moderate-to-severe chronic physical pain (262, 263), and are prescribed long-term use of opioids at over twice the rate of HIV-negative people (264). Almost 15% of new HIV infections in

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3 A version of this chapter will be submitted for publication: Lake S, Kerr T, Buxton J, Milloy MJ et al. Prescription opioid injection among HIV-positive people who inject drugs in a Canadian setting.

Canada are attributed to injection drug use (71). Past research has identified correlations between increasing pain levels and likelihood of non-medical PO use and dependence (265, 266). In light of the growing popularity of PO injection among IDU (45, 99), and despite both the high prevalence of PO use among people living with HIV/AIDS and the ongoing burden of HIV/AIDS among IDU, the prevalence and determinants of PO injection among IDU living with HIV/AIDS appears to be absent from the literature.

Over the previous decade, many jurisdictions in North America and abroad have established Treatment as Prevention (TasP)-based initiatives to control the HIV/AIDS pandemic. The goal of TasP is to optimize HIV testing and access to highly active antiretroviral therapy (HAART) to reduce individual-level HIV-1 plasma viral loads (VL) to below detectable levels in order to prevent progression to AIDS and virtually eliminate the possibility of onward transmission. In order to achieve its goal, TasP-based strategies aim to scale-up engagement in HAART, especially among traditionally hard-to-treat HIV-positive groups such as IDU (73, 82, 267). Although scale-up of HAART has led to dramatic declines in HIV/AIDS-associated morbidity and mortality among many groups worldwide (82, 268), IDU continue to exhibit significantly poorer HIV disease outcomes (269, 270) and reduced life expectancies (271) compared with other HIV-infected individuals. To date, little research has examined the possible impact of PO injection on rates of ART engagement or treatment outcomes among HIV-positive IDU in the context of universal no-cost ART coverage. This study was therefore undertaken to examine the prevalence and various social-, structural-, behavioural-, and clinical-level correlates of PO injection among HIV-positive IDU in Vancouver, Canada, during a community-wide TasP initiative.
4.2. METHODS

4.2.1. Study Sample

This study included participants from the ACCESS ongoing prospective study, described in detail in Chapter 1, section 5.2. As outlined in previous work (75, 272), the local setting includes a universal healthcare system offered at no cost to the patient, and a province-wide centralized free HIV/AIDS laboratory monitoring and ART dispensation program. Through a confidential linkage to this laboratory and dispensary, the study accesses a complete retrospective and prospective profile of all participant CD4 cell counts and plasma HIV-1 RNA viral load tests as well as records detailing each dispensation of antiretroviral agents, including regimen type and dosage.

4.2.2. Measures

The current study includes ACCESS participants who completed at least one interview between December 2005 and November 2013 and who had provided a blood sample for a CD4 and HIV-1 plasma RNA count within 180 days of the baseline interview. Participants who did not have these measures within 180 days of their baseline interview were included at the earliest follow-up interview within 180 days of providing them. Observations were further restricted to periods of active injection drug use for each participant (i.e., reporting injection drug use ≥ 1 time in the six months before an interview).

Measures for PO injection in the previous six months were self-reported and obtained exactly as described in Chapter 3, section 2. Various socio-demographic, social, structural, drug-related, and clinical explanatory variables were also
considered as potential correlates of PO injection, including: age (per 10-year increase); gender (male vs. female); ethnicity (Caucasian vs. other); relationship status (married/common-law vs. single); highest level of education (> secondary school vs. ≤ secondary school); employment status (employed vs. unemployed); homelessness (yes vs. no); incarceration (yes vs. no); heroin injection (yes vs. no), cocaine injection (yes vs. no); crack smoking (yes vs. no); methadone maintenance treatment (yes vs. no); drug dealing (yes vs. no); and sex work (yes vs. no.) With the exception of age, gender, ethnicity, and education, all variables refer to events or exposures in the six-month period prior to the study interview. Finally, the following HIV-related clinical characteristics were examined: recent (previous six-month) engagement in antiretroviral therapy (ART, ≥ 1 day dispensed vs. 0 days); CD4 cell count (per 100 cells/mL); and HIV-1 RNA viral load (using the Roche Amplicor Monitor Assay [Roche Molecular Systems, Mississauga, Canada]) Consistent with previous work (273), both CD4 and VL measures used all the observations available in the records of the clinical monitoring laboratory from tests conducted by the study or by the participant’s physician in the community. For both, the median value of all observations conducted in the six months prior to the study interview was used, or – if none, the most recent observation. To assess the possible relationship between PO injection and risk of onward transmission, the VL variable was dichotomized at 1500 c/mL (274).

4.2.3. Analysis

As a first step, descriptive characteristics of study participants at baseline were observed, and used Pearson’s Chi-square and Wilcoxon rank sum tests were used to compare categorical and continuous independent variables, respectively, among those who did and did not report injecting prescription opioids. Generalized estimating
equations (GEE) were used to model bivariable and multivariable associations between independent variables and PO injection at each follow-up period. As described in Chapter 3, this approach uses repeated measures to identify factors potentially associated with a time-updated binary outcome over an entire study period (220). As participants may have injected POs during some six-month follow-up periods but not others, this model can estimate the within- and between-subject correlation of each characteristic with periods of PO injection and non-injection.

First, the bivariable relationship between each independent variable and PO injection was examined with the use of a GEE model. The initial GEE multivariable model was built from the set of variables that were significant at $p<0.2$ in bivariable analyses. Then, covariates were removed one-by-one, beginning with the covariate with the highest $p$-value, and model Quasi-Akaike information criterion (QIC) was examined for each of these reduced models. The final multivariable model was chosen based on lowest QIC. Because of the correlation between ART exposure and HIV-1 plasma viral load, and as ART exposure is hypothesized to be on a causal pathway to viral load, viral load was excluded from the multivariable model building procedure. Data was analyzed using R (version 2.15.1, R Foundation for Statistical Computing, Vienna, Austria). All $p$-values are two-sided.

4.3. RESULTS

Between December 2005 and November 2013, 830 ACCESS participants were recruited and provided informed consent. In total, 735 (88.6%) had at least one CD4 and VL determination and were eligible for inclusion. Of these, 101 (13.7%) participants did not report injecting drugs over the study period and were excluded from the analysis. Thus, the analytical sample consisted of 634 people during periods
of active injection drug use, including 210 (33.1%) women. Participants contributed a median of 4 (interquartile range [IQR]: 2 – 8) study interviews, or a total of 3311 observations. As displayed in Table 4.1 (see end of chapter), at baseline, the median age of participants was 42.9 (IQR: 36.6 – 48.3) and 413 (65.1%) received ≥ 1 day of ART in the previous six months. In the six months before their baseline interview, 171 (27.0%) participants reported injecting POs (Table 4.1), and at the most recent follow-up (November 2013), 24.5% of participants were injecting POs. The prevalence of recent (i.e., past six month) PO injection at each interview period ranged from 10.6% to 27.6% (median: 24.2%). The trend in previous six-month prevalence of PO injection over the study period is summarized graphically in Figure 4.1 below.

Table 4.2 (see end of chapter) presents a summary of the bivariable and multivariable odds ratio estimates from the GEE models. As shown, Caucasian ethnicity, homelessness, incarceration, heroin injection, crack smoking, drug dealing and a VL > 1500 c/mL were all positively associated with PO injection, while age, being on methadone maintenance and recent dispensation of ART were all negatively associated with periods of PO injection at the bivariable level (p<0.05). Factors that remained associated with PO injection in the multivariable GEE model were age (adjusted odds ratio [AOR]: 0.97, 95% confidence interval [CI]: 0.96 – 0.99), Caucasian ethnicity (AOR: 1.65, 95% CI: 1.21 – 2.27), heroin injection (AOR: 2.24, 95% CI: 1.85 – 2.72), methadone maintenance treatment (AOR: 0.76, 95% CI: 0.61 – 0.93), and drug dealing (AOR: 1.88, 95% CI: 1.57 – 2.25).
Figure 4.1. Percent of ACCESS participants reporting PO injection in the previous six months at each study follow-up period, December 2005 – November 2013

As a follow-up to the finding of ART dispensation being significantly and negatively associated with PO injection at the bivariable level but not at the multivariable level, various two-term models with recent ART dispensation as a constant in each model were explored in order to understand which factor(s) rendered this association insignificant. In these sub-analyses, the association between ART dispensation and PO injection lost its significance in models with either heroin injection or age as the second term (data not shown).

4.4. DISCUSSION

In this study, which is among the first to identify the prevalence and factors associated with PO injection among actively injecting HIV-positive IDU, approximately one-quarter (24.2%) of participants reported injecting POs at any point
during the study period. A detailed discussion of the trend in PO injection prevalence will be provided in Chapter 5. While no other prevalence estimates of PO injection could be identified among studies restricted to HIV-positive IDU, similar to Chapter 3, the current rates are lower compared to those recorded in other studies of IDU. Independent associations between PO injection and other high-risk drug- and disease-related factors were identified, including heroin injection, drug dealing, and not being on methadone maintenance treatment.

Periods of PO injection appear to be most prevalent alongside other high-risk substance use. For example, the odds of injecting POs were more than double for people who inject heroin in the present analysis. This association was hypothesized to be strong considering the psychoactive and physiological properties shared by both types of opioids, and previous qualitative research describing the frequent substitution of heroin with POs when heroin is not imminently available (275). Numerous studies have also demonstrated the high frequency of heroin injection among PO-using IDU (45, 93, 150, 168, 276). The finding of an association with crack smoking in the unadjusted model adds to ethnographic research undertaken elsewhere in Canada demonstrating a high rate of PO injection among people who primarily smoke crack (277), and reflects the high rate of polydrug use involving both opioids and stimulants in the present setting. A significant and negative independent association between periods of methadone maintenance therapy and periods of PO injection was also observed. As opioid substitution therapy (OST), including methadone maintenance therapy, has widespread health benefits for IDU, including increasing the likelihood of ART uptake and adherence (278-280), this finding highlights the need to reduce barriers for OST among HIV-positive people who inject POs, which should include the expansion of evidence-based OST options (e.g.,
A strong and independent association between drug dealing and PO injection was also observed in the present analysis. While drug dealing among IDU has been previously linked with other intensive drug use, including daily heroin and cocaine injection (281), this study may be the first to consider drug dealing in relation to PO injection. The diversion of POs is unique from traditional drug-dealing pathways in that, except in a few cases of illicitly manufactured POs (e.g., illicit fentanyl powders (190)), POs are manufactured for medical purposes. Research tracking mechanisms of diversion demonstrate that most illicitly used POs originate in the medical system (e.g., obtained through a family or friend’s prescription, “doctor shopping”, pharmacy theft, prescription forgery (222, 282)), rather than through unregulated and illegal manufacturing and importation methods common to other illicit drugs, such as heroin. Considering these distinctions, the present association may be reflective of a group of PO-only dealers that may have emerged in parallel with the surge in the availability of illicit POs that took place in this setting just before the study period began (48). In fact, in a study of people who use illicit drugs in New York City, roughly one quarter of PO dealers sold POs exclusively (204), suggesting the absence of such dealers without the presence of POs on the illicit market. A further in-depth analysis of this finding will be needed to investigate the possibility that PO injecting drug dealers constitute a new and distinct group of drug dealers, and to document whether they experience similar high-risk lifestyle patterns (e.g., incarceration, overdose (281), and violence (283)) common to illicit drug dealers in this setting.

The bivariable analysis revealed that periods of PO injection were characterized by lower odds of engagement in HIV treatment and higher odds of having a VL > 1500 c/mL. However, in a multivariable model that included recent ART dispensation
among a number of other socio-demographic and behavioural vulnerabilities, there was not a significant association between PO injection and the odds of receiving ≥ 1 day of ART in the previous 180 days. A sub-analysis to investigate the drivers of this attenuated result revealed that age and heroin injection both significantly reduced the association between PO injection and engagement on ART. In the systematic review (Chapter 2), one study was identified that examined factors associated with buprenorphine injection among HIV-positive patients undergoing buprenorphine maintenance therapy for opioid dependence (159). However, in this study, even the unadjusted estimates for viral load did not differ significantly between those who were and were not injecting buprenorphine (159). This finding also appears to differ from studies of less intensive (i.e., non-injection) PO use among other HIV-positive populations. For example, in HIV-positive American military veterans with high rates of illicit substance use, non-medical PO use was not related to viral load (284). Future research might want to consider how links between PO injection and micro-social vulnerabilities, such as incarceration and homelessness, may interact to impact the likelihood of treatment access and optimal virologic response.

The current study highlights concerns related to illicit PO use among IDU, but reveals some areas for potential improvement, particularly in relation to the clinical management of HIV and associated morbidity in IDU. While chronic physical pain is prevalent among people living with HIV/AIDS (262, 263, 285), and is also known to be prevalent among IDU for various other reasons (286), previous work suggests it is under-treated in IDU (196), including those who are HIV-positive (285). Previous research in the current setting demonstrates that roughly two-thirds of IDU who are living with moderate-to-severe pain, have been denied a PO prescription (287). Furthermore, almost half of those who were denied a pain prescription went on the purchase diverted POs (287), suggesting that under-treatment of pain among IDU is
common and can influence high-risk illicit drug use involving POs. While further research is needed to characterize chronic pain among those who are injecting POs, research and clinical initiatives are urgently needed to better manage pain among high-risk HIV-positive patients. Second, as OST has shown durable success in reducing opioid use and improving HAART adherence and HIV outcomes among IDU (288), the findings of this study also strongly support the need for HIV physicians to integrate evidence-based addiction treatment into their clinical knowledge and management of IDU cases. In the present study, methadone maintenance treatment was found to be negatively associated with periods of PO injection, which outlined an important sub-group of IDU who may benefit from interventions to increase OST initiation, especially given the common reluctance to engage in methadone among this populations (253, 289). Furthermore, as retention in OST is a major contributor to successful virologic outcomes for IDU (280, 290), clinical and research efforts are needed to optimize patient retention on OST treatments. Finally, as observed in the present study, taking ART may be less likely to occur among people who inject POs. Therefore ensuring that HIV-positive IDU, including those who inject POs, have access to ART is a critical step to improving disease outcomes both on an individual and population level. Positive virologic outcomes are further re-enforced by adherence to ART for those who have access to it (291), often independent of co-occurring illicit drug use (270, 292, 293). Taken together, these points support the notion that HIV treatment for IDU be part of a continuum of care built through the integration of, and partnerships with, primary care, mental health and addiction medicine, and social services (288).

This research is bound by some limitations. First, there are limitations related to study sample and available data that span the current chapter and Chapter 3. These common limitations will be addressed in Chapter 5, section 4.2. Issues limiting the
current study included the inability to include a measurement for level of physical pain, as earlier versions of the ACCESS questionnaire did not assess pain. Instead of shortening the study period to measure pain, this measure was left out in order to preserve study power with a longer follow-up period. As a result, the role that pain played in this study could not be assessed.

In conclusion, periods of PO injection were common among HIV-positive IDU and associated with various socio-demographic and drug-related vulnerabilities. Factors independently associated with PO injection in multivariable analyses were younger age, Caucasian ethnicity, drug dealing, not being on methadone maintenance, and heroin injection. These findings highlight the critical need to develop comprehensive strategies addressing the widespread yet interconnected health care needs of IDU, including addiction, HIV and its associated symptoms, chronic pain, and other drug-related morbidity.
Table 4.1. ACCESS sample characteristics at baseline, stratified by prescription opioid injection (n = 634)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PO Injection</th>
<th>Odds Ratio (95% CI)</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>171 (27.0%)</td>
<td>463 (73.0%)</td>
<td></td>
</tr>
</tbody>
</table>

|                                | 95% CI       |          |
|                                |              |          |
|                                | 0.96 (0.95 – 0.99) | 0.002    |
|                                | 1.10 (0.76 – 1.60) | 0.616    |
|                                | 1.58 (1.10 – 2.27) | 0.014    |
|                                | 0.96 (0.95 – 0.99) | 0.002    |
|                                | 1.10 (0.77 – 1.57) | 0.612    |
|                                | 1.40 (0.87 – 2.25) | 0.162    |
|                                | 1.37 (0.96 – 1.94) | 0.082    |
|                                | 2.66 (1.85 – 3.84) | <0.001   |
|                                | 0.90 (0.56 – 1.43) | 0.648    |
|                                | 2.10 (1.34 – 3.31) | 0.001    |
|                                | 1.49 (1.03 – 2.17) | 0.033    |
|                                | 1.37 (0.96 – 1.94) | 0.082    |
|                                | 2.66 (1.85 – 3.84) | <0.001   |

|                                |              |          |
|                                |              |          |
|                                |              |          |
|                                |              |          |
|                                |              |          |

Age<sup>e</sup> (median, IQR)

- Per 10 year increase
  - Yes: 41 (35 - 37)
  - No: 43 (38 - 49)
- Gender
  - Male: 117 (66.3)
  - Female: 54 (31.6)
- Ethnicity
  - Caucasian: 111 (64.9)
  - Other: 60 (35.1)
- Relationship Status<sup>†</sup>
  - Partner: 57 (33.3)
  - Single: 114 (66.6)
- Education
  - ≥ Secondary: 88 (51.5)
  - < Secondary: 83 (48.5)
- Employed<sup>†</sup>
  - Yes: 28 (16.4)
  - No: 143 (83.6)
- Homeless<sup>‡</sup>
  - Yes: 63 (36.8)
  - No: 1088 (63.2)
- Incarcerated<sup>‡</sup>
  - Yes: 39 (22.8)
  - No: 132 (77.2)
- Heroin Injection<sup>‡</sup>
  - Yes: 142 (83.0)
  - No: 29 (17.0)
- Cocaine Injection<sup>‡</sup>
  - Yes: 105 (61.4)
  - No: 66 (38.6)
- Crack Smoking<sup>‡</sup>
  - Yes: 145 (84.8)
  - No: 26 (15.2)
- Methadone Program<sup>‡</sup>
  - Yes: 86 (50.3)
  - No: 85 (49.7)
- Drug Dealing<sup>‡</sup>
  - Yes: 81 (47.4)
  - No: 90 (52.6)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Yes</th>
<th>No</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex Work</strong> ‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (14.6%)</td>
<td>71 (15.3%)</td>
<td>0.95 (0.58 – 1.55)</td>
<td>0.824</td>
</tr>
<tr>
<td>No</td>
<td>146 (85.4%)</td>
<td>392 (84.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ART Exposure</strong> ‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1 day</td>
<td>105 (61.4%)</td>
<td>308 (66.5%)</td>
<td>0.80 (0.56 – 1.15)</td>
<td>0.039</td>
</tr>
<tr>
<td>0 days</td>
<td>66 (38.6%)</td>
<td>155 (33.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Viral Load</strong> ‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 1500 c/mL</td>
<td>47 (34.1%)</td>
<td>205 (44.3%)</td>
<td>1.45 (1.02 – 2.06)</td>
<td>0.230</td>
</tr>
<tr>
<td>≤ 1500 c/mL</td>
<td>91 (65.9%)</td>
<td>258 (55.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CD4 Count</strong> ‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>3.2 (1.8 – 4.6)</td>
<td>3.1 (2.0 – 4.8)</td>
<td>0.97 (0.90 – 1.06)</td>
<td>0.534</td>
</tr>
</tbody>
</table>

* 95% CI = 95% Confidence Interval

‡ Wilcoxon rank sum test used for continuous variables

‡ Denotes events in the previous six months
Table 4.2. Bivariable and multivariable GEE* analyses of factors associated with recent prescription opioid injection among 634 IDU

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unadjusted</th>
<th></th>
<th></th>
<th>Adjusted</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>p - value</td>
<td>Odds Ratio (95% CI)</td>
<td>p - value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Per 10 year increase)</td>
<td>0.97 (0.96 – 0.99)</td>
<td>&lt;0.001</td>
<td>0.97 (0.96 – 0.99)</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Male vs. female)</td>
<td>1.18 (0.87 – 1.60)</td>
<td>0.283</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity (Caucasian vs. other)</td>
<td>1.34 (1.00 – 1.79)</td>
<td>0.053</td>
<td>1.65 (1.21 – 2.27)</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relationship Status† (Partner vs. single)</td>
<td>0.99 (0.80 – 1.49)</td>
<td>0.960</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education Status† (&gt; Sec. vs. ≤ sec.)</td>
<td>1.11 (0.83 – 1.49)</td>
<td>0.486</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed† (Yes vs. no)</td>
<td>0.96 (0.78 – 1.17)</td>
<td>0.659</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homeless† (Yes vs. no)</td>
<td>1.43 (1.17 – 1.76)</td>
<td>0.001</td>
<td>1.15 (0.95 – 1.40)</td>
<td>0.154</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incarcerated† (Yes vs. no)</td>
<td>1.36 (1.07 – 1.74)</td>
<td>0.001</td>
<td>1.07 (0.84 – 1.36)</td>
<td>0.602</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin Injection (Yes vs. no)</td>
<td>2.44 (1.91 – 3.13)</td>
<td>&lt;0.001</td>
<td>2.24 (1.85 – 2.72)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine Injection† (Yes vs. no)</td>
<td>1.04 (0.83 – 1.29)</td>
<td>0.738</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crack Smoking† (Yes vs. no)</td>
<td>1.41 (1.10 – 1.79)</td>
<td>0.006</td>
<td>1.20 (0.96 – 1.49)</td>
<td>0.108</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone Maintenance† (Yes vs. no)</td>
<td>0.76 (0.59 – 0.97)</td>
<td>0.031</td>
<td>0.76 (0.61 – 0.93)</td>
<td>0.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Dealing† (Yes vs. no)</td>
<td>2.14 (1.74 – 2.63)</td>
<td>&lt;0.001</td>
<td>1.88 (1.57 – 2.25)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex Work† (Yes vs. no)</td>
<td>1.35 (0.99 – 1.84)</td>
<td>0.059</td>
<td>1.07 (0.81 – 1.42)</td>
<td>0.614</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART dispensation† (≥ 1 day vs. 0 days)</td>
<td>0.73 (0.57 – 0.94)</td>
<td>0.014</td>
<td>1.02 (0.82 – 1.27)</td>
<td>0.834</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral Load (&gt;1500 vs. ≤ 1500 c/mL)</td>
<td>1.34 (1.06 – 1.69)</td>
<td>0.013</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 Cell Count (Per 100 cells/mL)</td>
<td>0.95 (0.89 – 1.01)</td>
<td>0.097</td>
<td>1.02 (0.92 – 1.02)</td>
<td>0.271</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GEE = Generalized estimating equation; 95% CI = 95% Confidence interval
† Denotes events/exposures in the previous six months
- Indicates variable was excluded from multivariable model-building protocol
5. SUMMARY OF FINDINGS, IMPLICATIONS FOR POLICY, AND FUTURE DIRECTIONS

5.1. SUMMARY OF FINDINGS

As PO injection is prevalent among IDU in Canada and the United States and elsewhere, the present research was conducted to gain insight into various health-related aspects of PO injection, including reviewing and summarizing health outcomes associated with injecting POs, investigating the impact of PO injection on non-fatal overdose among IDU, and characterizing PO injection among HIV-positive IDU. This work aims to improve understanding of how the emergence of POs within the illicit drug market has impacted socio-environmental conditions, substance use behaviours, and health outcomes among IDU in Vancouver, Canada. Furthermore, the present findings highlight various implications for promising structural-level policy and programming interventions that aim to improve health outcomes for IDU in the context of prevalent PO injection.

5.1.1. Health Outcomes Associated with Illicit PO Injection

The work for this thesis began with a systematic review to identify existing high-quality, peer-reviewed studies that have identified associations between PO injection and health outcomes. Through systematically identifying and reviewing 31 original research articles, several consistent and inconsistent trends were outlined: injecting POs appears to be associated with increased likelihood of positive hepatitis C virus (HCV) sero-status, poor mental health status (including substance dependence,
depression and suicidality), and poor physical health status; associations with overdose, HIV, and cutaneous infections were less consistent. Furthermore, research related to PO injection was lacking in the context of IDU living with HIV/AIDS. Important areas for future research include longitudinal examination of overdose and injection-related cutaneous infection, studies of specific mental illnesses and clinical-level HIV outcomes, and more rigorous adjustment for confounding. An in-depth exploration of the 31 studies included in this review confirmed the high-risk nature of many people who inject POs, which is an important consideration when planning health interventions for illicit drug-using populations. This study provided the basis for research questions addressed in Chapters 3 and 4 of this thesis.

5.1.2. Prevalence of Prescription Opioid Injection among People who Inject Drugs in Vancouver’s Downtown Eastside

In Chapters 3 and 4, the rates of PO injection at various points over an 8.5- and 8-year period, respectively, were monitored. In both studies, just under one-quarter of participants reported recent (i.e., previous six-month) injection of POs. In Chapter 3, the proportion of total (VIDUS and ACCESS) IDU participants reporting recent PO injection appeared to increase at the study start, peak at 35% between December 2006 and May 2007, gradually decrease to its lowest point (16%) between December 2011 and May 2012, before gradually increasing thereafter. While a slightly steadier prevalence trend occurred among the ACCESS participants examined in Chapter 4, a noticeable prevalence drop-off to 11% occurred between December 2011 and May 2012 before gradually increasing again. Both trends were found to decrease significantly over time (p<0.05).

The decreasing trends recorded in both studies are at odds with an increasing temporal trend in PO injection among IDU from Montreal, Canada over part of the
same time period (2005 – 2009 (45)). The trends observed in the present studies may be a product of one or more policy-level influences. The decreasing trend appears to correlate with actions taken at various points over the study period to curb rates of non-medical PO use, including the introduction of so-called “abuse-deterrent” POs (294), the removal of certain POs from the provincial drug formulary (247), and simply more stringent individual-level physician prescribing practices due to increased awareness of non-medical PO use (295). These regulatory moves, and the implications they may have for people who inject POs, will be discussed in further detail in section 3 of this chapter. Second, the reduction in the prevalence of PO injection may be related to reductions in injection of other drugs (e.g., heroin) locally, which have coincided with considerable improvements in available health and social services for people who inject drugs locally, including housing, harm reduction and methadone maintenance therapy (48). Further research will be needed to understand whether these temporal trends in PO injection are meaningful in the context of reformed prescribing practices and/or changes in social and health services for IDU, or simply a result of naturally-occurring illicit drug market supply fluctuations.

5.1.3. The Impact of Prescription Opioid Injection on Non-Fatal Overdose

Chapter 3 sought to understand the effect of PO injection on non-fatal overdose among IDU. In order to achieve this, participants in the VIDUS and ACCESS studies were categorized according to injection opioid use (heroin only, PO only, both heroin and PO versus non-opioid injection), and correlations between opioid injection and non-fatal overdose at every six month follow-up were examined for an 8.5 year period using GEEs. This analysis revealed that those who injected POs but not heroin were not significantly more likely than non-opioid injectors to overdose, while heroin injectors had almost twice the odds, and those who injected both types of opioids had
2.5 times the odds of overdosing. These results support the hypothesis stated in Chapter 1, section 5.3, that PO injection would only increase risk for non-fatal overdose in the context of high-intensity poly-opioid use. In addition, incarceration, public injecting, requiring help injecting, heavy alcohol use, and non-injection PO use were significantly and positively associated with non-fatal overdose in this analysis, while methadone maintenance treatment was negatively associated.

5.1.4. Characterizing Prescription Opioid Injection among HIV-Positive People who Inject Drugs

As outlined in Chapter 2, little is known about PO injection among HIV-positive IDU. Chapter 4 sought to begin addressing this gap by both examining the prevalence of PO injection among HIV-positive IDU, and characterizing socio-environmental-, behavioural-, and clinical-level correlates of PO injection among them. In this study roughly one quarter of HIV-positive participants reported injecting POs at each six-month follow-up period between December 2005 and November 2013. Using GEE, PO injection was found to be independently associated with younger age, Caucasian ethnicity, heroin injection, drug dealing, and not being on methadone maintenance treatment. It was hypothesized that exposure to ART would be less likely during periods of PO injection. This hypothesis was not fully supported, as periods of ART dispensation negatively correlated with periods of PO injection, but this relationship lost significance after controlling for younger age and heroin injection in the multivariable model. Nonetheless, the findings of this study exemplify ongoing high-risk behaviours and health vulnerabilities among HIV-positive people who inject POs, and point to several key areas for future investigation and strategies to improve their health.
5.2. CONTRIBUTION OF RESEARCH

In the context of an opioid epidemic in North America, the study of non-medical PO use is critical; however, IDU have been largely excluded from the research in this field. This thesis contributes to the ongoing study of illicit PO use by focusing on PO injection – the route of administration associated with the most harm (142, 177). The findings of this thesis supply a growing field of research that uses a risk environment approach to understand the intersecting social-, environmental-, and structural-level factors that shape risk for harm among vulnerable populations, such as IDU. This approach has informed various structural harm reduction interventions that have effectively prevented substantial morbidity and mortality among drug using populations locally and elsewhere (296).

Since the non-medical use of POs is a relatively recent public health issue, the literature regarding the harms associated with PO injection had yet to be critically reviewed and summarized. This gap was addressed in Chapter 2 by systematically identifying and summarizing the existing research in this field. The findings from this chapter will help inform health care providers of the potential clinical profiles of people who inject POs; policy makers of critical areas for intervention; and health researchers of key directions for future study.

To my knowledge, this thesis encompasses the first study to describe the effect of PO injection on non-fatal overdose with and without concurrent heroin injection. This novel approach was helpful in determining specific groups of IDU to which overdose prevention and response strategies should be tailored, and may be useful in examining other harms related to specific injection drugs, such as cutaneous injection-related infection and HCV.
Chapter 4 is one of the first studies to record the prevalence of, and characteristics associated with, PO injection among HIV-positive IDU. The only other identified study of this kind was conducted among buprenorphine maintenance patients, as opposed to IDU more broadly, and only measured the injection of buprenorphine, as opposed to a variety of readily available and commonly-used POs (159). While some findings from this study confirmed those from other research of IDU populations – particularly the strong correlation between PO injection and heroin injection (93, 150, 297), several novel results were also identified: namely, periods of drug dealing are strongly and positively associated with PO injection, and periods of methadone maintenance treatment are negatively associated with PO injection. These findings contribute to a growing literature base seeking to understand the demographic and behavioural profile of IDU who use POs, but also established an understanding the co-occurring demographic-, social- clinical-level factors related to injecting POs among a sub-group of particularly vulnerable IDU. Findings from this research will act as a foundation on which future studies of HIV-positive IDU can be built, in the context of ongoing high rates of PO injection.

5.3. IMPLICATIONS FOR HEALTH POLICY AND PROGRAMMING

In response to high rates of non-medical PO use, there have been several regulatory moves to prevent their illicit use. One intervention geared towards injection prevention was the introduction of so-called abuse-deterrent POs, which were designed to be resistant to physical changes that facilitate snorting and injecting (298). In 2010, the United States Federal Drug Administration (FDA) approved a reformulated extended-release oxycodone to replace OxyContin (299). This reformulated version was designed to resist tampering for snorting or injection via
physicochemical barriers (299). While some natural experiments have demonstrated this intervention to be effective in reducing rates of injection of OxyContin (245, 299, 300), several coinciding alarming substance use trends have also been noted, including significant increases in the injection of other high-potency POs (other oxycodone (299), oxymorphone (246), hydromorphone, and fentanyl (245)) and heroin (245, 299). The removal of OxyContin may have also unintentionally played a role in supporting the local emergence of extremely harmful counterfeit OxyContin made from illicit fentanyl analogues (as discussed in Chapter 3, section 4). Studies have also shown that so-called abuse-deterrent POs are still altered for injection by a substantial portion of users (245), likely requiring extra preparation steps, inviting potential for injection-related infection (e.g., soft tissue infection, HCV). As discussed in Chapter 4, efforts to prevent IDU from using POs illicitly appear to have led to instances of discrimination against IDU within the medical system. IDU who seek POs for pain relief are frequently denied a prescription, resulting in their seeking POs on the street (287), which exemplifies another way in which relying solely on abstinence-based interventions may create new unintended public health problems. Therefore, the current study supports interventions that approach PO injection through comprehensive harm reduction, rather than abstinence-based, models.

Chapter 4 demonstrated that, among HIV-positive IDU, periods of methadone maintenance therapy were less likely during periods of PO injection. This finding, alongside an extensive body of research demonstrating the success of opioid substitution treatment (OST) in improving ART initiation and adherence through reducing opioid use (278, 301, 302), confirms the central role OST plays in improving health outcomes among HIV-positive people who inject POs. Medical programs across North America should incorporate addiction medicine into their training, and current practitioners – especially those treating patients with HIV and substance use
issues – should integrate addiction medicine into practice in order to optimize not only rates of OST admission and retention, but also ART initiation and adherence. Recent and ongoing local clinical trials are investigating the efficacy of alternative OST therapies, including diacetylmorphine (prescription heroin (252)) and hydromorphone (303). Findings from these trials have demonstrated (alongside past trials conducted in Europe (254-256)) that, among people who have not benefitted previously from methadone, treatment with injectable diacetylmorphine is significantly more effective at retaining patients and treating opioid dependence (253). A pilot study also suggests similar results for injectable hydromorphone (Dilaudid (289)), and research is ongoing to confirm this (303). The finding of a negative association with methadone suggests that these alternative OST options may prove promising for people who inject POs.

As discussed in Chapter 1, relying solely on behaviour change approaches at the individual level to prevent overdose (e.g., injecting with others, “tasting” the drug first to gauge potency) has been criticized for its oversimplification of the complex social, economic, physical, and political interactions that may place IDU at risk of overdose (108). Structural interventions are needed in order to ensure rates of overdose are reduced at the population level. Chapter 3 revealed that: 1) the majority of people who reported injecting POs also reported injecting heroin; and 2) these individuals had over two-times the odds of overdosing compared with non-opioid injectors. This finding highlights the frequency and dangers of poly-drug use in this cohort, and supports the expansion of structural programs that facilitate safer injection of opioids.

Safe injection facilities (SIFs) are legally-sanctioned sites where IDU can inject their drugs under medical supervision. Currently, Vancouver’s Insite is the only legally operating SIF in Canada. An extensive body of literature has confirmed the
success of Insite’s impact on reducing fatal overdose rates (304, 305) and facilitating treatment and detoxification uptake (306, 307), among a number of other positive health and social outcomes (255, 308). Studies have also shown that the people who are most likely to use this facility are some of the highest at risk of overdose in the community (309). However, Insite currently operates at full capacity (310), which may lead those suffering withdrawal to forgo the wait in order to inject elsewhere (often an alleyway or other public space) immediately (310). The findings of this thesis stand in stark contrast to efforts made by the Federal Government to further impede the opening new SIFs and disrupt the smooth-running of Insite (311) with the passing of Bill C-2: The Respect for Communities Act (312). Rather, the current findings support the call by expert Canadian health researchers to expand SIFs in both Vancouver and to other cities across Canada (310, 313).

Take-home naloxone (THN), an injectable or intranasal drug that is safe (i.e. cannot be used for euphoric purposes) and can reverse an opioid overdose (314), has shown great promise locally (315) as well as throughout the United States (244, 316) and the United Kingdom (317, 318). Based on the findings of Chapter 3, people who inject POs should have access to naloxone – especially those who alternate between injecting POs and heroin. While opioid users are eligible to receive THN from any of the 70 sites across the province (319), many still do not have it or are unsure of how to use it (320). Inter-community collaboration between primary physicians, naloxone prescribers and distributors, and social service providers are needed to increase users’ awareness of, and access to, THN. Beyond community-based interventions, several important health policy modifications at the provincial and federal levels need to be made in order to successfully optimize naloxone coverage through reducing barriers to its acquisition: provincially, naloxone should be included in drug formularies to reduce financial costs; federally, naloxone should be re-scheduled as an over-the-
counter medication, made available to friends and family of opioid users (rather than solely opioid users), and approved in the easy-to-administer intranasal form (225).

5.4. STRENGTHS AND LIMITATIONS

5.4.1. Study Strengths

Access to rich longitudinal data provided the basis for various strengths of the present research. Using longitudinal methods, Chapter 3 quantified the risk of non-fatal overdose according to differing types of opioid injection, which was a novel approach to a research question identified through systematic review. As outlined in Chapter 2, the vast majority of other studies that have examined the effect of PO injection on overdose were cross-sectional (125, 156, 162, 163, 165-169, 321), while many did not include a multivariable analysis (165-168), and some lessened the probability of finding a temporal association by measuring lifetime, as opposed to recent, PO injection or overdose (125, 166, 168, 169). Through the use of GEEs, correlations between PO injection and non-fatal overdose were observed at 17 six-month periods over 8.5 years, rather than at one point in time. It should be noted, however, that through this method, it is not possible to determine the timing of each event within each six month period (i.e., whether an overdose occurred before, after, or during the reported PO injection events). As PO injection is an ongoing public health crisis, having access to measures that were recorded as recently as November 2013 (Chapter 4) and May 2014 (Chapter 3) was a major strength of this thesis, as it provided an up-to-date characterization of PO injection that can support current policy decisions. Chapter 2 was immensely strengthened with the addition of a second reviewer who independently screened full-text articles, reviewed final article
summary information, and assessed final articles for quality in order to record inter-rater reliability and ensure validity of findings.

5.4.2. Study Limitations

While study-specific limitations are discussed in each chapter, there were certain limitations shared across data-driven studies. First, as there are no existing registries of IDU, including HIV-positive IDU, neither VIDUS nor ACCESS is a random sample. Despite extensive recruitment efforts to produce as representative a sample as possible, findings from Chapters 3 and 4 may not be generalizable to other Canadian IDU populations and should therefore be interpreted in light of this – especially considering Vancouver’s unique illicit drug scene characterized by the high availability of heroin (48), and reduced rate of illicit PO use compared to other Canadian settings (18). As is the case in most observational research, despite extensive interview data, there may be residual confounding in the present analyses. Particularly, this study was limited by certain factors that were not captured in the questionnaire. For example, studies examining non-medical PO use and dependence (i.e., non-injection and injection) demonstrate that non-medical PO use is positively associated with pain (222, 276) and various mental illnesses (e.g., depression (96, 201, 322, 323)). Although it is not yet clear whether these links persist for PO injection among IDU populations, it was not possible to assess and include these measures as confounders (Chapter 3) or covariates (Chapter 4) in the present research, as data for these variables were not available for the entire study period. Descriptive information related to types of POs used over time was limited by the fact that the study questionnaire underwent yearly modifications to reflect market availability of POs. Earlier versions of the questionnaire were not coded in a way that allowed distinction between types of POs used by participants. However, modifying the questionnaire
was critical to capturing rates of current PO injection as accurately as possible. Finally, although self-report among substance users, including IDU, has demonstrated a reasonable level of reliability and validity (324), the possibility cannot be ruled out that the self-reporting of various behaviours and exposures in the current studies introduced some bias in the form of recall inconsistencies or socially desirable responding.

5.5. FUTURE RESEARCH DIRECTIONS

The present research has shed light on various aspects of PO injection that require further investigation. While this thesis assessed two critical knowledge gaps identified through the systematic review (Chapter 2), several other key areas that require attention beyond the scope of this thesis were outlined. Particularly, future research should evaluate whether PO injection increases risk of cutaneous injection-related infection, especially as crushing and injecting pills or capsules originally intended for oral consumption might yield a more contaminated product (140). Chapter 3’s finding of an increased risk of overdose for people who inject both POs and heroin but not those who inject POs only warrants a focused and detailed follow-up analysis in order to fully understand behavioural differences between these two groups. For example, qualitative research would be useful in understanding different reasons for PO injection between these two groups. Third, in Chapter 4, periods of drug dealing were significantly and positively associated with periods of PO injection. Due to key differences in supply routes of POs compared with other illicit drugs, future ethnographic and qualitative research is needed to understand how drug-dealing practices have been altered in the context of illicit PO availability. Fourth, as changes to regulation involving POs (e.g., the replacement of OxyContin with
OxyNEO) continue to take place, ongoing research is needed to monitor trends in PO injection prevalence as well as potential impacts on other illicit drug use. Finally, while the current research focuses on an aging cohort of IDU, the injection of POs is highly prevalent among young and inexperienced IDU (100, 150), who face a distinct set of socio-structural risk exposures (325, 326). Thus, future research should continue to characterize young people who inject POs, including their risk for overdose and access and to medical services, such as antiretroviral therapy (for HIV-positive young IDU), opioid substitution treatment, and other harm reduction services.
REFERENCES


300. Butler SF, Cassidy TA, Chilcoat H, Black RA, Landau C, Budman SH, et al. Abuse rates and routes of administration of reformulated extended-release...


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APPENDICES

Appendix I. Search strategy for systematic review (Chapter 2)

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<th>DATABASE</th>
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<td></td>
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<tr>
<td></td>
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<tr>
<td></td>
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2. (NMPOU or “non?medical prescription opioid use” or “nonmedical prescription opioid use” or inject* or intraven* or “intravenous drug abuse*” or “intravenous injection*”)  
3. 1 and 2
4. (injection drug user* or intravenous drug user* or IDU or people who inject drugs or PWID or street drug user*)  
5. 3 and 4
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1. analgesics, opioid[MeSH Terms]
2. (*prescription opioid* OR “prescribed opioid” OR “prescription painkiller” OR “prescribed painkiller” OR “prescription pill” OR “prescription tab” OR “opioid analgesic” OR “opioid painkiller” OR “prescription pain?reliever” OR narcotic* OR “prescription narcotic” OR “prescribed narcotic” OR “painkiller”)  
3. 1 or 2
4. (“NMPOU” OR “non?medical prescription opioid use” OR “nonmedical prescription opioid use”)  
5. (inject* or intraven*)  
6. 4 or 5
7. 3 and 6
8. (“PWID” OR “IDU” OR “people who use drugs” OR “injection drug user” OR “intravenous drug user” OR “street drug user”)  
9. 7 and 8
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Restrict 3 to species = homo

1. (“prescription opioid*” or “prescription opioid analgesic*” or “opioid analgesic*” or “prescription painkiller*” or painkiller* or “prescription narcotic*”)

2. Limit 1 to 1990-2014
### Appendix II. Checklist for quality assessment of eligible studies (Chapter 2)

(Derived from Downs & Black, J Epidemiol Community Health, 1998; 52:377-384)

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<td><strong>Reporting</strong></td>
<td><strong>Is the hypothesis/aim/objective of the study clearly described?</strong> <strong>Are the main outcomes to be measured clearly described in the Introduction or Methods section?</strong> <strong>Are the characteristics of the individuals included in the study clearly described?</strong> <strong>Are the distributions of principal confounders in each group of subjects to be compared clearly described?</strong> <strong>Are the main findings of the study clearly described?</strong> <strong>Does the study provide estimates of the random variability in the data for the main outcome (IQR, standard deviation, etc.)?</strong> <strong>Have actual probability values been reported (e.g., 0.035 rather than &lt;0.05 for the main outcomes except where the probability value is &lt;0.001)?</strong></td>
<td>yes (1) or no (0)</td>
</tr>
<tr>
<td><strong>External Validity</strong></td>
<td><strong>Were the subjects that were asked to participate in the study representative of the entire population from which they were recruited?</strong> <strong>Were those subjects who were prepared to participate in the study representative of the entire population from which they were recruited?</strong></td>
<td>yes (1), no (0) or undetermined (0)</td>
</tr>
<tr>
<td><strong>Internal Validity – Bias</strong></td>
<td><strong>If the results of the study were based on “data dredging”, was this made clear?</strong> <strong>In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the exposure and outcomes the same for cases and controls?</strong> <strong>Were the statistical tests used to assess the main outcomes appropriate?</strong> <strong>Were the main outcome measures used accurate (valid and reliable)?</strong></td>
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<tr>
<td><strong>Internal Validity – Confounding</strong></td>
<td><strong>Were the patients in different groups (trials or cohort studies) or were cases and controls (case-control studies) recruited from the same population?</strong></td>
<td>yes (1), no (0) or undetermined (0)</td>
</tr>
</tbody>
</table>
Were study subjects in different groups (trial and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?  
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?  
Were losses to follow-up taken into account?  

<table>
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<th>Power</th>
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