Nonmedical Prescription Opioid Initiation, Ongoing Use, and Related Overdose Among People who use Drugs in Vancouver, Canada

by

Tessa Cheng

M.P.P., Simon Fraser University, 2013
B.A. (Hons.), Acadia University, 2007

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Approval

Name: **Tessa Cheng**

Degree: **Doctor of Philosophy**

Title: ***Nonmedical prescription opioid initiation, ongoing use, and related overdose among people who use drugs in Vancouver, Canada***

Examining Committee: **Chair:** Pablo Nepomnaschy
Associate Professor

Will Small
Senior Supervisor
Associate Professor

Robert Hogg
Co-Supervisor
Professor

Kora DeBeck
Supervisor
Assistant Professor
School of Public Policy

Shira Goldenberg
Internal Examiner
Assistant Professor

Peter Davidson
External Examiner
Associate Professor
Department of Medicine
University of California,
San Diego

Date Defended/Approved: December 12, 2018

Ethics Statement

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Abstract

Background: The prevalence and harms associated with nonmedical prescription opioid use (NMPOU) have risen in Canada, and the prevailing policy response has restricted the supply of prescription opioids (POs) and promoted more responsible patient behaviour. Despite this quick action to address NMPOU, there are key knowledge gaps related to NMPOU initiation, ongoing use, and associated harms among people who use illegal street drugs (PWUD).

Objectives: (i) conduct a systematized review of the extant literature related to NMPOU, (ii) identify the prevalence and correlates associated with NMPOU-related initiation trajectories and engaging in recent NMPOU, and (iii) investigate the impact of acquiring POs from physicians for the purposes of NMPOU.

Methods: Multiple databases were systematically searched for extant literature on NMPOU. For the empirical studies, data were derived from the Vancouver Drug Users Study, which is an open prospective cohort study of youth and adult PWUD in Vancouver, Canada. Utilizing cross-sectional and longitudinal regression techniques and various sub-samples, I assessed the relationship between various risk factors and the following outcomes: engaging in recent NMPOU, initiating NMPOU before illegal street drugs (vs. after), initiating NMPOU using a physician prescription, and recent non-fatal overdose.

Results: The review found some consistent indicators of risk related to NMPOU and gaps in knowledge related to NMPOU among hidden populations. In the empirical analyses, engaging in NMPOU was associated with a higher risk profile regardless of age and sex, and initiating NMPOU before illegal street drugs was also linked with a higher risk profile when compared with those who never engaged in NMPOU. Initiating NMPOU with a physician prescription was not a key indicator of high-intensity substance use or socio-structural vulnerability and acquiring POs using a physician prescription was not associated with recent non-fatal overdose.

Conclusions: The results indicate that engaging in NMPOU is associated with a higher risk profile; however, NMPOU-related initiation trajectories and acquisition source do not appear to be a meaningful target for policy solutions or interventions. This dissertation provides some evidence for developing unique strategies to address ongoing NMPOU among younger and older PWUD that includes opioid agonist treatment and income generation opportunities.

Keywords: prescription opioids; at-risk youth; substance use; pain; overdose; cohort study

To Nick and our little bean

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To participants in the At-Risk Youth Study (ARYS) and Vancouver Injection Drug Users Study (VIDUS), I am constantly in awe of your courage and ability to navigate seemingly impossible environments. Thank you for your willingness to share your stories and your life with study staff. I sincerely hope this dissertation helps make a positive contribution to your lives. In addition, I would like to thank past and present ARYS and VIDUS study staff, co-investigators, and co-authors on my manuscripts.

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List of Acronyms

Term	Initial components of the term
AIC	Akaike Information Criterion
AOR	Adjusted Odds Ratio
ARYS	At-Risk Youth Study
BC	British Columbia
CI	Confidence Interval
GEE	Generalized Estimating Equation
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus
IQR	Inter-Quartile Range
MPOU	Medical Prescription Opioid Use
NMPOU	Nonmedical Prescription Opioid Use
OAT	Opioid Agonist Treatment
OR	Odds Ratio
PO	Prescription Opioid
PWUD	People Who Use Illegal Street Drugs
QIC	Quasi-likelihood under the Independence model Criterion
SFU	Simon Fraser University
USA	United States of America
VDUS	Vancouver Drug Users Study
VIDUS	Vancouver Injection Drug Users Study

Glossary

Term	Definition
Illegal street drugs	Controlled substances that are illegal to possess and consume at all times. These include: heroin, crack, cocaine, and crystal methamphetamine.
Illicitly manufactured synthetic opioid	Clandestinely manufactured opioids that are highly toxic and surreptitiously added to illegal street drugs (e.g., illicitly produced fentanyl)
Inappropriate medical PO use	A person self-treating a medical condition with POs. For example, self-escalating the dosage of POs that were prescribed for pain in order to attain additional pain relief.
Medical prescription opioid use	A person using pharmaceutical-grade legally manufactured POs that were prescribed for them and according to physician recommendations.
Nonmedical prescription opioid use	A person using pharmaceutical-grade legally manufactured POs that were not prescribed for them or that they took only for the experience or feelings that POs cause, as defined in the US National Survey on Drug Use and Health pre-2015. Other terms used interchangeably in the extant literature include: PO misuse, unsanctioned PO use, and extramedical PO use.
Overprescribing of POs	A phenomenon where physicians prescribe POs in ways that are seen as unnecessary or unsafe. This may include prescribing POs for conditions that have other more effective treatments, prescribing too many POs at once, and prescribing a higher dosage of POs than medically necessary.
Pain	In the context of the statistical analysis, “pain” describes “moderate to extreme” pain that may be either acute or chronic as measured by the Euroqol EQ-5D health utility instrument.

Preface

This statement certifies that the work presented in this thesis was conceived, designed, and written by the candidate, Tessa Cheng (TC). All research described in this dissertation was approved by the Simon Fraser University Office of Research Ethics (#2015s0340) and the University of British Columbia/Providence Healthcare Research Ethics Board (H15_03008). This dissertation uses secondary data from the At-Risk Youth Study (ARYS) and Vancouver Injection Drug Users Study (VIDUS), and permission to use this data was granted by the Principal Investigators of each study, Dr. Kora DeBeck (KD) and Dr. Evan Wood.

The systematized review presented in Chapter 2 was designed, executed, and synthesized by TC with substantive guidance from KD and Dr. Will Small (WS).

The data and text presented in Chapters 3-5 were all written as manuscripts and circulated to co-authors: KD, WS, Dr. Robert S. Hogg (RSH), Dr. Ekaterina Nosova (EN), Huiru Dong (HD), Dr. Thomas Kerr (TK), and Dr. Kanna Hayashi (KH). All co-authors made contributions in accordance with supervisory committee, collegial, or co-author duties. For each analysis, TC was primarily responsible for the literature review, designing the study, and interpreting and contextualizing the results, with substantive guidance and input from KD. HD and EN conducted the statistical analyses for Section 3.1. EN conducted the statistical analyses for all other chapters and sections. The remaining co-authors on each manuscript (WS, RSH, TK, KH) provided substantive input on the manuscript drafts and revisions.

A version of Section 3.1 has been published as Open Access and is reused here as per BioMedCentral's Copyright and License rights for authors: Cheng T, Small W, Dong H, Nosova E, Hayashi K, DeBeck K. **An age-based analysis of nonmedical prescription opioid use among people who use illicit drugs in Vancouver, Canada**. Substance Abuse Treatment, Prevention, and Policy, 2018:13(41). A version of Chapter 3.2 is currently under review for peer-reviewed publication: Cheng T, Nosova E, Small W, Hogg RS, Hayashi K, DeBeck K. **A gender-based analysis of nonmedical prescription opioid use among people who use illicit drugs**.

A version of Chapter 4 has been published as Open Access and is reused here as per BioMedCentral's Copyright and License rights for authors: Cheng T, Small W, Nosova E, Hogg R, Hayashi K, Kerr T, DeBeck K. **Nonmedical prescription opioid use and illegal drug use: Initiation trajectory and related risks among people who use illegal drugs in Vancouver, Canada**. BMC Research Notes, 2018:11(35).

Chapter 1.

Introduction

"Every system is perfectly designed to get the results it gets" - Paul Batalden

1.1. Background

Since the prohibition of psychoactive substances, North America has historically experienced successive crises of drug use that capture the public's interest and generate a flurry of media coverage and reactive policies (1). Beginning in the late 1800's and early 1900's, opium was identified as a problematic substance in Canada and the United States (1, 2). Concerns regarding alcohol and related harms led to the emergence of the Temperance movement, which gained momentum in the early 1900's, and alcohol prohibition in the 1920's (1, 3). In the 1960's, cannabis was sensationalized as a scourge among youth, and crack cocaine became the new drug crisis in the 1980's (1). In the 1990's and 2000's, crystal methamphetamine became the drug of interest for the media and politicians (4, 5), while prescription opioid (PO) use was starting to escalate in Canada and the United States of America (6, 7). In the 2010's, the increased consumption of POs among people who were and were not prescribed POs resulted in alarming rates of opioid dependence, non-medical prescription opioid use (NMPOU), PO-related mortality, and a new cycle of considerable media interest (8, 9). Between 2011 and 2013, another opioid crisis was building: the adulteration of the street drug supply with illicitly manufactured synthetic opioids such as fentanyl (10, 11). By the mid-2010's, many jurisdictions across Canada and some settings in the United States were experiencing these two intersecting opioid crises (10, 12, 13) that were at times misleadingly conflated (14).

This dissertation focuses on NMPOU, which describes a person using pharmaceutical-grade legally manufactured POs that were not prescribed for them or that

they took only for the experience or feelings that POs cause, as defined in the US National Survey on Drug Use and Health (pre-2015) (15, 16). Other terms that are often used interchangeably with NMPOU are PO misuse, unsanctioned PO use, and extramedical PO use (17). NMPOU includes the nonmedical use of natural opioids derived from the opium poppy (e.g., morphine and codeine), semi-synthetic opioids created from opiates that occur naturally (e.g., oxycodone and buprenorphine), and synthetic opioids (e.g., methadone, fentanyl) (18, 19). For the purposes of this dissertation: (i) NMPOU includes using pharmaceutical-grade legally manufactured POs obtained from a physician or from a diverted source, such as a friend, family member, or street-based drug dealer; and (ii) NMPOU may occur through any route of administration, such as smoking, oral ingestion, snorting, and injecting. This dissertation does not consider the following as engaging in NMPOU: (i) any use of clandestinely manufactured opioids (e.g., illicitly produced fentanyl); (ii) any use of injectable opioids that are administered as treatment for opioid use disorder (e.g., diacetylmorphine as part of heroin assisted treatment); or (iii) self-treatment of a medical condition (e.g., self-escalating the dosage of POs that were prescribed for pain in order to attain additional pain relief) (hereinafter referred to as “inappropriate medical PO use”).

When POs are not directly obtained from a pharmacy or hospital, the ability to distinguish between pharmaceutical-grade legally manufactured POs and clandestinely manufactured opioids can be difficult. Hence, although this dissertation focuses on NMPOU, there are expected to be some instances where participants unknowingly consumed clandestinely manufactured opioids. In contrast to the non-medical use of pharmaceutical-grade legally manufactured POs, there is a growing epidemic of consumption of clandestinely manufactured synthetic opioids (hereafter referred to as the “illicitly manufactured synthetic opioid crisis”). As noted above, these clandestinely manufactured opioids are sometimes marketed and sold as pharmaceutical-grade legally manufactured POs, but they also appear to be surreptitiously contaminating the illegal street drug supply ranging from heroin to illicit stimulants such as crack, cocaine, and crystal methamphetamine (hereinafter referred to as “illegal street drugs”). A recent drug checking study in Vancouver found that only 19% of drug samples sold as opioids contained the expected substance, and only 13% of “heroin” samples contained any amount of diacetylmorphine (20). The substitution or adulteration of illegal street

stimulants with clandestine fentanyl is less prevalent but still problematic, as the same study found that 5% of stimulants tested positive for fentanyl (20).

Various studies of the American general population estimate that the prevalence of engaging in medical prescription opioid use was as high as 38% in 2015 (21) with the prevalence of past-year NMPOU estimated at between 4.5% and 4.9% (21-23). In addition, the prevalence of meeting the criteria for PO-related clinical abuse or dependence among the American general population was estimated at 0.8% and 0.9% (21, 23), with one study finding that 13% of those who engage in NMPOU meet the criteria for abuse or dependence (22). Numerous factors have been linked with the rise of medical PO use and NMPOU, such as a lack of physician education related to pain treatment; deceptive marketing of opioids by pharmaceutical companies; recognition of pain as the fifth vital sign and increased importance of relieving pain; and the relative efficiency of prescribing a pill (i.e., opioid) for short-term pain management compared to a more in-depth clinical examination (24, 25). Alarming rises in PO prescriptions and dispensing contributed to increases in PO use, such that oxycodone prescriptions rose 50% between 1999 and 2002 in the United States (26), and opioid prescriptions increased steadily from 2005 to 2011 across Canada (27).

Recent efforts to address overprescribing of POs, inappropriate medical PO use, and NMPOU have primarily focused on a suite of policies designed to reduce the supply of POs and promote more responsible patient behavior. Policies to encourage supply-reduction include prescription monitoring programs, restrictions on opioid dosages, and titrating patients down to “acceptable” dosage levels (28), with some physicians refusing to prescribe opioids or treat patients taking opioids (29). Responsible patient behavior has been encouraged by multiple levels of governments and healthcare providers, such that the Canadian federal government implemented mandatory labeling on PO pill bottles to ensure that patients are aware that “[o]pioids may cause dependence, addiction and overdose” (30), provincial insurance plans provided coverage for an abuse deterrent PO formulation (OxyNEO) (31), national and clinical opioid prescribing guidelines recommended measures to increase patient compliance with PO treatment that included urine drug screens and prescription drug monitoring (28, 32), and multi-sectoral initiatives increased awareness of PO-related risks and harms through public information campaigns

(33-35). There have also been some efforts to reduce demand for opioids by improving awareness of, and access to, opioid agonist therapy (28, 36). In addition, various jurisdictions including British Columbia (BC) have filed lawsuits aimed at holding pharmaceutical companies to account for PO-related healthcare expenses incurred (37) and for violating self-regulation agreements and misleading advertising (Massachusetts, Tennessee) (38, 39).

NMPOU among people who use illegal street drugs (hereinafter referred to as People Who Use Drugs; PWUD) is of special interest from a public health perspective. PWUD are often criminalized, socially marginalized, have very low incomes, and experience a range of health-related harms (40, 41). NMPOU is prevalent among people with a history of substance dependence, such that studies have found rates of lifetime NMPOU between 9% and 81% (42-45), and rates of current or recent use from 31% to 79% (42, 46). This population also reports high intensity NMPOU, as an American study of PWUD found that 25% of participants engage in NMPOU on a daily basis (46). A Canadian study found that the rates of NMPOU have increased among PWUD, such that more people are engaging in NMPOU than heroin use (47). Research from street-based PWUD in Australia and New Zealand found moderate to high proportions of people using predominantly diverted pharmaceutical morphine (62%) and over-the-counter codeine non-medically (35%) (48, 49), and high proportions of participants injecting methadone (73%) (48). NMPOU is also found to be common among street-involved youth (50), as a Canadian study found a prevalence of PO injection as high as 75% among those who inject drugs in a cohort of street-youth (51). In addition, a range of studies among PWUD have found that: NMPOU predicted initiation into injection drug use among at-risk youth (52); easy access to POs facilitated initiation of NMPOU among young American PWUD (53); non-treatment seeking outpatients in America who engaged in NMPOU had more education than those who used cocaine (54); and Canadian PWUD who engaged in NMPOU were more likely to receive legal income than those who use heroin (55).

While a better understanding of NMPOU among street-entrenched populations in Canada and the USA is developing, there remain clear knowledge gaps and the need to further investigate NMPOU initiation trajectories, socio-demographic and socio-structural risk factors associated with NMPOU, and the impact of acquiring POs from physicians on

NMPOU-related trajectories. Despite quick action by governments and healthcare providers to address hazards related to NMPOU, less is known about whether some subgroups are more at risk for initiating, engaging in, and experiencing harms associated with NMPOU, and there is a similar paucity of evidence related to how PO acquisition and availability impacts NMPOU initiation and harms among PWUD. This is particularly important in the current context, as there is an urgent need to identify and characterize trends regarding trajectories and risk factors among subgroups as the next crisis of illicitly manufactured synthetic opioids has emerged and quickly become entwined with NMPOU.

1.2. Study justification

Street-entrenched, hidden, or otherwise socio-economically marginalized populations experience negative health-related outcomes resulting from social and structural factors that interact with illegal street drug use (40, 41). Street-involved youth who use illegal street drugs are particularly vulnerable, given the young age at which they begin to struggle with housing instability, limited financial resources, and spend a significant portion of their day meeting their immediate survival needs (56, 57). This social and economic exclusion from mainstream society occurs due to the cumulating effects of negative familial, societal, and educational outcomes during childhood and adolescence (58, 59), and is also perpetuated by housing instability, interactions with police and the criminal justice system, and involvement in the street economy (60, 61).

PWUD are further disenfranchised by inequitable and stigmatizing de facto and formalized healthcare practices in Canada and other settings. First, the inverse care law states that the availability and provision of good medical care is inversely related to the need of the population (62, 63). In other words, populations with the most medical needs are more likely to receive sub-optimal care, whereas healthier populations with fewer medical needs are more likely to receive optimal care. While the inverse care law is exacerbated by medical care provided through a free market, countries with universal healthcare systems such as Canada are not immune (64, 65). Second, street-entrenched PWUD are targeted by drug prohibition and profoundly harmful anti-drug strategies that typically use law enforcement as the primary intervention for reducing substance use (66, 67). These strategies often do not prioritize a medical-based approach that includes

mobilizing evidence-based treatments and interventions for those who use drugs (66-68). Drug policies that predominantly rely on law enforcement have shown few if any benefits for meaningfully addressing substance use (69).

As health and socio-economic disparities persist for PWUD, the rise of NMPOU appears to be a new problem. Compared with illegal street drugs, POs are different given that they have therapeutic uses, are manufactured using pharmaceutical-grade ingredients and regulated processes, are available from healthcare sources, and are legal to purchase and use with a prescription. Although POs and illegal street drugs are substantially different, the NMPOU crisis has produced similar outcomes to illegal street drug use, such as high rates of dependence (70), an underground market (71), and estrangement from healthcare providers (72). In addition, POs (and other prescription drugs that are also controlled substances) are only legal for an individual to possess in Canada (73) and the United States of America (74) when that individual was prescribed those drugs by a doctor. As emerging research on NMPOU in the general Canadian and American population indicates that NMPOU is a serious public health concern, less is known regarding whether NMPOU is a significant marker of risks and harms among PWUD who already experience socio-economic marginalization.

Although gaps remain in our understanding of how the risks and harms of NMPOU impact street-entrenched populations, policy-makers and healthcare providers have moved swiftly to address this issue in the absence of sufficient knowledge regarding dynamics, trajectories, or trends among sub-populations. Research is urgently needed to characterize the risks and harms of NMPOU among street-entrenched populations and inform policies to address NMPOU, which have primarily focused on reducing the supply of opioids, fostering responsible patient behavior, and increasing public awareness. The objective of this thesis is to provide scientific evidence describing the context and circumstances of NMPOU among PWUD in Vancouver. This objective will be achieved by (i) reviewing the extant literature of NMPOU initiation, ongoing use, and associated harms, (ii) characterizing NMPOU among PWUD, (iii) investigating initiation trajectories of NMPOU, and (iv) examining the impact of PO source on NMPOU-related outcomes. It is expected that the results from this dissertation will point to opportunities for healthcare

providers and policy-makers to reduce the prevalence and associated harms of NMPOU among PWUD, and provide an evidence base to inform future policy solutions.

1.3. Study objectives and hypotheses

This dissertation has two overarching aims: (i) to characterize the prevalence, risks, and harms associated with NMPOU initiation and ongoing use among PWUD, and (ii) to investigate the impact of acquiring POs from physicians among PWUD who engage in NMPOU. The research studies in this dissertation have the following objectives and hypotheses, and utilize data from two open prospective cohort studies of street-entrenched PWUD in Vancouver (with the exception of the systematized review):

1. **Systematically review the extant literature related to NMPOU in general and street-entrenched populations**. Chapter 2 presents the results of this systematized review that examines literature investigating the prevalence of NMPOU, and NMPOU-related initiation, ongoing use, and harms. The objectives and hypotheses for Chapter 3 – 5 were generated based on the findings of this review.
2. **Identify the prevalence of NMPOU and characterize the risks and harms associated with engaging in NMPOU among PWUD**. The systematized review identified age (younger) (75-78) and gender (female) (79-82) as indicators of risk for engaging in NMPOU, however the extant literature also found that older age groups (79, 83) and men (78, 84, 85) are at risk for NMPOU. To investigate the age-related and sex-related (as a proxy for gender) risks and harms of NMPOU among PWUD, the studies in Chapter 3 use stratified analyses to characterize the unique risks associated with NMPOU among (i) younger and older participants, and (ii) female and male participants. Given that the systematized review consistently found that lower socio-economic status, mental health issues, and poly-substance use were associated with NMPOU, it is hypothesized that participants who engage in NMPOU, regardless of age or sex, will have a higher risk profile and markers for vulnerability when compared with those who only engage in illegal street drug use. The systematized review found that younger age was consistently associated with NMPOU, therefore *I hypothesize that the prevalence of NMPOU will be higher*

among the younger age group in the age-stratified analyses, and this age group will have a higher risk profile than the older age group. For the sex-based analysis, I hypothesize that the prevalence of NMPOU will be higher among females who engage in NMPOU, given that the systematized review found that women are generally more likely to engage in NMPOU; females will also have a higher risk profile than men who engage in NMPOU.

3. **Assess the prevalence and examine the correlates of initiating NMPOU before illegal street drugs among PWUD**. As physicians have begun restricting PO prescriptions and abuse-deterrent formulations have been introduced in response to the NMPOU crisis, there have been documented reports of patients with an opioid prescription transitioning to illegal street drugs such as heroin due to difficulty accessing POs (86-89). There are key knowledge gaps related to these initiation trajectories among street-entrenched populations, as there are few if any studies investigating this phenomenon among adults, and the youth-focused studies are largely qualitative and descriptive (53, 90) or lack a broad focus on socio-structural risk factors (91). Given that less is known about the prevalence and correlates associated with initiating NMPOU before illegal street drugs among street-entrenched PWUD, the objective of this chapter is to document the prevalence and characterize the risks and harms associated with initiating NMPOU before illegal street drugs, versus after. *I hypothesize that the prevalence of initiating NMPOU before illegal street drug use will be lower among younger participants, and associated with an overall lower risk profile and fewer markers of vulnerability.*
4. **Investigate the impact of acquiring POs from a physician on initiating NMPOU and experiencing a non-fatal overdose among people who engage in NMPOU**. The acquisition of POs is an important aspect of NMPOU, however, little is known about how PWUD acquire POs for non-medical use. Previous research identified numerous sources of POs among different socio-demographic groups that include diverted sources (friends, family, drug dealers) and non-diverted sources (physicians and pharmacists) (71). While acquiring POs from diverted sources has been described as risky (92), it is unclear whether acquiring POs from physicians at the time of NMPOU initiation is linked with key markers of risk and whether acquiring POs from physicians is associated with non-fatal overdose. The studies presented in Chapter 4 will test *my hypothesis that acquiring POs from physicians is either a*

protective risk factor or not significantly associated with risks and harms among people who engage in NMPOU. For the analysis investigating NMPOU initiation specifically, *I hypothesize that initiating NMPOU with POs acquired from a physician will be associated with reporting moderate to severe pain, initiating NMPOU at a younger age, and fewer high-risk behaviours.* For the study investigating the relationship between acquiring POs from a physician and experiencing a non-fatal overdose, *I hypothesize that this relationship is confounded by well-established socio-structural markers of overdose risk, such as homelessness, binge drug use, incarceration, and risky income generation.*

An overview of the statistical analyses presented in Chapters 3-5 is provided in Table 1 below.

Table 1: Overview of statistical analyses in Chapters 3-5

Chapter	Brief description	Sample	Outcome	Analysis type
3.1	Age-based analysis of risk factors associated with NMPOU	All participants	NMPOU in last six months	Longitudinal
3.2	Sex-based analysis of risk factors associated with NMPOU	All participants	NMPOU in last six months	Longitudinal
4.1	Initiate NMPOU before illegal street drugs	All participants	Initiate NMPOU before illegal street drugs	Cross-sectional
4.2	Initiate NMPOU before illegal street drugs	Participants reporting lifetime NMPOU	Initiate NMPOU before illegal street drugs	Cross-sectional
5.1	Initiate NMPOU with a physician prescription	Participants reporting lifetime NMPOU	Initiate NMPOU with a physician prescription	Cross-sectional
5.2	Acquire POs for nonmedical use exclusively from physicians	De facto participants reporting NMPOU in the last six months	Acquire POs for nonmedical use exclusively from physicians in last six months	Cross-sectional
5.3	Acquire POs for nonmedical use exclusively from physicians and overdose	De facto participants reporting NMPOU in the last six months	Overdose in last six months	Longitudinal

1.4. Methods

1.4.1. Systematized review

Chapter 2 presents a systematized review of NMPOU-related initiation, ongoing use, and associated harms. Systematized reviews are a type of review that may or may not include systematic searching and quality assessments (93). This review type is recognized to be productive in facilitating doctoral research and dissertation projects where the principles of a systematic review are followed as much as possible but without meeting the full rigorous criteria for a systematic review.

The systematized review methodology was used for this dissertation given that the full requirements of a systematic review were not met and not feasible for a dissertation. In addition, systematic reviews typically require a team of individuals working together, and this was not appropriate for this dissertation work. Despite not conducting a systematic review, the review in this dissertation includes a comprehensive systematic search, a narrative synthesis with tabular accompaniment, and analysis of what is known along with the strengths and limitations of the findings.

1.4.2. VDUS methodology

The research presented in Chapters 3–5 uses secondary data from the Vancouver Drug Users Study (VDUS), which is a prospective cohort study funded by the National Institutes of Health. VDUS harmonized and combined two previously independent prospective cohorts: the At-Risk Youth Study (ARYS) and the Vancouver Injection Drug Users Study (VIDUS).

The ARYS study began in 2005 and has recruited approximately 1,000 street-involved youth who live primarily in downtown Vancouver, British Columbia. The eligibility criteria for participating in this study are: being between the ages of 14 and 26; recent use of an illegal street drug (including NMPOU) other than or in addition to cannabis; and willingness to provide informed consent. Participants are also required to be “street-involved”, which is defined as being recently homeless, having used services designated

for street-youth, or heavily participating in street-life through buying and selling drugs and/or sex and engaging in criminal activity (94-97).

VIDUS is an open prospective cohort study established in 1996. Beginning in May 1996, participants were recruited through street outreach and self-referral in the Greater Vancouver Regional District. Eligibility criteria included having injected illegal street drugs at least once in the previous month.

Participants in ARYS and VIDUS complete an interviewer-administered questionnaire at the baseline visit and semi-annually thereafter. Study visits also include a meeting with a study nurse to provide a blood sample for serologic testing that includes HIV and Hepatitis C. The stipend for participating in the ARYS and VIDUS studies before June 2013 was $20; after June 2013, the stipend was raised to $30 to appropriately compensate participants for their time.

The University of British Columbia/Providence Health Care's Research Ethics Board approved VDUS. Both Simon Fraser University's Office of Research Ethics and the University of British Columbia/Providence Health Care's Research Ethics Board approved the use of secondary data from the VDUS study for this doctoral project.

There are numerous reasons for using VDUS as the main data source in this dissertation that underscore the utility and appropriateness of these data for the study objectives. First, VDUS is a unique NIH-funded dataset that includes nearly 22 years of data from VIDUS, one of the longest-running cohorts of people who inject drugs in the world. This VIDUS data is now harmonized with ARYS, which is also noteworthy as one of few cohort studies to recruit and successfully follow injection-naïve youth through to transitions into injecting drugs. Second, the wide scope of questions in the study instrument allows for the exploration of numerous hypotheses using the same data source. Topics explored in the VDUS study instrument include: socio-demographic characteristics, housing stability, drug use and other behavioral patterns, income-generation sources and experiences, childhood trauma, interactions with police and the criminal justice system, and accessing a range of services including health care, community-based social services, harm reduction programs, and addiction treatment. Third, the data collected

through VDUS study visits is of high quality as there are professional full-time teams devoted to interviewing participants, data cleaning, and monitoring data quality.

1.4.3. Conceptual Framework

This dissertation uses the Risk Environment Framework, which situates drug-related harms within the "risk environment" of PWUD (41). The risk environment is a complex intersection of intrapersonal, microenvironmental, and macroenvironmental factors that influence drug use (98) and constrain individual ability to reduce drug-related harms, such as overdose and HIV infection (41, 99). By extension, the potential success of interventions to reduce drug use and associated harms is dependent on various social, political, and economic factors that may facilitate or impede the intervention's effectiveness. This framework shifts the focus for change from the individual to extra-individual factors, such as social, structural, and political-economic environments that shape health behaviours, access to health and social services, and risk for harm among PWUD. Thus, the Risk Environment Framework shifts the focus in our understanding of the production of drug-related harm to these factors that are beyond the control of any one individual and helps promote a human rights approach to public health (100).

The Risk Environment Framework is appropriate and applicable for researching substance use and related health outcomes, as compared to an overly individualistic approach that does not account for the full range of risk and burden of negative health outcomes among PWUD (40). Historically, health research has been dominated by a constellation of theories that focus on risk-related decision-making among individuals, such as theories of "reasoned action", "self-efficacy", "health beliefs", and "planned behavior" (41, 101-103). Although these theories provide some insight into the psychology of PWUD, this overly individualistic approach ignores socially constructed power inequalities and context-dependent risks that shape health behaviours and outcomes (41).

This theoretical orientation is especially useful for informing policy solutions, which is arguably the most ethical outcome for research involving a population that has been historically marginalized and discriminated against by healthcare providers and policy-makers. Situating the responsibility for change with healthcare providers and policy-

makers is also a more effective strategy, given the decision-making power and privilege of status afforded to this group. Furthermore, at the time of writing this dissertation, research investigating neuropsychological, genetic, and other biological factors associated with substance use has produced neither stronger evidence for modifiable risk or protective factors, nor clearer directions for policy solutions to address substance use. Although there may be key biological or psychological factors contributing to NMPOU among PWUD that are not accounted for by the Risk Environment Framework, a comprehensive understanding of these factors is not necessary for developing sound interventions and drug policy (98).

The Risk Environment Framework is a well-established theoretical orientation for situating research on substance use and related issues, as three seminal papers describing the Risk Environment Framework published since 2002 (41, 99, 100) have accumulated nearly 2,000 citations (based on Google Scholar), and is cited by landmark studies in the field of substance use and HIV/AIDS (104-106). Previous research using the Risk Environment Framework to investigate drug use in Vancouver found that fears of street predators and police contributed to rushed injections and decreased use of safer injecting practices that prevent infection (107). Additional research from the same setting found that the introduction of a supervised injecting facility with immediate emergency response (a microenvironmental intervention), ameliorated many socio-structural risk factors for overdose such as injecting alone, purchasing adulterated drugs or drugs of unknown quality, and fear of police (108).

The Risk Environment Framework distinguishes between intrapersonal, microenvironmental, and macroenvironmental factors, as well as four subcategories for each: physical, social, economic, and political (41). Given that all these factors and categories are inextricably intertwined and intersect in numerous ways (41) and would require resources beyond what is available for this dissertation to investigate, the following simplified categories were used in this dissertation: individual, socio-structural, and environmental.

1.5. Summary

My thesis consists of six chapters. Chapter 1 provides an overview of NMPOU and the current policy response, the justification for this research, study objectives, study design, and conceptual framework. Chapter 2 presents the systematized review investigating NMPOU initiation, ongoing use, and associated harms, and Chapters 3–5 present the data-driven analyses of this dissertation. Specifically, Chapter 3 presents stratified age-based and sex-based analyses of NMPOU among PWUD in Vancouver and explores risk factors associated with engaging in NMPOU. To specifically assess trajectories of drug use among PWUD, Chapter 4 presents the data from an analysis investigating the prevalence and correlates of transitioning from NMPOU to illegal street drug use. Chapter 5 investigates the impact of acquiring POs from physicians on NMPOU initiation and non-fatal overdose. Finally, Chapter 6 synthesizes the key findings from these analyses and discusses the study results, methodological limitations, policy implications, and future directions for NMPOU-related research.

Chapter 2.

Systematized review of the risks and harms associated with NMPOU in high income countries

2.1. Introduction

NMPOU is among the latest substance use trends to rise across North America and now represents an epidemic in many jurisdictions (109). Studies investigating NMPOU indicate that the prevalence of NMPOU is as high as 16% among Canadian elementary and secondary school students (110) and 4.1% among adults in the American general population (111). Clinical abuse of and dependence on POs has increased in the United States (70), and proxy markers indicate that the United Kingdom and Australia are likely experiencing modest increases in NMPOU due to problematic prescribing practices (112, 113).

Research on NMPOU in the general Canadian and American populations clearly indicates that NMPOU is a serious public health and economic concern (7, 111, 114), and PO use has been linked with alarming increases in overdose deaths, even surpassing motor vehicle accidents as a source of mortality in some areas (109). Recommended policies to address NMPOU focus on electronic monitoring and surveillance programs (7, 115, 116), which aim to reduce the overall prescribing rates for POs and detect aberrant prescribing patterns among both physicians and patients. Although these policies have been implemented with increasing urgency, numerous and significant gaps in the scientific understanding of NMPOU remain.

Despite the publication of several systematic reviews related to NMPOU (71, 117-126), none investigate the initiation, ongoing use, and multiple associated harms of NMPOU among samples that are not restricted to a single jurisdiction, age group, route of administration, or medical diagnosis such as pain or mental illness. Synthesizing this knowledge is imperative given that POs remain legal and used for therapeutic purposes, yet POs are also used nonmedically and distributed through social networks and unregulated markets similar to illegal street drugs. Therefore, a comprehensive

understanding of the initiation, ongoing use, and harms of NMPOU is necessary to inform policy responses that effectively reduce NMPOU without producing the unintended consequences common among policies intended to restrict illegal street drug use. Given the increasing prevalence of NMPOU and alarming rates of overdose fatalities in the United States and Canada in particular, we identified a comprehensive range of NMPOU-related outcomes and systematically reviewed the literature to provide a broad evidence base to inform policies aimed at addressing NMPOU.

2.2. Methods

This study comprehensively reviewed 15 years of scientific research related to NMPOU to investigate what is known about the initiation, ongoing use, and associated harms of NMPOU in Canada, the United States of America (USA), the United Kingdom, Ireland, Australia, and New Zealand. The outcomes for this review included several aspects of NMPOU, including the (i) circumstances and context of NMPOU initiation and use (motivations, acquisition and availability of POs, and routes of administration), (ii) risk factors and characteristics associated with NMPOU (socio-demographic characteristics, pain, concurrent substance and polydrug use, and mental health), and (iii) health-related harms associated with NMPOU (overdose and mortality, infectious diseases, and trajectories and changes in drug use). These outcomes were selected a priori and adapted based on recurring themes in the literature.

For the purpose of this review, NMPOU was defined as any use of POs, including opioid agonist treatment (OAT), for nonmedical purposes (e.g. to get high or experiment) or any use of POs that is not compliant with a physician's orders for a patient (e.g. self-escalating dosage). Studies included in this review met the following criteria: written in English, conducted original replicable research on humans in primarily English-speaking high-income countries (Canada, USA, the United Kingdom, Ireland, Australia, and New Zealand), and published in a peer-reviewed journal between January 1, 1999 and December 31, 2014. Studies that did not meet these criteria were excluded, as well as those that used review methodologies, and articles where the distinct effects of NMPOU were not clear (e.g. NMPOU data were amalgamated with data about other substance use).

The following databases were searched using terms related to the outcomes described above: MEDLINE, CINAHL, PsycINFO, EBSCO, Criminal Justice Abstracts, Web of Science, Social Sciences with Full Text, Health Source: Nursing/Academic Edition, Cochrane Collection Plus and Academic Search Premier. Database searches were purposefully broad to capture a wide swath of literature, and controlled vocabulary terms were used where possible. The MEDLINE search strategy is outlined in Table A1 (Appendix A). Results from the database searches were imported into EndNote reference manager (version X7).

After performing the database searches and undertaking a search for duplicate citations, the primary author (TC) screened publication titles to identify articles that clearly did not meet the inclusion criteria. Articles deemed potentially relevant moved on to the abstract screening stage and were screened again for relevancy. If the publication was deemed to be potentially relevant at this stage, a full-text copy of the article was retrieved and screening for inclusion criteria continued.

A standardized form was created to manage data extraction for each eligible record. Information regarding the methods and results of each study were entered by one author (TC) and checked independently for accuracy and completeness by another (JR). The final selection of articles was analyzed thematically according to outcomes of interest.

2.3. Results

2.3.1. Literature Search Results

The results from the database searches and screening process are outlined in the PRISMA diagram (Figure 1). Briefly, 3,198 records were identified through database and hand searches. After removing 351 duplicates, 2,847 articles were screened for the eligibility criteria. Full-text copies of 323 articles were assessed, and data were extracted from 154 articles that met all the eligibility criteria. Data from each article are summarized in Table A2 (Appendix A).

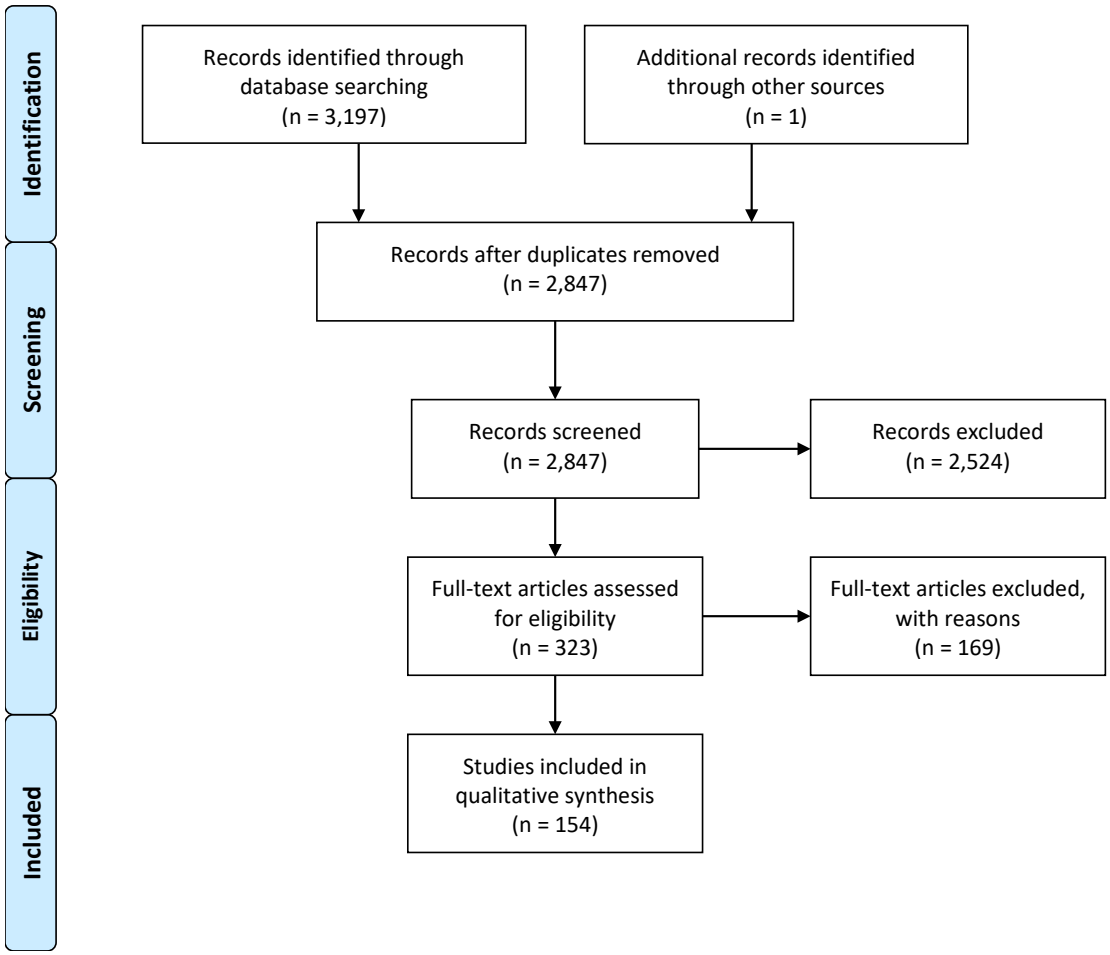

Figure 1: Adapted PRISMA flow diagram

2.3.2. Summary of included studies

The articles in this review conducted research in the USA (n=127, 83%), Canada (n=17, 11%), Australia and New Zealand (n=7; 5%), the United Kingdom (n=1; 1%), and Ireland (n=1; 1%). The majority of articles in this review were cross-sectional quantitative studies (n=95, 62%), with 38 longitudinal quantitative studies (25%), 11 qualitative studies (7%), 7 mixed methods studies (5%), 1 experimental study (1%), and 1 case report (1%). A total of 78 studies used population-level sampling techniques (51%), 71 used non-probability sampling methods (46%), and the remaining studies used mixed sampling or the sampling method was not specified (n=4, 3%).

2.3.3. Circumstances and Context of NMPOU Initiation and Use

Initiating NMPOU

Two studies reported that participants who engaged in NMPOU frequently did so after requiring treatment for injuries or pain (127, 128), and an Australian study found that NMPOU was significantly associated with initiating opioid use (versus heroin) due to pain (129). In addition, the easy availability of POs was found to facilitate NMPOU initiation among young Americans (53). Researchers also found that young adults in the USA who were experienced drug users frequently initiated NMPOU with buprenorphine (130), and individuals in treatment for NMPOU had initially engaged in NMPOU to manage their cocaine use (128). Alcohol and illegal street drug use were associated with subsequently initiating NMPOU (131, 132), although amphetamine use was identified as the strongest predictor of future NMPOU among young American adults (133).

Various studies found that NMPOU initiation most frequently occurred among adolescents and young adults (131, 134-137) suggesting a possible cohort effect, and initiation often occurred before the age of 21 (134, 135). Initiating NMPOU at a younger age was associated with using methadone acquired from diverted sources daily or weekly (versus less frequently) (138), and rural residence (versus urban) (139). American women were more likely to initiate NMPOU later than men (127), however, women increased their use at a faster rate (127). A high proportion of American women (42%) also reported that their initiation into NMPOU occurred within a close romantic relationship with a man who engaged in NMPOU (128).

Motivations Associated with NMPOU

Studies identified in this review reported many different motivations for engaging in NMPOU, such as getting high (43, 140-147), relieving pain (82, 140, 141, 144), coping with stress and anxiety (127, 141, 144), avoiding withdrawal from POs or heroin (141), having a good time/increasing energy or facilitating daily activities (43, 144, 145), relieving boredom/unhappiness or “escaping” (43, 148), sleeping (144), feeling “normal” (141), moderating the effects of other drugs (141), and experimenting (145). Population-level studies in Canada and the USA found a low prevalence of people using POs to get high (0.4-9%) (149, 150), and a high prevalence of engaging in NMPOU to relieve physical pain

(45-95%) (151, 152). Researchers also found that multiple motivations for engaging in NMPOU were common (153), and multiple motivations were linked with higher scores on the Drug Abuse Screening test (140). In addition, motivations changed over time, where pain relief was frequently reported as the initial reason for engaging in NMPOU (144).

Those who engaged in NMPOU to get high were more likely to be of younger age or older adolescents (142), First Nations, Metis, or Inuit ancestry (versus non-Aboriginal ancestry) (142), and the evidence indicates mixed support for whether gender was associated with engaging in NMPOU to get high (142, 154, 155). Those who were motivated by pain relief (and relaxation) were more likely to be female (153, 155). An American study found no significant differences in the prevalence of Caucasian versus non-Caucasian (primarily African American) individuals using POs to get high, achieve pain relief, or both (156).

Acquisition & Availability of POs for Nonmedical Use

Acquiring POs from healthcare providers (physicians/pharmacists)

One American study examining PO sources found that physicians were a source of opioids among a high proportion of the population (91%) (144), although some studies showed lower rates of physician-acquired POs (31-49%) (157-159) and only 15% of American adolescents who engaged in NMPOU and attended an emergency room reported currently having a prescription for opioids (160). A study of American adults who engaged in NMPOU found that a physician source for POs was independently associated with PO misuse or dependence, and 36% of participants with a physician prescription for POs reported at least one other source for POs (family or friends) (158). In addition, 75% of sampled American chronic pain patients with PO prescriptions were not complying with their prescribed regimen as determined by urine testing (161). Women who engaged in NMPOU were more likely to have first obtained POs through a physician prescription (162), and a prescription for opioids was the strongest predictor of NMPOU among women as compared to men (163).

Two studies also suggested that POs were obtained from healthcare sources and re-sold for personal profit as part of informal arrangements (148, 164), and elaborate schemes with third-party “brokers” coordinating the acquisition and diversion of these POs

from doctors known for prescribing POs and small pharmacies illegally selling POs (164). Gender differences associated with doctor shopping, where an individual visits multiple physicians for an opioid prescription, were negligible (165).

Acquiring POs from diverted sources (friends, family, street-based drug dealers)

The studies in this review indicated that POs were easier to acquire than traditional illegal street drugs (e.g., heroin, cocaine, crystal methamphetamine) in certain New Zealand and Canadian cities (48, 166), and 39-85% of people using POs had no prescription (160, 167). One study found that 72% of Canadian secondary students who engaged in NMPOU obtained POs from people with whom they shared a home (168), although other studies of various groups found that 6-85% obtained POs from friends (144, 147, 155, 168, 169), 12-49% obtained POs from a parent or family member (144, 155, 169), and 91% of Americans with a history of drug use purchased POs from a street-based drug dealer (170); however, only 12% of American methadone patients with a prescription for POs reported sharing their POs with others (12%) (171). Factors associated with acquiring POs from diverted sources included more frequent misuse of POs (172), greater adverse events (defined as “serious health risks” such as dizziness, altered mood, seizures, shallow breathing, etc.), (152) and greater cravings for POs, which may be associated with riskier PO use (173); depression was not significantly associated with sharing behaviours (174). Some studies suggested that American males were more likely to obtain POs from family, friends and dealers (84), and acquire diverted Oxycodone and Oxycontin from more “aggressive forms” of diversion such as street-based drug dealers (175). Hydrocodone (versus oxycodone) was more likely to be obtained through doctors, friends, or family members (versus street-based drug dealers) (175). Methadone was commonly acquired from friends, dealers, and family members (138), however, two studies among adults in Baltimore (USA) found that diverted OAT medications were often used for their medical purpose (176, 177).

The internet was also identified as a source for POs in the USA (178), partially due to the lack of prescription medication coverage before the introduction of the Affordable Care Act (152). American researchers found, however, that only 2-6% of adults in addiction treatment and in the general population obtained POs through the internet (144,

157), and street-based populations were less likely to acquire POs via the internet due to cost (164).

Route of Administration

Based on the studies included in this review, the most common route for administration of NMPOU were oral consumption (ingestion or chewing) (62-91%), followed by intranasal use (11-53%), and smoking (15%) (127, 146, 179). The prevalence of PO injection varied from 17-89% among people with a history of illegal street drug use or with other markers of vulnerability (46, 146, 179-182), and a Canadian study found a significant increase in PO injecting from 2004 to 2009 (21% to 75%) (51). However, other studies found that injection drug use was not associated with clinical abuse of, or dependence on, POs (84) and lower proportions of consumption via injection were observed for POs compared with heroin (46, 183-185). Three studies found that 22-73% of young people and adults who use illegal street drugs initiated intravenous drug use with POs (53, 180, 186).

American secondary students who used POs to get high were more likely to use non-oral routes of administration (153), and American adults in the general population who began using oxycodone because of pain were marginally more likely to use intranasally (versus intravenously) (187). Intranasal use was also frequent among nonmedical OxyContin users (147) and buprenorphine users (130). Hydromorphone was the most frequently injected opioid among a sample of Canadians on methadone (186), and hydrocodone was used more often than oxycodone through non-intravenous routes among Americans seeking addiction treatment (175). With respect to gender differences associated with the route of administration, one study found that American males were more likely to crush and snort POs (versus chew or inject) (127), but another found no significant gender differences in the prevalence of New Yorkers (USA) using POs intravenously or intranasally (187).

2.3.4. Risk Factors and Characteristics Associated with Engaging in NMPOU

Socio-Demographic Characteristics and NMPOU

NMPOU was significantly and independently associated with a number of socio-demographic variables such as Caucasian ethnicity (55, 79, 188, 189), lower socio-economic status and unemployment (85, 144, 160, 190-192), and poor academic performance and less education (160, 188, 193); only one study found no significant differences among these variables (167) and another found that Americans recruited using street-based methods and who actively engaged in NMPOU were more likely to have higher education (189). Residency in rural areas (versus urban) was linked with NMPOU in multiple studies (139, 193-195), with one study finding the converse (193) and another finding no significant difference (196). Compared with individuals who use heroin and cocaine, those who engaged in NMPOU were more likely to receive income from paid work (55), had more education (54) and were less likely to drop out of school (184). In addition, those who injected POs were more likely to be unemployed than those who used POs intranasally (187).

The results consistently indicated that adolescents and young adults were more likely than older youth and adults to engage in NMPOU (75-79, 84, 131, 136, 142, 154, 188, 193, 197, 198), and share and receive any class of prescription medications (171). Evidence suggests that there are significant birth cohort effects, where more recent birth cohorts have higher lifetime and past-year prevalence of prescription opioid-use disorder due to NMPOU (83); these birth cohort effects have been attributed to increased availability of POs (75). In addition, those who engaged in NMPOU were more likely to be younger than those engaging in other illegal street drug use (54, 199), which may be linked to adolescents' high rates of injury requiring treatment with opioids (168, 193, 200). Among older age groups, the risk for NMPOU increased (79, 83), and acquiring POs via doctor shopping generally decreased with age (165, 201). Youth were reported to prefer OxyContin, younger males were more likely to use oxycodone, and older age groups were more likely to use hydrocodone nonmedically (143, 175).

There was conflicting data about whether females or males were more likely to engage in NMPOU. Numerous studies reported an increased likelihood of engaging in

NMPOU among females in the American general population, in grade school, in addiction treatment, and club-goers (76, 79, 81, 82, 163, 188, 193), and fewer studies reported that males were more likely to engage in NMPOU (78, 84, 85, 202, 203). However, few significant differences in the proportion of males and females engaging in NMPOU were found among American youth (184) and young adults (204), and Canadian adults (154). Researchers also found birth cohort effects, where younger females (aged 15-19) were almost two times more likely to engage in NMPOU than older females and slightly more likely than younger males to engage in NMPOU (75). Males were more likely than females to use oxycodone, Percocet, codeine, Demerol, morphine, and Methadone (175, 205, 206); females were more likely to engage in nonmedical hydrocodone use (162, 175).

Pain Associated with NMPOU

Studies suggested that between 40-70% of those who engaged in NMPOU also experienced pain (144, 207), although support for a statistically significant link between pain and NMPOU was mixed (77, 163, 208, 209). A study of the general American population found that levels of pain were highest among those who engaged in NMPOU (versus the nonmedical use of other prescription drugs) (210). NMPOU was also linked with reports of being disabled by pain (211), moderate to severe levels of pain (49), and engaging in medical PO use for pain (133, 167), although one study found no differences in pain intensity between Americans who engaged in NMPOU or medical PO use (167). Engaging in NMPOU to relieve pain (versus other reasons), however, was associated with lower odds of other substance use (151).

Among people experiencing pain, there were no significant differences between rates of chronic pain and other pain among those engaging in NMPOU, and those with chronic pain did not engage in significantly different NMPOU-related acquisition and abuse patterns (versus those with some or no pain) (212, 213). Nearly one-quarter of American young adults were denied POs by physicians (23%), and this group reported more pain problems than those not denied a prescription (214). American women were more likely than men to engage in NMPOU to cope with pain (162), however, another study found that American women who engage in NMPOU were less likely to report a pain problem than men (163).

Poly-substance and Concurrent Substance Use and NMPOU

Overall, moderate and high rates of concurrent or poly-substance use were reported by a number of Canadian (51, 159, 186) and American (42, 76, 77, 79, 82, 84, 155, 160, 184, 187-189, 191, 196, 204, 215-222) studies, such that the strongest predictors of NMPOU were the use of other illegal street drugs (190), the frequency of alcohol use (221), and other prescription drug classes (42). Concurrent substance use disorders involving NMPOU increased significantly between 1991 and 2002 ($p<0.01$) (223), and high proportions of those who engaged in NMPOU met DSM-IV criteria for another past-year substance use disorder (223), had at least one diagnosis of non-opioid drug abuse (203), and were more likely to experience future general or opioid-related substance use disorders (224). However, studies also found lower odds of nonmedical OxyContin use among people who had not used heroin or other illegal street drugs (146), and those who used methadone nonmedically were less likely to have used heroin or cocaine recently (177).

This review suggested support for a relationship between younger age and poly-substance use that includes NMPOU (221, 225), although one study found that adolescents were less likely to report other substance use issues (versus adults) (226). In addition, American youth who engaged in poly-substance use were more likely to live in lower income households and experience lifetime anxiety (227). Some studies found similar rates of concurrent substance use among men and women (110, 206), however, males were more likely to engage in concurrent polydrug (227, 228), hallucinogen (163), and cannabis use (110) and females were more likely to engage in the concurrent use of inhalants (163). American females who engaged in NMPOU and other substance use had higher rates of mood/anxiety disorders than men (228), and the results were mixed regarding which gender was more at risk for concurrent alcohol use (110, 162, 163).

Mental Health and NMPOU

Moderate and high rates of psychiatric and mental health issues among people who engaged in NMPOU were supported by a number of Canadian (159), American (42, 77, 82, 84, 144, 170, 184, 188, 189, 196, 207, 227, 229-232), and Australian (129) studies. With the exception of a singular American study that found no relationship between

depression and NMPOU (133), multiple studies found that mental illness was significantly associated with NMPOU (78, 174, 203, 233), and clinical dependence on POs along comorbid mood or anxiety disorder diagnosis was associated with higher addiction severity (230). One study of the American general population found that mood/anxiety disorders both precede and follow NMPOU, and are associated with incident opioid use disorder due to NMPOU (233). Indeed, the population-attributable risk for NMPOU due to mental health disorders was likely much greater than the risk for NMPOU resulting from medical opioid use (234), and mental health issues accounted for 38% of the variance in the potential for misusing POs among Americans with chronic pain presenting to emergency departments (235).

American youth who initiated NMPOU at an earlier age were more likely to have difficulty coping and regulating emotions (236), and both males and females who engaged in NMPOU were more likely to experience psychological issues (154, 207, 211). Females who engaged in NMPOU, however, were more likely to report a serious mental illness (206), serious psychological distress (84), use POs to cope with negative affect or interpersonal stress (127, 162), and attain higher scores on the prescription drug use questionnaire (PDUQ), which indicates higher likelihood of a substance use disorder (211). Males were more likely to experience legal and behavioural problems (211), and depression (163). Both males and females were at risk for suicidal ideation (110, 231), although a Canadian survey of the general population found an association between NMPOU and suicidal ideation for women but not men (110). American females were more likely to have attempted suicide (231).

Findings Related to Specific POs

Nonmedical buprenorphine use was associated with lifetime use of a greater number of POs (130), and nonmedical hydrocodone users were more likely to be older and less likely to inject (175). Numerous negative outcomes were associated with the nonmedical use of OxyContin, such as higher intensity drug use, dependency and avoiding painful withdrawal symptoms, impairing ability to meet work or school commitments, and negative impacts on families and the community (46, 148, 237); although Americans who used OxyContin nonmedically (versus other NMPOU) did not significantly differ on other risk factors and characteristics (46).

2.3.5. Health-Related Harms Associated with NMPOU

Overdose and Mortality Associated with NMPOU

Based on the results from multiple studies, PO-related mortality has risen in the United States since 1997 (189, 238, 239), and a high proportion of American youth who engage in NMPOU reported a history of overdose involving POs (42%) (240). Other research from the USA and Australia suggests, however, that the prevalence of overdose or mortality due to NMPOU is relatively low among their general populations (0.2-4%) (44, 241).

Numerous studies indicate that NMPOU poses a risk for overdose (44, 129, 189, 209, 241-245) and POs were the most frequently used class of lethal substance among Canadians who died by suicide (246); one Canadian study found, however, that NMPOU was not significantly associated with non-fatal overdose (55). Doctor shopping increased the risk of overdose (165), and moderate to high proportions of those who experienced an NMPOU-related overdose engaged in NMPOU for non-pain reasons (209), engaged in heavy amounts of NMPOU (209), obtained POs from diverted sources or doctor shopping (209, 238, 247, 248), were of African American ancestry (239), or were in “places other than a residence” at the time of death (239). Older age was associated with mortality due to unintentional overdose (249), although younger age was more common among decedents of methadone-related overdoses (versus overdoses due to other POs) (245). High proportions of other substances, primarily non-opioid classes of prescription drugs, were found among those who died due to fatal NMPOU-related overdose (246, 248-250). The evidence is mixed regarding the effect of prescriptions on NMPOU-related overdose, as some studies found low proportions of those who died by overdose received a prescription for POs (244, 248, 250), but another found that a prescription for certain POs, such as buprenorphine, fentanyl, hydromorphone, methadone, or oxycodone, was associated with an increased risk for overdose (249). Two studies found conflicting evidence linking intravenous PO use and overdose (243, 250).

Infectious Diseases and NMPOU

American researchers found considerable overlap between populations who engage in NMPOU and also test positive for Hepatitis C (HCV) (189, 203), and that PO

injection was associated with HCV infection and HCV-RNA positivity (51, 180, 251). The evidence suggests that the risk of hepatitis and HIV may be as high as 18% (242), and arises from a number of different injection-related factors, such as higher frequency of PO injection events (51), sharing injection paraphernalia (252), the unique chemical properties of POs (versus other illegal street drugs) that leave enough residue on paraphernalia to re-liquefy and re-use (181), and extraordinary efforts to overcome tamper-resistant formulations (253); however, the evidence for syringe sharing and NMPOU was mixed (55, 180, 252). Researchers found no relationship between NMPOU and sexually transmitted infections (254) and the evidence for the relationship between NMPOU and sexual risk behaviours was mixed (185, 255).

Trajectories and Changes in NMPOU Over Time

Numerous studies reported instances of individuals initiating NMPOU and then transitioning to heroin use (46, 53, 86, 87, 91, 134, 147) and of the opposite trajectory – using illegal street drugs and then transitioning to NMPOU (133, 147, 237). The proportion of Americans in the general population who engaged in NMPOU before initiating heroin use increased from 64% in 2002-2004 to 83% in 2008-2010 (218), however, the prevalence of engaging in NMPOU first was only 40% in a 2011 study of young American who inject drugs (91). It is estimated that among young people (≤30 years old) in the USA, heroin initiation occurred 2.0 years after any NMPOU (134), although another American study found that polyopioid use was associated with quicker progression to heroin use among people who use illegal street drugs (46).

The decision to transition from NMPOU to other hard drugs, such as cocaine and crystal methamphetamine but most commonly heroin, was influenced by the high cost and low availability of POs (87, 256). An American study found that those who transitioned from NMPOU to injecting heroin were less likely to have ever been tested for HIV, and also believed themselves to be at lower risk for HIV than other people who inject drugs (91).

One American study found that those who engaged in NMPOU to relieve pain were more likely to engage in NMPOU before medical PO use *and* after medical PO use. In addition, those who used POs to get high, relax, and regulate their affect were all more

likely to engage in NMPOU before medical PO use (153). Study findings also indicate that patterns of NMPOU may change over time, where 24% of the American general population who engaged in NMPOU developed prescription drug abuse during their lifetime, and earlier age of NMPOU initiation was associated with the development of clinical dependence on prescription drugs (135). In addition, those using OxyContin for nonmedical purposes transitioned to intravenous OxyContin use after a median of three years (257).

2.4. Discussion

This systematized review identified over 150 studies investigating NMPOU across primarily English-speaking high income countries, with most studies reporting data from the USA, and conducting population-level, observational, and quantitative research. The results from this review found that the circumstances and context of initiating and engaging in NMPOU are heterogeneous; however, younger age groups, female gender, lower socio-economic status, physical pain, mental health issues, and poly-substance use were most consistently linked with NMPOU and its initiation, ongoing use, and associated harms. The harms of NMPOU included non-fatal and fatal overdose, HCV and STIs, and intensifying drug-use trajectories, which clearly indicate serious negative consequences as a result of engaging in NMPOU.

While this review did not find a complete consensus among the literature, numerous risk factors were consistently linked with NMPOU. The relationship between mental health issues and NMPOU was among the strongest and most consistent identified in this review (78, 174, 203, 233-235), as well as poly-substance use and NMPOU (42, 51, 76, 77, 79, 82, 84, 155, 159, 160, 184, 186-191, 196, 204, 215-222). Pain was frequently cited as a motivator for engaging in NMPOU (82, 140, 141, 144) and was linked with engaging in NMPOU (49, 133, 163, 167, 209, 211), although some studies found otherwise (77, 167, 208, 212, 213). In addition, certain socio-demographic groups such as females (76, 79, 81, 82, 163, 188, 193), younger age groups (75-79, 84, 131, 134-137, 142, 154, 188, 193, 197, 198), and those of lower socio-economic status or education level (85, 144, 160, 190-192) were consistently more likely to engage in NMPOU or experience elevated risk for harms associated with NMPOU.

Among a representative sample of the American population, nearly one-quarter of adults who engaged in NMPOU reported progressing to clinical abuse of POs (135), and numerous risk factors such as female gender (211), younger age (83, 135), poly-substance use (203, 223, 224), and mental health issues (mood/anxiety disorders especially) (230, 233) were each linked with risk for, or diagnosis of, a substance use disorder. Given this evidence, tailored programming to facilitate participation in harm reduction programs including OAT for individuals who are female, younger, experiencing mental health issues, or engaging in poly-substance use should be a priority. Harm reduction services such as syringe programs, drug consumption sites, and OAT all provide numerous benefits to people who use drugs (258), and OAT in particular is documented as reducing the risk for substitution effects, where some individuals use drugs such as heroin when POs are unavailable (218). Barriers to enrolling and maintaining engagement in OAT remain in many settings (259, 260), despite recommendations to improve or scale-up OAT services from numerous government (261), quasi-government (7), and non-government (116, 262, 263) organizations.

This review consistently pointed to the need for harm reduction and treatment programs for at-risk groups, however, the results provide few directions for informing prevention-oriented policy solutions which are necessary for reducing NMPOU incidence. The wide variety of motivations for engaging in NMPOU (43, 82, 127, 140-148) and mixed findings related to the role of healthcare sources in relation to diversion and acquisition of POs (144, 157-160, 167) suggests enormous heterogeneity related to the contexts of initiating and engaging in NMPOU. Further research delineating at-risk groups, critical PO acquisition pathways, and key intervention points that precede NMPOU initiation will be important for developing policies aimed at preventing the acquisition of POs and initiation of NMPOU.

Although this review yielded firm conclusions related to some at-risk groups, numerous research gaps and limitations within the existing scientific literature were identified. The high number of studies using data from nationally representative surveys (n=42) or other population-level data sources (n=36) increases the generalizability of this review's conclusions, but studies focusing on socio-economically marginalized groups were limited. These groups are often under-represented in population-level data sources

that depend on having health insurance or accessing health services, as well as national household surveys that undercount hidden populations such as those who are homeless (264, 265). Those who are socio-economically marginalized are more likely to engage in substance use and experience harms associated with substance use (40), therefore, there is a clear need for more research to inform tailored policies and services for these groups.

Other noteworthy gaps in knowledge and areas for future research include outcomes associated with specific POs other than OxyContin. In addition, there is a need for research investigating other outcomes associated with engaging in NMPOU such as incarceration and HIV, and the potentially protective effects of NMPOU versus street drugs. Better understanding of each of these issues will support the development of policy responses to prevent the incidence of NMPOU, reduce associated harms, and increase access to evidence-based addiction treatment programs.

The strength of this review's conclusions are also limited due to numerous conflicting findings and difficulties drawing comparisons among included studies. The wide range of study participants, comparison groups, and PO-related variable definitions reduce the comparability of the results and leave gaps in knowledge despite the large number of published studies. A strategic research agenda may provide researchers with a tool for coordinating research investigating these gaps in knowledge using consistent variable definitions and comparison groups, and ultimately support the development of a better understanding of NMPOU and policy solutions.

Limitations of review protocol

This review had strict eligibility criteria regarding English-language and peer-reviewed publications reporting original research, therefore the results were limited by the exclusion of many articles in the grey literature, articles that did not adequately describe their methodology, reviews, and quasi-government and government surveillance reports. In addition, research from only six countries was included in this review, which excludes peer-reviewed published research from many parts of the globe. Given the focus on informing policy-making, however, a review of high-quality research articles from settings similar in economic advancement and policy was deemed more useful than an exhaustive global review of the scientific and grey literature.

2.5. Conclusion

This review found clear indications that NMPOU is a pervasive issue across many segments of the American, Canadian, Australian, New Zealand, United Kingdom, and Irish populations. Numerous socio-demographic risk factors were associated with NMPOU, including mental health issues, poly-substance use, and a history of pain. The findings also included serious harms associated with NMPOU, including HCV, overdose, and transitions to higher intensity drug use. Despite few directions for prevention policies and the need for a coordinated research strategy to address key gaps in knowledge related to the unique effects of different POs and drug-related risk behaviours, the results point to policy solutions that may reduce the incidence, prevalence, and harms of NMPOU. A multi-pronged approach that includes a suite of tailored harm reduction programs for at-risk individuals and broad improvements to addiction services should be implemented and integrated into the spectrum of healthcare services to reduce NMPOU and associated morbidity and mortality.

Chapter 3.

The Prevalence and Correlates of Engaging in NMPOU Among PWUD

3.1. An age-based analysis of NMPOU among people who use drugs in Vancouver

3.1.1. Introduction

As rates of medical and nonmedical prescription opioid use (NMPOU) are rising across both Canada and the United States (13), research consistently indicates that adolescents and young adults are more likely to engage in NMPOU than older youth and adults (75, 84, 142, 154, 188, 193, 197, 198, 266). Evidence suggests that these differences in prescription opioid (PO) use are associated with statistically significant birth cohort effects, where more recent birth cohorts have higher lifetime and past-year prevalence of prescription opioid-use disorder due to NMPOU (83). Adolescents and young adults in the United States are more likely to initiate NMPOU than older age groups (127, 134, 137, 266), and a study of the American general population found that the most frequently reported age of NMPOU initiation was 16-18 years (267). This effect has been attributed to the increased availability of POs (75), and other research among street-involved youth has found that the easy availability of POs facilitates NMPOU (53). In addition, those who engage in NMPOU are more likely to be younger than those engaging in other illegal street drugs (54), and adolescents and young adults are also more likely to share and receive any class of prescription medications, including POs, than older age groups (171). For the purposes of this study, “youth”, “young adult”, and “younger age groups” are used to describe individuals in their late teens and up to the late 20’s (268). “Adult” and “older age groups” include those over the age of majority but focuses on those in their mid-life and older.

Youth-specific strategies to address substance use are often prioritized due to the developmental harms associated with licit and illegal substances (269); however, the prevalence of NMPOU among adults up to age 64 is significantly higher than among adults

over the age of 65 (111), and the ubiquity of PO use has resulted in a significant risk of engaging in NMPOU that increases with age (83). The increase in PO use among older individuals is especially problematic given that age-related physiological changes (e.g., drug absorption) increase the harms of PO use among older adults, such as hyperalgesia (270). Research has also identified a key difference related to NMPOU among younger and older age groups, where pain is a more frequent motivator for engaging in NMPOU among adults (21) and youth are more likely to engage in NMPOU for its euphoric effects (142).

Although younger and older age groups are both at risk for engaging in NMPOU, the majority of research findings related to NMPOU rely on population-level sampling and national surveys that often exclude marginalized groups who are unstably housed or have low incomes. Despite previous research investigating NMPOU among people who use illegal street drugs (PWUD) in Canadian and American settings (53, 55, 91, 139, 177, 180, 240, 271-274), there have been few if any studies characterizing age-based differences associated with NMPOU among PWUD. Given that this population already experiences numerous risks and harms related to substance use (98), this study investigates age-based differences associated with NMPOU among younger and older PWUD in Vancouver.

3.1.2. Methods

Data from this study were drawn from two prospective open cohort studies: The At-Risk Youth Study (ARYS) and the Vancouver Injection Drug Users Study (VIDUS). ARYS and VIDUS use a harmonized study questionnaire and study participants can attend a study visit at either study office regardless of their cohort enrollment. ARYS and VIDUS have both been described in detail previously (97, 275). VIDUS is a cohort of HIV-negative adult PWUD who injected illegal street drugs at least once in the month prior to enrolment. Participants in the VIDUS cohort are recruited through self-referral and street outreach, which has been ongoing since 1996. In brief, ARYS has been operating since 2005 as a cohort study of street-involved youth. To be eligible, participants must be aged 14–26 years at recruitment and also have used substances other than cannabis in the past 30 days, provide written informed consent, and be ‘‘street-involved’’. In this cohort,

‘‘street-involved’’ is defined as being absolutely, periodically, or temporarily homeless (e.g., having no fixed address, sleeping on the street, couch surfing, or staying in a shelter or hostel), and includes those who are not homeless but have used services designated for street-youth (e.g., youth-specific drop-in centres, social services, and harm reduction services) in the last year. Youths’ street involvement and eligibility to participate are assessed during a semi-structured in-person interview with an ARYS staff member.

At enrolment, and on a semi-annual basis, participants in ARYS and VIDUS complete an interviewer-administered questionnaire that includes questions related to demographic information and drug use patterns. At each study visit, participants are provided with a stipend ($30 CDN) for their time. The ARYS and VIDUS studies have been approved by the University of British Columbia/Providence Health Care Research Ethics Board.

All ARYS and VIDUS participants who completed a study visit between December 2013 and May 2015 were eligible for the present analyses, as PO-related questions were added to the study instrument during the summer of 2013. The dependent variable for these analyses was engaging in NMPOU through any route of administration, based on responses to the question: “In the last 6 months, when you were using, which of the following non-injection prescription opiates did you use when they were not prescribed for you or that you took only for the experience or feeling they caused, and how often did you use them?” and “In the last 6 months, have you injected any of the following prescription opiates?” (yes vs. no). To identify factors associated with engaging in NMPOU, we considered a number of potential explanatory variables of interest. The following socio-demographic variables of interest were included: age (per year younger); sex; Caucasian or white ethnicity; and homelessness, defined as having no fixed address, sleeping on the street, couch surfing, or staying in a shelter or hostel in the last six months. The following variables related to drug use were also included: any injection or non-injection heroin use; any injection or non-injection crack cocaine use; any injection or non-injection cocaine use; any injection or non-injection crystal methamphetamine use; binge drug use, defined as a period of using injection or non-injection drugs more often than usual; and experiencing a non-fatal drug overdose due to injection or non-injection drug use, based on responses to the question “In the last 6 months, have you overdosed by accident (i.e.,

where you had a negative reaction from using too much drugs)?". Behavioural and socio-structural risk factors hypothesized to be associated with NMPOU included: regular employment, defined as having a regular job, temporary work, or being self-employed; drug dealing, defined as selling drugs as a source of income; engaging in sex work, defined as exchanging sex for money, drugs, gifts, food, clothes, shelter or favours; incarceration, defined as being in detention, jail, or prison; and difficulty accessing services, based on responses to the question "In the last 6 months, was there a time you were in need of a service (e.g., housing, counselling) but could not obtain it?". All variables were binary and referred to activities, behaviours, and experiences in the previous six months unless otherwise indicated.

All analyses were conducted separately for ARYS and VIDUS participants, using cohort enrollment as a proxy marker for younger and older age groups, respectively. At the time of enrollment, ARYS participants must be between 14 and 26 years old; however, as a prospective cohort study with substantial resources devoted to maintaining follow-up, the ARYS participant pool necessarily includes participants who are older than 26. These participants and their data are not excluded from the analyses given that this data provides a rich source for tracking and understanding long-term risk trajectories associated with street-involvement during a key developmental phase. While this practice may limit the applicability of our results to street-involved adolescents, we controlled for possible biases associated with these older participants in the youth cohort by including the continuous "per year younger" variable in the analyses to ensure that age differences within the cohort were accounted for. For consistency and to similarly control for a wide age range within the cohort, we also included the "per year younger" variable in the VIDUS analysis.

First, a descriptive analysis of the study sample was conducted using Pearson's chi-square test. Characteristics for participants who reported nonmedical prescription opioid use (NMPOU) were measured at their first visit (during the study period: 2013–2015), which involved a report of NMPOU; characteristics for all other participants were measured from the first study visit during the study period. Second, to model factors associated with engaging in NMPOU over time and to analyse longitudinal correlated within-subject data (276, 277), generalized estimating equation (GEE) analyses were performed. These methods provide standard errors adjusted by multiple observations per

person using an exchangeable working correlation structure. The GEE estimating mechanism uses all available pairs method to encompass any missing data from dropouts or other intermittent missing. All non-missing pairs of data are used in the estimators of the working correlation parameters.

As a first step, GEE bivariate analyses were conducted to determine factors associated with engaging in NMPOU. Variables significant in the bivariate analyses at $p<0.10$ were considered for a full multivariate model. A backwards selection procedure was used to identify the model with the best overall fit as indicated by the lowest quasi-likelihood under the independence model criterion (QIC) value (278). The QIC value was selected instead of the more recently developed Correlation Information Criterion (CIC), as the CIC is used to select the appropriate intracluster correlation structure, and is not used for covariate selection; we required a mechanism that could address both these needs simultaneously (279). All statistical analyses were performed using SAS software version 9.4 (SAS, Cary, NC). All *p*-values were two sided.

3.1.3. Results

A total of 405 ARYS and 757 VIDUS participants were eligible for this study. For ARYS, 313 (77.3%) participants were enrolled before December 2013 and 92 (22.7%) participants were newly enrolled during the study period. For the 313 participants, the median age at the first study visit within the study period for the current analysis was 26 (IQR: 23 – 28); and for the 92 participants, the median age at study enrollment was 21 (IQR: 20 – 23). For VIDUS, 697 (92.1%) participants were enrolled before December 2013 and 60 (7.9%) participants were newly enrolled during the study period. Among these 697 participants, the median age at the first study visit within study period was 49 (IQR: 42–55); and for the 60 newly recruited participants, the median age at study enrollment was 31 (IQR: 28–34).

The number of ARYS participants with at least one study follow-up visit was 294 (72.6%) and ARYS participants attended a median of 2 study visits (IQR: 1-3). A total of 646 (85.3%) VIDUS participants had at least one study follow-up visit and attended a median of 3 study visits (IQR: 2-3). The first ARYS observation used in this study was

recorded on December 2, 2013 and the last observation was recorded on May 28, 2015. ARYS participants contributed a total of 889 observations, of which 239 (26.9%) included a report of NMPOU. The first VIDUS observation used in this study was recorded on December 2, 2013 and the last was recorded on May 29, 2015. VIDUS participants contributed 1877 observations, of which 411 (21.9%) included a report of NMPOU. Among 405 ARYS participants included in this analysis, 39.5% (n=160) reported engaging in NMPOU throughout the study period. Among a total of 757 VIDUS participants, 34.6% (n=262) reported engaging in NMPOU throughout the study period.

Among ARYS participants in this sample, 135 (33.3%) were female, and 250 (61.7%) were of Caucasian or white ethnicity; VIDUS participants were 33.9% (n=257) female and 59.7% (n=452) Caucasian or white. Descriptive statistics for younger (ARYS) and older (VIDUS) participants are displayed in Table 2 and Table 3. The bivariate and multivariate analyses for younger participants are displayed in Table 4, and Table 5 displays the bivariate and multivariate analyses for older participants. In the multivariate analyses, engaging in NMPOU was independently and positively associated with the following factors among both younger and older participants: injection or non-injection heroin use (ARYS: Adjusted Odds Ratio [AOR]=3.12, 95% Confidence Interval [CI]: 2.08-4.68; VIDUS: AOR=2.79, 95% CI: 2.08-3.74); drug dealing (ARYS: AOR=2.22, 95% CI: 1.58-3.13; VIDUS: AOR=1.87, 95% CI: 1.40-2.49); and difficulty accessing services (ARYS: AOR=1.47, 95% CI: 1.04–2.09; VIDUS: AOR=1.74, 95% CI: 1.32–2.29).

Factors positively and independently associated with NMPOU among younger (ARYS) participants only included: younger age (AOR=1.12, 95% CI: 1.05-1.19); crack cocaine use (AOR=1.56, 95% CI: 1.06–2.30); and binge drug use (AOR=1.41, 95% CI: 1.00–1.97). Among older (VIDUS) participants only, engaging in NMPOU was independently and positively associated with injection or non-injection crystal methamphetamine use (AOR=1.97, 95% CI: 1.46-2.66), non-fatal overdose (AOR=1.76, 95% CI: 1.20–2.60), and sex work (AOR=1.49, 95% CI: 1.00–2.22).

Table 2: Characteristics of younger participants stratified by engaging in NMPOU over the study period, 2013–2015 (n=405)

Characteristic[a]	Total (%) (n=405)	NMPOU		*p*-value
		Yes (%) (n=160)	No (%) (n=245)	
Age (M [IQR])	25 (22-28)	23 (21-26)	26 (23-28)	<0.001
Any cocaine use[b,c]	123 (30.4)	60 (37.5)	63 (25.7)	0.012
Any crack cocaine use[b,c]	138 (34.1)	70 (43.8)	68 (27.8)	<0.001
Any crystal meth use[b,c]	268 (66.2)	121 (75.6)	147 (60.0)	0.001
Any heroin use[b,c]	193 (47.7)	114 (71.3)	79 (32.2)	<0.001
Any non-fatal overdose[b,c]	93 (23.0)	54 (33.8)	39 (15.9)	<0.001
Binge drug use[b,c]	208 (51.4)	108 (67.5)	100 (40.8)	<0.001
Caucasian or white ethnicity	250 (61.7)	100 (62.5)	150 (61.2)	0.796
Difficulty accessing services[b,d]	151 (37.3)	73 (45.6)	78 (31.8)	0.005
Drug dealing[b]	131 (32.3)	78 (48.8)	53 (21.6)	<0.001
Female	135 (33.3)	49 (30.6)	86 (35.1)	0.35
Homeless[b]	202 (49.9)	95 (59.4)	107 (43.7)	0.002
Incarceration[b]	57 (14.1)	26 (16.3)	31 (12.7)	0.297
Regular employment[b]	191 (47.2)	81 (50.6)	110 (44.9)	0.259
Sex work[b]	48 (11.9)	26 (16.3)	22 (9.0)	0.027

a. Comparison is yes versus no unless otherwise specified.
b. Refers to activities, behaviours, and experiences in the last six months.
c. Includes injection and non-injection drug use.
d. Includes health and social services.

Table 3: Characteristics of older participants stratified by engaging in NMPOU over the study period, 2013–2015 (n=757)

Characteristic[a]	Total (%) (n=757)	NMPOU		*p*-value
		Yes (%) (n=262)	No (%) (n=495)	
Age (M [IQR])	48 (40-55)	47 (38-53)	49 (41-56)	<0.001
Any cocaine use[b,c]	205 (27.1)	98 (37.4)	107 (21.6)	<0.001
Any crack cocaine use[b,c]	332 (43.9)	135 (51.5)	197 (39.8)	0.002
Any crystal meth use[b,c]	223 (29.5)	124 (47.3)	99 (20.0)	<0.001
Any heroin use[b,c]	362 (47.8)	200 (76.3)	162 (32.7)	<0.001
Any non-fatal overdose[b,c]	60 (7.9)	43 (16.4)	17 (3.4)	<0.001
Binge drug use[b,c]	235 (31.0)	118 (45.0)	117 (23.6)	<0.001
Caucasian or white ethnicity	452 (59.7)	164 (62.6)	288 (58.2)	0.239
Difficulty accessing services[b,d]	149 (19.7)	78 (29.8)	71 (14.3)	<0.001
Drug dealing[b]	171 (22.6)	95 (36.3)	76 (15.4)	<0.001
Female	257 (33.9)	92 (35.1)	165 (33.3)	0.622
Homeless[b]	149 (19.7)	76 (29.0)	73 (14.7)	<0.001
Incarceration[b]	51 (6.7)	28 (10.7)	23 (4.6)	0.002
Regular employment[b]	202 (26.7)	59 (22.5)	143 (28.9)	0.059
Sex work[b]	72 (9.5)	36 (13.7)	36 (7.3)	0.004

a. Comparison is yes versus no unless otherwise specified.
b. Refers to activities, behaviours, and experiences in the last six months.
c. Includes injection and non-injection drug use.
d. Includes health and social services.

Table 4: Bivariate and multivariate analyses of factors associated with engaging in NMPOU among younger participants (n=405)

Characteristic[a]	Unadjusted			Adjusted	
	Odds Ratio (95% CI)	*p*-value		Odds Ratio (95% CI)	*p*-value
Age (per year younger)	1.18 (1.12 – 1.25)	<0.001		1.12 (1.05 – 1.19)	<0.001
Any cocaine use[b,c]	1.68 (1.18 – 2.39)	0.004		1.31 (0.88 – 1.95)	0.181
Any crack use[b,c]	2.16 (1.53 – 3.05)	<0.001		1.56 (1.06 – 2.30)	0.023
Any crystal meth use[b,c]	2.06 (1.42 – 2.98)	<0.001			
Any heroin use[b,c]	4.82 (3.34 – 6.96)	<0.001		3.12 (2.08 – 4.68)	<0.001
Any non-fatal overdose[b,c]	2.24 (1.61 – 3.12)	<0.001		1.43 (0.97 – 2.10)	0.07
Binge drug use[b,c]	2.36 (1.76 – 3.15)	<0.001		1.41 (1.00 – 1.97)	0.049
Caucasian or white ethnicity	1.24 (0.85 – 1.80)	0.269			
Difficulty accessing services[b,d]	1.70 (1.27 – 2.27)	<0.001		1.47 (1.04 – 2.09)	0.03
Drug dealing[b]	2.76 (2.03 – 3.75)	<0.001		2.22 (1.58 – 3.13)	<0.001
Female	0.91 (0.61 – 1.36)	0.662			
Homeless[b]	1.59 (1.16 – 2.17)	0.004			
Incarceration[b]	1.32 (0.88 – 1.99)	0.177			
Regular employment[b]	1.23 (0.92 – 1.64)	0.168			
Sex work[b]	2.11 (1.35 – 3.29)	<0.001			

a. Comparison is yes vs. no unless otherwise specified.
b. Refers to behaviours, activities, and experiences in the last six months.
c. Includes injection and non-injection use.
d. Includes health and social services.

Table 5: Bivariate and multivariate analyses of factors associated with engaging in NMPOU among older participants (n=757)

Characteristic[a]	Unadjusted			Adjusted	
	Odds Ratio (95% CI)	*p*-value		Odds Ratio (95% CI)	*p*-value
Age (per year younger)	1.03 (1.10 – 1.04)	<0.001		0.99 (0.97 – 1.00)	0.12
Any cocaine use[b,c]	1.53 (1.18 – 1.99)	0.001			
Any crack use[b,c]	1.42 (1.12 – 1.81)	0.004			
Any crystal meth use[b,c]	2.95 (2.25 – 3.88)	<0.001		1.97 (1.46 – 2.66)	<0.001
Any heroin use[b,c]	3.81 (2.90 – 4.99)	<0.001		2.79 (2.08 – 3.74)	<0.001
Any non-fatal overdose[b,c]	3.09 (2.12 – 4.48)	<0.001		1.76 (1.20 – 2.60)	0.004
Binge drug use[b,c]	1.71 (1.37 – 2.14)	<0.001			
Caucasian or white ethnicity	1.20 (0.90 – 1.60)	0.225			
Difficulty accessing services[b,d]	2.11 (1.65 – 2.69)	<0.001		1.74 (1.32 – 2.29)	<0.001
Drug dealing[b]	2.75 (2.10 – 3.58)	<0.001		1.87 (1.40 – 2.49)	<0.001
Female	0.97 (0.73 – 1.31)	0.864			
Homeless[b]	2.05 (1.50 – 2.79)	<0.001			
Incarceration[b]	2.28 (1.47 – 3.54)	<0.001		1.55 (0.98 – 2.44)	0.061
Regular employment[b]	0.78 (0.60 – 1.00)	0.055			
Sex work[b]	2.05 (1.41 – 2.98)	<0.001		1.49 (1.00 – 2.22)	0.049

a. Comparison is yes vs. no unless otherwise specified.
b. Refers to behaviours, activities, and experiences in the last six months.
c. Includes injection and non-injection use.
d. Includes health and social services.

3.1.4. Discussion

Similar proportions of younger and older PWUD reported engaging in NMPOU in this study (40% of ARYS; 35% of VIDUS), and in separate multivariate analyses, NMPOU was positively associated with heroin use, drug dealing, and difficulty accessing services among both age groups. In addition, younger participants who engaged in NMPOU were more likely to be younger, use crack cocaine, and engage in binge drug use; older participants who engaged in NMPOU were more likely to use crystal methamphetamine, report a recent non-fatal overdose, and engage in sex work. While younger and older PWUD in these analyses shared risk factors for engaging in NMPOU, this study also found

important differences between these two age groups that highlight opportunities to develop targeted efforts that address NMPOU and unique risks for each age group.

The association between NMPOU and age was not found to be statistically significant in the analysis of older participants, which suggests that birth cohorts were not a meaningful indicator of NMPOU among this sample. Conversely, the association between NMPOU and younger age was statistically significant among younger participants, and this finding may reflect recent trends where PO use is increasingly prevalent among young age groups (75, 83, 110). The increasing use of POs has been attributed to the availability of POs (53, 75, 280), although the increased risk for younger birth cohorts using POs may be more strongly related to the linkages between youth observing their parents modelling substance use (i.e., PO use) and then concluding that PO use is safe (75).

Younger and older participants who engaged in NMPOU were significantly more likely to use heroin, which previous research has found to be used as a replacement for POs when PO availability is low (86). Although heroin and POs are both opioids and central nervous system depressants, POs are originally obtained from regulated healthcare sources, and heroin is only available through unregulated illegal street drug markets. Acquiring substances from the street is especially problematic in our study setting, where the toxic synthetic opioid fentanyl has adulterated a substantial proportion of the illegal street drug supply (281, 282), and fentanyl-related overdose mortality has increased alarmingly in various settings across Canada and the United States (283-286). To reduce reliance on illegal heroin, oral medications such as buprenorphine/naloxone (Suboxone), methadone, naltrexone, and slow release morphine have been recommended in recent opioid treatment guidelines as effective treatments (287), and injectable opioids such as diacetylmorphine and hydromorphone are emerging as options for treatment-refractory opioid dependence (288, 289). The international and North American evidence base for heroin assisted treatment (diacetylmorphine) is strong (288-290), and although less research has been conducted on hydromorphone as an injectable opioid treatment, scaling up these treatments may be an important tool to reduce NMPOU and exposure to contaminated illegal street drugs in Vancouver. It is important to note that PWUD have long advocated for access to a wider spectrum of opioid agonist therapies

through collaborations with researchers and coordinated advocacy efforts (291-296). This study did not control for intentional or unintentional exposure to fentanyl or other illicitly manufactured synthetic opioids, and future research using the ARYS and VIDUS cohorts would benefit from including exposure to fentanyl in analyses.

More differences than similarities were found with illegal street drug use patterns between younger and older participants. Despite both younger and older PWUD who engaged in NMPOU being significantly more likely to engage in heroin use, younger participants who engaged in NMPOU were more likely to also engage in crack cocaine use and binge drug use, while older participants were more likely to use crystal methamphetamine in addition to engaging in NMPOU. Crystal methamphetamine use may be an important marker of risk for NMPOU among older individuals in Vancouver, and this finding is concerning given local reports of increasing crystal methamphetamine use among adults in Vancouver (297-299). Historically, crystal methamphetamine use has been more prevalent among street-involved youth in Vancouver (97), as 66% of all participants in the younger age group reported using crystal methamphetamine at baseline; in addition, crystal methamphetamine has been associated with initiating injection drug use among this cohort of youth (300).

The findings from the multivariate model indicate that NMPOU among younger participants was not associated with a significantly increased risk for non-fatal overdose, whereas older participants who engaged in NMPOU were significantly more likely to report a recent non-fatal overdose; however, it should be noted that the confidence intervals for these adjusted odds ratios overlap considerably and these findings may be attributable to differences in selection criteria for the ARYS and VIDUS cohorts. This null result for youth was unexpected given the increased rate of overdose associated with PO use (301), and that the comparison group in this analysis included non-opioid users. These findings align with previous research findings that older age is associated with mortality due to unintentional PO-related overdose (249). Further research investigating protective factors associated with a lower risk of overdose among youth who engage in NMPOU is needed, which may include specific routes of administration or harm reducing practices related to using a substance with a known dosage and purity (e.g., prescription opioids versus unregulated heroin of unknown purity and composition). Regardless, harm reduction

services are critical to ensure that older PWUD, as well as younger PWUD, who engage in NMPOU have access to overdose prevention and reversal services such as supervised drug consumption spaces/services and the widespread distribution of Naloxone/Narcan in the community and among PWUD. The reach of harm reduction services may also be increased by strategically mobilizing key peers within PWUDs' social networks, which are an untapped resource and could become important facilitators of harm reduction supplies and information (302, 303).

Improved access to health and social services is also especially important in Vancouver, as this study found that older and younger PWUD who engage in NMPOU were more likely to report difficulty accessing services. Despite a saturation of services in the neighbourhoods where ARYS and VIDUS participants primarily live and congregate (the Downtown South and Downtown Eastside, respectively), there remain important gaps in service design and access. Previous research among youth in the ARYS cohort found that local youth-focused shelters and housing services had strict rules governing entry into- and continued use of- the service that deterred participants; conversely, adult or non-youth-specific services were perceived as unsafe or inappropriate for youth (304). Qualitative research among the VIDUS cohort has found that a local supervised injection site often has long wait times that result in people giving up and using drugs elsewhere (305) and "area restrictions" used by police to prohibit entry into "drug scenes" impedes access to services and supports tailored for PWUD and are often specifically located in areas with high drug use (306). This finding among younger PWUD is consistent with previous research from around the world; youth who use illegal street drugs often experience difficulty accessing services due to stigma and discrimination from service providers, as well as a lack of youth-centric health and social services that are preferred but not widely available (307, 308). Although the results indicate high rates of illegal street polysubstance use in the ARYS and VIDUS cohorts, participants who only engage in NMPOU may experience additional difficulties accessing harm reduction services that are tailored to people who use illegal street drugs, since they and their social networks may be outside the scope of outreach activities conducted by these services (51, 309). More research is required to better understand specific barriers to accessing health and social services among youth and adults who engage in NMPOU, as well as inform effective solutions to fill an important service gap for these individuals.

Participants in both age groups who engage in NMPOU were more likely to report recent drug dealing, and older participants were more likely to report sex work. Drug dealing has been associated with more intense illegal street drug use among PWUD of Caucasian or white ethnicity (310), and dealing illegal street drugs has been associated with a higher likelihood of NMPOU among American youth (190). Our findings reflect the well-established relationship between socio-economic marginalization and drug dealing (311, 312), and align with consistent research findings that income from drug dealing (313) and sex work (314) is often used to sustain ongoing substance use. Despite aligning with previous research, it is not clear why drug dealing and sex work remained significantly associated with engaging in NMPOU after controlling for other illegal street drug use; more research is needed investigating NMPOU and income generation among individuals not typically recruited in population-level surveys. Given that difficulty accessing services was also significantly associated with NMPOU among younger and older participants, there is a clear need to improve employment and other services for PWUD who engage in NMPOU as an intervention to increase socio-economic independence, particularly among people who engage in sex work. Similar efforts to facilitate entry into evidence-based addiction treatments for opioid use such as OAT, heroin assisted treatment, and injectable opioid therapy may reduce the prevalence of NMPOU and risky income generating activities.

As there is a lack of evidence to support the effectiveness of POs for treating chronic pain (28), safer prescribing to limit the supply and availability of POs is important for reducing the incidence and prevalence of NMPOU in the study setting. However, as the supply of POs becomes more restricted, close surveillance and a suite of interventions are needed to ensure that those who engage in NMPOU are not at greater risk for substituting PO use with contaminated illegal street drugs that have increased overdose risks. Low barrier harm reduction services to connect with those who engage in NMPOU and have had difficulty accessing services may also be an important link to supportive healthcare services, social services, and a range of treatment options for opioid use among younger and older age groups. In addition, future research investigating the correlates of incident and recurrent NMPOU over time is needed to better understand how access to services and changes in healthcare practices impact NMPOU among high-risk individuals who use illegal street drugs.

There are limitations to this research. First, ARYS and VIDUS participants may not be representative of all PWUD in Vancouver and the results therefore not generalizable to other settings in the city. However, extensive street-based and outreach efforts were undertaken in order to recruit a representative sample, and the socio-demographic characteristics of participants in the ARYS and VIDUS studies are similar to other studies in Vancouver (315, 316). Second, this study compares data from two cohort studies with different inclusion criteria, which may result in cohort or selection effects. Second, this study compares data from two cohort studies with different inclusion criteria, which may result in cohort or selection effects. These cohort effects may affect the results related to homelessness and injection drug use, as these risk factors are also inclusion criteria for ARYS and VIDUS, respectively. Given the longitudinal nature of these cohort studies and extensive efforts to track participants over multiple study visits, the ARYS and VIDUS studies have observed changes in behaviours and risk factors over time. For example, we have previously reported on transitions out of homelessness among ARYS participants (317) and injection cessation among VIDUS participants (318, 319). In addition, ARYS and VIDUS have previously been combined in quantitative and qualitative analyses (306, 320-322). Third, social desirability and recall bias may have resulted in erroneous reporting of our outcome and independent variables. Previous research on substance use has found discrepancies between self-reported substance use and bioassay test results among American adult male arrestees (323) and noted concerns that youth may not be truthful about substance use when speaking with authority figures who are able to assign punishment (324). Despite these findings, self-reported substance use, criminality, and HIV-related risk-taking among PWUD has also been deemed sufficiently reliable and valid (325). Training and engaging PWUD (“peers”) in survey administration and data collection methods when conducting substance use research may be an important mechanism to reduce social desirability response biases and increase capacity within communities of PWUD (326). To reduce socially desirable reporting from participants, the ARYS and VIDUS interviewers are trained in building trust and rapport, and study instruments situate sensitive questions towards the end of the questionnaire to allow interviewers to build rapport with participants. Although some socially desirable reporting is inevitable, any such reporting from participants would be expected to under-estimate the prevalence of sensitive risk factors and therefore our findings likely represent conservative estimates. Less is known about the accuracy of self-reporting NMPOU among PWUD; however,

efforts to improve the accuracy of reporting NMPOU among ARYS and VIDUS participants included using both the generic and brand name of POs, and showing pictures of a wide variety of POs during study visits. Fourth, no other information about the circumstances surrounding non-fatal overdose were included in this analysis (e.g., what substance was used at the time of overdose, whether substances were used alone or with another person, or whether fentanyl contributed to the overdose); however, the focus of this study was whether recent NMPOU was an independent marker for overdose among other risk factors. A more detailed investigation of the circumstances of overdose among people who engage in NMPOU is outside the scope of this analysis but is a promising direction for future research.

3.1.5. Conclusion

The shared risk factors among younger and older participants who engage in NMPOU underscore the importance of addressing barriers to accessing health and social services, as people who engage in NMPOU appear to be particularly under-supported and under-served by existing services for PWUD. Adult PWUD who engage in NMPOU are also at greater risk of overdose, which highlights the need for youth and adult-specific strategies that focus on reducing high intensity substance use among youth and providing low barrier overdose prevention and reversal services for adults. There is an urgent need to design and implement initiatives to improve healthcare providers' skills with managing and treating substance dependence (327), as well as developing pain treatment strategies tailored for PWUD (272). In addition to developing services that address youths' and adults' unique needs, policy-makers and healthcare providers are urged to reduce systematic barriers to a range of addiction treatment options for opioid use that may contribute to reductions in the prevalence of NMPOU and provide an additional benefit of preventing other PWUD from initiating injection drug use (328).

3.2. A sex-based analysis of NMPOU among people who use drugs in Vancouver

3.2.1. Introduction

The prevalence and incidence of NMPOU remain high in Canada (114) and the USA (111), such that an estimated average of 5,800 people initiate NMPOU each day in the USA (329). Although the global prevalence of substance use disorders is higher among men (330), the impact of substance use among females remains an important area of research as females who use substances experience risks and harms that are unique to their sex/gender such as intimate partner violence and reproductive issues (331). Females who use drugs also experience unique barriers to accessing addiction treatment in various settings (331, 332), despite American research findings that females and non-male participants who enroll in methadone treatment are more likely to be retained in treatment than males (333, 334). International research findings also indicate that females who use drugs experience difficulty accessing generic health and social services such as hospitals (335), as well as services for preventing and treating HIV (336).

Numerous population-level nationally representative surveys in the USA and Canada suggest mixed evidence for whether women (76, 79, 188, 193, 337) or men (78, 84, 85, 338) are more likely to engage in NMPOU. Research on the prevalence of NMPOU among youth and young adults found similarly conflicting results, where some studies found that certain groups of young females (81, 82, 188, 193) and males are more likely to engage in NMPOU (211, 338, 339), as well as no substantive differences between genders (204).

The majority of this research on NMPOU was conducted among the general population, and it is unclear if these results are generalizable to hidden populations such as PWUD. PWUD are often economically and socially marginalized from regular employment, healthcare, and social services due to stigma (340). In addition, a scoping review found that rigorous statistical analyses investigating NMPOU among women are lacking (341). Given the unique risks experienced by females who use substances and the mixed evidence from existing research investigating gender and NMPOU, there is a need to fill this knowledge gap and help inform policy solutions that may reduce the

prevalence and harms of NMPOU among PWUD. This study was undertaken to investigate sex differences (as a proxy for gender) in the prevalence and correlates of NMPOU among PWUD.

3.2.2. Methods

Data for this study are from two linked prospective open cohorts with similar methodologies: The At-Risk Youth Study (ARYS) and the Vancouver Injection Drug Users Study (VIDUS). The VIDUS and ARYS cohorts have been described in detail previously (275, 342). In brief, participants are recruited using extensive snowball sampling and street outreach, and attend an in-person semi-structured interview with an ARYS staff member to assess eligibility. At recruitment, participants are eligible for the ARYS study if they are between the ages of 14 and 26; have used substances other than or in addition to cannabis in the past 30 days; and are "street-involved", defined as being absolutely, periodically, or temporarily homeless (e.g., having no fixed address, sleeping on the street, couch surfing, or staying in a shelter or hostel), and includes those who are not homeless but have used services designated for street-youth in the last year. VIDUS is a prospective cohort of people who injected street drugs at least once in the month prior to cohort enrollment and who are HIV-negative; people who are HIV-positive and recently injected drugs are invited to enroll in a sister cohort (AIDS Care Cohort to evaluate Exposure to Survival Services [ACCESS]). VIDUS participants are recruited through street outreach and self-referral. All ARYS and VIDUS participants provide written information consent to participate. At baseline and every six months thereafter, participants in both cohorts complete an interviewer-administered questionnaire and provide blood samples for HIV and Hepatitis C serology. At each study visit, participants are provided with a stipend ($30 CDN) in compensation for their time. The ARYS and VIDUS studies have received ethical approval by the University of British Columbia/Providence Health Care Research Ethics Board.

All ARYS and VIDUS participants who attended a study visit between 2013 and 2017 were eligible for these analyses. The primary outcome of these analyses was engaging in NMPOU (yes vs. no), as defined by affirmative responses to the question "In the last 6 months, when you were using, which of the following non-injection prescription

opiates did you use when they were not prescribed for you or that you took only for the experience or feeling they caused, and how often did you use them?" and/or "In the last 6 months, have you injected any of the following prescription opiates?".

For the purposes of this study, NMPOU includes using pharmaceutical-grade legally manufactured POs obtained from a physician or from a diverted source, such as a friend, family member, or street-based drug dealer; and NMPOU may occur through any route of administration, such as smoking, oral ingestion, snorting, and injecting. This study does not consider the following substance use as NMPOU: the use of illicitly manufactured synthetic opioids (e.g., fentanyl), injectable opioids that are administered as treatment for opioid use disorder (e.g., diacetylmorphine as part of heroin assisted treatment), or self-treatment of a medical condition (e.g., self-escalating the dosage of POs that were prescribed for pain in order to attain additional pain relief). When POs are not directly obtained from a pharmacy or hospital, the ability to distinguish between pharmaceutical-grade legally manufactured POs and clandestinely manufactured opioids can be difficult; therefore, it is expected that some instances of unknowingly consuming clandestinely manufactured opioids where recorded as NMPOU.

To identify factors associated with NMPOU, we considered a number of potential explanatory variables of interest. The following socio-demographic variables of interest were included: age (per year older); Caucasian or white ethnicity (white vs. non-white); and homelessness, defined as having no fixed address, sleeping on the street, couch surfing, or staying in a shelter or hostel (yes vs. no). Multiple variables related to substance use were also included: any injection or non-injection heroin use (yes vs. no); any injection or non-injection crack cocaine use (yes vs. no); any injection or non-injection cocaine use (yes vs. no); any injection or non-injection crystal methamphetamine use (yes vs. no); binge drug use, defined as a period of using injection or non-injection drugs more often than usual (yes vs. no); and non-fatal drug overdose (yes vs. no). This analysis also included a range of other individual and socio-structural risk factors hypothesized to be associated with NMPOU: regular employment, defined as having a regular job, temporary work, or being self-employed (yes vs. no); drug dealing, defined as selling drugs as a source of income (yes vs. no); engaging in sex work, defined as exchanging sex for money, drugs, gifts, food, clothes, shelter or favours (yes vs. no); incarceration, defined

as being in detention, jail, or prison (yes vs. no); and reporting difficulty accessing health and social services, based on responses to the question "'In the last six months, was there a time you were in need of a service (e.g., housing, counselling) but could not obtain it?" (yes vs. no). All variables except for age and ancestry referred to activities, behaviours, and experiences in the previous six months unless otherwise indicated.

All analyses were conducted separately for female and male participants. First, a descriptive analysis of the study sample was conducted using data from the first study visit during the study period when participants reported engaging in NMPOU; characteristics for participants who did not report NMPOU were measured using the first study visit during the study period. The frequencies of the baseline characteristics between the two groups were compared using Pearson's chi-square test for categorical variables and the Mann-Whitney test for continuous variables. Second, a generalized estimating equation (GEE) analysis was conducted to model factors associated with engaging in NMPOU over time and to analyse longitudinal within-subject data (276, 277). These methods provided standard errors adjusted by multiple observations per person using an exchangeable correlation structure. Missing data were addressed through the GEE estimating mechanism which uses all available pairs method to encompass the missing data from dropouts or intermittent missing data. All non-missing pairs of data were used in the estimators of the working correlation parameters. As a first step, GEE bivariate analyses were used to assess factors associated with engaging in NMPOU. Variables that reached $p<0.10$ in the bivariate analyses were considered for a multivariate model using a backwards selection procedure. The model with the best overall fit was determined based on the lowest quasi-likelihood under criterion (QIC) value (278). All statistical analyses were performed using R software version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria). All *p*-values are two sided.

3.2.3. Results

A total of 1,459 participants attended a study visit between 2013 and 2017, and were included in this analysis. Among this sample, 534 (37%) were female and 925 (63%) were male. Nearly half of female participants were Caucasian or white (49%, n=262), while 64% of male participants were Caucasian or white (n=596). The median age among

females was 32 (interquartile range [IQR]: 25-46) years, and among males the median age was 35 (IQR: 25-51) years. A total of 452 (85%) female participants and 811 (88%) male participants attended at least one study follow-up visit, with a median of 4 study visits (IQR: 2-6) for females and 5 study visits (IQR: 2-7) for males. Female participants contributed 2,283 observations for these analyses, of which 484 (21%) included a report of NMPOU. Male participants contributed 4,236 observations for these analyses, of which 939 (22%) included a report of NMPOU. Among 534 female participants included in this analysis, 46% (n=247) reported engaging in NMPOU at their first study visit within the study period, and 48% of male participants (n=447) reported engaging in NMPOU during the same time period among a total of 925 male PWUD.

Descriptive statistics for females and males are displayed in Table 6. The bivariate analyses are displayed in Table 7, and Table 8 displays the multivariate analyses. In the multivariate analyses, engaging in NMPOU was independently and positively associated with the following factors among females and males: any heroin use (females: Adjusted Odds Ratio [AOR]=1.88, 95% Confidence Interval [CI]: 1.40-2.53; males: AOR=2.57, 95% CI: 2.10-3.14); non-fatal overdose (females: AOR=1.44, 95% CI: 1.07–1.92; males: AOR=1.46, 95% CI: 1.19-1.80); drug dealing (females: AOR=1.72, 95% CI: 1.31–2.26; males: AOR=1.76, 95% CI: 1.44–2.15); and difficulty accessing services (females: AOR=1.35, 95% CI: 1.08-1.69; males: AOR=1.44, 95% CI: 1.22-1.71). Factors positively and independently associated with NMPOU among female participants only, included: Caucasian or white ethnicity (AOR=1.49, 95% CI: 1.12–2.00); any cocaine use (AOR=1.37, 95% CI: 1.06–1.77); any crystal methamphetamine use (AOR=1.93, 95% CI: 1.48–2.51); regular employment (AOR=1.49, 95% CI: 1.14–1.96); and sex work (AOR=1.39, 95% CI: 1.06-1.80). Among male participants only, engaging in NMPOU was independently and positively associated with any crack cocaine use (AOR=1.39, 95% CI: 1.15–1.68), and binge drug use (AOR=1.22, 95% CI: 1.04–1.44); NMPOU was negatively associated with older age (AOR=0.98, 95% CI: 0.98-0.99).

Table 6: Characteristics of females and males who use illegal street drugs stratified by engaging in NMPOU over the study period, 2013–2017 (n=1,459)

Characteristic[a,b]	Females (n=534)			Males (n=925)	
	Yes (%) (n=247)	No (%) (n=287)		Yes (%) (n=447)	No (%) (n=478)
Older age [M (IQR)]	31 (24-46)	33 (27-46)		33 (25-48)	41 (26-53)
Caucasian/white	129 (52.2)	133 (46.3)		288 (64.4)	308 (64.4)
Homeless[c]	94 (38.1)	75 (26.1)		201 (45.0)	149 (31.2)
Any heroin use[c,d]	185 (74.9)	107 (37.3)		316 (70.7)	156 (32.6)
Any crack cocaine use[c,d]	126 (51.0)	115 (40.1)		192 (43.0)	152 (31.8)
Any cocaine use[c,d]	100 (40.5)	76 (26.5)		176 (39.4)	114 (23.8)
Any crystal meth use[c,d]	158 (64.0)	95 (33.1)		264 (59.1)	198 (41.4)
Binge drug use[c,d]	152 (61.5)	93 (32.4)		232 (51.9)	171 (35.8)
Any non-fatal overdose[c,d]	56 (22.7)	28 (9.8)		110 (24.6)	50 (10.5)
Regular employment[c]	64 (25.9)	53 (18.5)		167 (37.4)	214 (44.8)
Drug dealing[c]	86 (34.8)	48 (16.7)		185 (41.4)	84 (17.6)
Sex work[c]	76 (30.8)	67 (23.3)		37 (8.3)	11 (2.3)
Incarceration[c]	20 (8.1)	13 (4.5)		73 (16.3)	51 (10.7)
Difficulty accessing services[c,e]	101 (40.9)	68 (23.7)		168 (37.6)	108 (22.6)

a. Characteristics for participants who reported nonmedical prescription opioid use were measured at their first visit (during the study period: 2013–2017), which involved a report of NMPOU. Characteristics for all other participants were measured from the first study visit during the study period.

b. Comparison is yes versus no unless otherwise specified.

c. Refers to activities, behaviours, and experiences in the last six months.

d. Includes injection and non-injection drug use.

e. Includes health and social services.

Table 7: Bivariate analyses of factors associated with engaging in NMPOU among females and males who also use illegal street drugs, 2013–2017 (n=1,459)

Characteristic[a]	Females (n=534)			Males (n=925)	
	Odds Ratio (95% CI)	*p*-value		Odds Ratio (95% CI)	*p*-value
Older age (per year older)	0.98 (0.96-0.99)	0.002		0.97 (0.97-0.98)	<0.001
Caucasian/white	1.36 (1.01-1.83)	0.042		1.01 (0.81-1.28)	0.906
Homeless[b]	1.86 (1.47-2.34)	<0.001		1.78 (1.50-2.10)	<0.001
Any heroin use[b,c]	2.86 (2.21-3.70)	<0.001		3.45 (2.86-4.17)	<0.001
Any crack cocaine use[b,c]	1.62 (1.28-2.04)	<0.001		1.66 (1.39-1.97)	<0.001
Any cocaine use[b,c]	1.74 (1.37-2.21)	<0.001		1.50 (1.26-1.78)	<0.001
Any crystal meth use[b,c]	2.89 (2.28-3.66)	<0.001		1.96 (1.62-2.37)	<0.001
Binge drug use[b,c]	1.84 (1.51-2.24)	<0.001		1.72 (1.48-1.99)	<0.001
Any non-fatal overdose[b,c]	2.15 (1.63-2.83)	<0.001		2.12 (1.73-2.58)	<0.001
Regular employment[b]	1.15 (0.92-1.45)	0.217		0.94 (0.81-1.01)	0.456
Drug dealing[b]	2.22 (1.72-2.87)	<0.001		2.41 (1.99-2.91)	<0.001
Sex work[b]	2.01 (1.58-2.57)	<0.001		2.12 (1.45-3.10)	<0.001
Incarceration[b]	1.57 (1.02-2.41)	0.040		1.53 (1.23-1.91)	<0.001
Difficulty accessing services[b,d]	1.61 (1.31-1.98)	<0.001		1.67 (1.43-1.95)	<0.001

a. Comparison is yes versus no unless otherwise specified.
b. Refers to activities, behaviours, and experiences in the last six months.
c. Includes injection and non-injection drug use.
d. Includes health and social services.

Table 8: Multivariate analyses of factors associated with engaging in NMPOU among females and males who also use illegal street drugs, 2013–2017 (n=1,459)

Characteristic[a]	Females (n=534)			Males (n=925)	
	Adjusted Odds Ratio (95% CI)	*p*-value		Adjusted Odds Ratio (95% CI)	*p*-value
Older age (per year older)				0.98 (0.98-0.99)	<0.001
Caucasian/white	1.49 (1.12-2.00)	0.007			
Homeless[b]					
Any heroin use[b,c]	1.88 (1.40-2.53)	<0.001		2.57 (2.10-3.14)	<0.001
Any crack cocaine use[b,c]	1.28 (0.99-1.66)	0.064		1.39 (1.15-1.68)	0.001
Any cocaine use[b,c]	1.37 (1.06-1.77)	0.017		1.20 (0.99-1.45)	0.059
Any crystal meth use[b,c]	1.93 (1.48-2.51)	<0.001			
Binge drug use[b,c]	1.19 (0.95-1.48)	0.124		1.22 (1.04-1.44)	0.015
Any non-fatal overdose[b,c]	1.44 (1.07-1.92)	0.015		1.46 (1.19-1.80)	<0.001
Regular employment[b]	1.49 (1.14-1.96)	0.004			
Drug dealing[b]	1.72 (1.31-2.26)	<0.001		1.76 (1.44-2.15)	<0.001
Sex work[b]	1.39 (1.06-1.80)	0.015			
Incarceration[b]					
Difficulty accessing services[b,d]	1.35 (1.08-1.69)	0.008		1.44 (1.22-1.71)	<0.001

a. Comparison is yes versus no unless otherwise specified.
b. Refers to activities, behaviours, and experiences in the last six months.
c. Includes injection and non-injection drug use.
d. Includes health and social services.

3.2.4. Discussion

The prevalence of NMPOU was similar for males (48%) and females (46%) in this study, and the analyses found that heroin use, illegal street stimulant use (cocaine and crystal methamphetamine for females; crack cocaine for males), non-fatal overdose, drug dealing, and difficulty accessing services were risk factors for engaging in NMPOU among both males and females in the study setting. Unique factors associated with NMPOU among females included Caucasian or white ethnicity, regular employment, and engaging in sex work. Among males, those who engaged in NMPOU were less likely to be older and more likely to report binge drug use.

Females and males who engaged in NMPOU were both more likely to use heroin, illegal street stimulants, and experience a non-fatal overdose than PWUD who did not engage in NMPOU. These results indicate substantial polysubstance use among study participants who engaged in NMPOU, which aligns with previous research findings of high rates of polysubstance use among males and females in the general American population who engage in NMPOU (206). Analyses of national American mortality databases have also found that the risk of PO-related overdose is increased for males, as well as those using either heroin or benzodiazepines concurrently with POs (343, 344). This study also found that males were more likely to report binge drug use, which has previously been linked with polysubstance use among PWUD in the study setting (345).

Polysubstance use that includes central nervous system depressants such as heroin is a known risk factor for overdose (346-348), however, engaging in NMPOU and illegal street drugs in the study setting may result in a particularly high risk of overdose due to the adulteration of the local illegal street drug supply with toxic and clandestinely produced fentanyl as well as synthetic analogues (e.g., carfentanil) (349, 350). Fentanyl was found to be involved in 81% of illegal street drug overdose deaths in the province of British Columbia in 2018 (349), and recent drug testing in Vancouver found that only 13% of “heroin” samples contained any amount of the expected substance (i.e., diacetylmorphine) (20); an increasing number of drug samples (up to 21%) in the study setting also contain carfentanil, an analogue of fentanyl (350). Consequently, any illegal street drug use in the study setting increases the risk for overdose substantially, in addition to the considerable overdose risk attributed to PO use. The findings from this research indicate that male PWUD who engage in NMPOU were significantly more likely to engage in binge drug use, which may be linked to the increased risk of overdose borne by this group. Given the prevalence of polysubstance use and risk of overdose in this sample, linkages to healthcare and addiction treatment for opioid use are particularly important for both sexes and all genders.

The analyses found that drug dealing was a risk factor for engaging in NMPOU among male and female participants. Drug dealing (313, 351) and sex work (314) have previously been identified as important income generating strategies to sustain ongoing substance use, and previous research among females in this setting has also identified

drug dealing as a strategy to reduce the need to generate income through sex work (352). It is not clear why those who engage in NMPOU are significantly more likely to report drug dealing than those who use other substances. Although resolving the dynamics underlying this association is beyond the scope of the study, this result may be due to (i) increasingly restrictive prescribing practices in this setting and a correspondingly greater demand for POs (353) that incentivize those with a prescription for opioids to sell their pills, (ii) a lack of proper clinical safeguards and over-prescribing contributing to an excess supply of POs that are diverted as a means of income generation (354), or (iii) the escalation of substance use resulting from an increased access to drugs as part of drug dealing activities (355). Given that the type of substance sold through drug dealing was not tracked for this analysis, this area of research warrants further investigation.

Despite finding that females who engaged in NMPOU in this study were more likely to report drug dealing and sex work than those who did not engage in NMPOU, the results also indicate that females who engaged in NMPOU were more likely to report regular employment; this indicates substantial variability in economic vulnerability among female PWUD who engage in NMPOU in this study. This range of economic vulnerability is consistent with previous research findings of both unemployment (85, 144, 191, 192) and increased likelihood of paid work (55) among people who engage in NMPOU; more research is clearly needed to understand this variability among female PWUD who engage in NMPOU and identify specific factors associated with economic stability versus instability. For those females and males who engage in NMPOU and lack economic independence, targeted support services and low-barrier employment opportunities may increase economic empowerment among this group.

PWUD experience numerous barriers to accessing services (332, 335, 356, 357), however, this study found that those who engaged in NMPOU reported an increased likelihood of having difficulty accessing services when compared to those who report only using illegal street drugs. Given the risk of polysubstance use and risky income generation among PWUD who also engage in NMPOU in this setting, low barrier health and social services are particularly important for reaching out to those who engage in NMPOU and facilitate linkages to treatment for opioid use.

This study has limitations. First, the results may not be generalizable to other PWUD in Vancouver or other settings. This limitation was mitigated as much as possible, however, through extensive street-based outreach efforts of the cohort study staff to recruit a representative sample. In addition, other studies involving PWUD in this setting report similar socio-demographic characteristics as ARYS and VIDUS participants (315, 316). Second, self-reporting in our study may have been biased by social desirability and recall and response biases. Previous research, however, has found that self-reported substance use is reliable and valid (325), and study staff aimed to increase the accuracy of PO-related reporting by using both the generic and brand name of POs and showing pictures of POs during the semi-structured interviews for clarification purposes or if requested by the participant. Despite these efforts, misclassification of NMPOU may have occurred as participants who acquired POs from diverted sources (e.g., friends, family, street) could have unwittingly received illicitly manufactured POs that were indistinguishable from pharmaceutical-grade POs. Third, the categories for sex in this study were binary and based on sex at birth; they did not account for transgender identities due to different timelines for data collection. There are, however, very few transgender or non-binary participants in VDUS as only 2% of the male sample (n=14) and 5% of the female sample (n=26) reported being either transgender or gender non-conforming. Further research among gender minority sub-populations is warranted.

3.2.5. Conclusion

Nearly half of the male and female participants in this study reported engaging in NMPOU, and the analyses found key risk factors associated with NMPOU among both sexes, including non-fatal overdose, difficulty accessing health and social services, drug dealing, heroin use, and illegal street stimulant use. While engaging in NMPOU appears to be linked to similar risks and harms among both sexes, noteworthy risk factors that were unique to each sex included indicators of both economic vulnerability and stability among females and binge drug use among males. These findings highlight the need for a comprehensive public health approach to address NMPOU that integrates overdose prevention and reversal services, employment opportunities, and better access to services for women and men in this population.

Chapter 4.

NMPOU Initiation trajectory and related risks among people who use illegal street drugs in Vancouver

4.1. Introduction

As NMPOU continues to rise across North America, researchers have identified an alarming trend of individuals initiating NMPOU and then later transitioning to using illegal street drugs, such as heroin, cocaine, crack, and crystal methamphetamine (46, 86, 87, 91, 134). Among a sample of people who use heroin in the United States, researchers found that the prevalence of engaging in NMPOU before transitioning to heroin use increased from 64% in 2002-2004 to 83% in 2008-2010 (218); the prevalence of this particular trajectory was 40% among young heroin injectors in San Diego (91).

Previous research has found key differences in employment and education outcomes between those who engage in illegal street drug use and those who engage in NMPOU (54, 55, 184); however, fewer studies have compared transitions to and from NMPOU with those who only use illegal street drugs, as well as within-group differences among those who engage in NMPOU. Given these gaps in knowledge, the present study investigates the prevalence of, and risk factors associated with, transitioning from NMPOU to illegal street drugs vs. transitioning from illegal street drugs to NMPOU use among a sample of street youth and adults who use illegal street drugs in Vancouver, Canada.

4.2. Methods

Data for this cross-sectional research are drawn from two open prospective cohort studies of youth and adults who use illegal street drugs with harmonized procedures and survey instruments: The At-Risk Youth Study (ARYS) and the Vancouver Injection Drug Users Study (VIDUS). Recruitment for both cohorts uses extensive snowball sampling, self-referral, and street outreach. The eligibility criteria for participating in ARYS includes: being between the ages of 14 and 26; use of substances other than, or in addition to,

cannabis in the past month; and “street-involvement”, defined as being recently homeless or having used services designated for street youth (94-97). The VIDUS cohort includes adults (≥18 years of age) who are HIV-negative and who injected drugs at least once in the previous month. All participants must provide written informed consent to participate. At baseline and every six months thereafter, participants in both cohorts complete a harmonized interviewer-administered questionnaire and receive a stipend ($30 CDN) for their time. The ARYS and VIDUS studies receive ethical approval from the University of British Columbia/Providence Health Care Research Ethics Board.

All ARYS and VIDUS participants were eligible for the primary statistical analyses, which were two analyses investigating risk factors associated with (i) transitioning from NMPOU to illegal street drug use, and (ii) transitioning from illegal street drug use to NMPOU; the comparison group for both analyses were participants who reported never engaging in NMPOU. A report of NMPOU was defined as ever engaging in injection or non-injection NMPOU (yes vs. no) between 2013 and 2016. Transitions to and from NMPOU were categorized based on responses to the following question: “Did you use prescription opioids when they were not prescribed for you or that you took only for the experience or feeling they caused before you had ever used any of the following hard illegal drugs: heroin, cocaine, crack, or crystal methamphetamine?” (yes, non-medical use of POs came before other hard drug use vs. no, non-medical use of POs came after other hard drug use).

The following socio-demographic, early-life, and mental health variables of interest were included: age per year older; male sex (male vs. female); Caucasian or white ethnicity (white vs. non-white); ever experienced homelessness, defined as having no fixed address, sleeping on the street, couch surfing, or staying in a shelter or hostel (yes vs. no); high school incompletion (yes vs. no); a baseline score of 13 or higher on the Childhood Trauma Questionnaire (CTQ), which indicates moderate to severe abuse due to physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect (yes vs. no); and a baseline score of 22 or higher on the Center for Epidemiological Studies Depression Scale (CES-D), which indicates a relatively higher level of depressive symptoms among vulnerable individuals (358) (yes vs. no). Multiple variables related to substance use patterns were also included: daily injection or non-injection heroin use (yes

vs. no); daily injection or non-injection of stimulant drugs, including daily use of either crack cocaine, cocaine, or crystal methamphetamine use (yes vs. no); binge drug use, defined as a period of using injection or non-injection drugs more often than usual (yes vs. no); amount of money spent on drugs per day (<median vs. ≥ median); ever experiencing a non-fatal drug overdose (yes vs. no); and ever accessing methadone treatment, which was the most widely available form of OAT in this setting during the study period (359) (yes vs. no). This analysis also includes a range of socio-structural risk factors hypothesized to be associated with this transition pattern: emergency room visit (yes vs. no); experience of violence (yes vs. no); ever been incarcerated (yes vs. no); regular employment, defined as having a regular job, temporary work, or being self-employed (yes vs. no); drug dealing, defined as selling drugs as a source of income (yes vs. no); and ever engaging in sex work, defined as exchanging sex for money, drugs, gifts, food, clothes, shelter or favours (yes vs. no). All variables refer to activities, behaviours, and experiences in the previous six months unless otherwise indicated.

Questions related to NMPOU were added to the ARYS and VIDUS survey instrument in June 2013. For participants reporting NMPOU, data for the outcome were drawn from the first study visit where participants reported ever engaging in NMPOU; data for the independent variables were drawn from participants' baseline study visit. For participants who did not report engaging in NMPOU between 2013 and 2016, data for the outcome and independent variables were also drawn from participants' baseline study visit.

To assess factors associated with transitions to and from NMPOU (vs. never engaging in NMPOU), bivariate logistic regression analyses were conducted for ARYS and VIDUS participants separately. For variables significant at $p<0.10$ in the bivariate analyses, a full multivariate model was constructed. The model with the best overall fit was selected using the Akaike Information Criterion (AIC). All statistical analyses were performed using R version 3.2.4 (360). All *p*-values are two sided.

Sub-analyses were conducted using a restricted sample of only those who reported engaging in NMPOU. The outcome of these analyses was transitioning from NMPOU to illegal street drug use (vs. transitioning from illegal street drugs to NMPOU),

and these analyses used the same independent variables and statistical approach as the primary analysis.

4.3. Results

A total 512 ARYS and 833 VIDUS participants were eligible for the primary analyses. A high proportion of these cohort participants reported ever engaging in NMPOU during a study visit between 2013 and 2016 (ARYS: n=452, 88%; VIDUS: n=750, 90%). Among 512 ARYS participants, 334 (65%) were male, 314 (61%) were Caucasian or white, and the median age was 24 years (Inter-Quartile Range [IQR]: 22-27). The majority of VIDUS participants were male (n=530, 64%) and Caucasian or white (n=487, 59%); the median age was 47 years (IQR: 38-54). Within each cohort, 160 (31%) ARYS participants (total n=512) and 276 (33%) VIDUS participants (total n=833) reported transitioning from NMPOU to illegal street drugs. The descriptive characteristics of ARYS and VIDUS participants are displayed in Table 9, and the bivariate analyses investigating PO-related substance use trajectories are shown in Table 10. The results from the multivariate analyses are displayed in Table 11.

Table 9: ARYS and VIDUS participant characteristics stratified by trajectory of NMPOU (n=1,345)

Characteristic[a]	ARYS (n=512)			VIDUS (n=833)		
	Never NMPOU (%) (n=60)	NMPOU first (%) (n=160)	Illegal drugs first (%) (n=292)	Never NMPOU (%) (n=83)	NMPOU first (%) (n=276)	Illegal drugs first (%) (n=474)
Age per year older [M (IQR)]	26 (22-28)	24 (21-26)	24 (22-27)	49 (42-56)	48 (38-54)	47 (37-54)
Male sex	37 (61.7)	115 (71.9)	182 (62.3)	51 (61.4)	169 (61.2)	310 (65.4)
Caucasian/white	35 (58.3)	97 (60.6)	182 (62.3)	37 (44.6)	158 (57.2)	292 (61.6)
Homeless	55 (91.7)	153 (95.6)	275 (94.2)	72 (86.7)	260 (94.2)	444 (93.7)
High school incompletion	27 (45.0)	56 (35.0)	100 (34.2)	39 (47.0)	140 (50.7)	231 (48.7)
Daily heroin use[b,c]	5 (8.3)	45 (28.1)	89 (30.5)	10 (12.0)	77 (27.9)	125 (26.4)
Daily stimulant use[b,c,d]	22 (36.7)	43 (26.9)	102 (34.9)	21 (25.3)	82 (29.7)	139 (29.3)
Binge drug use[b,c]	21 (35.0)	90 (56.3)	181 (62.0)	22 (26.5)	101 (36.6)	175 (36.9)
$ spent on drugs/day[b,c,e]	22 (36.7)	64 (40.0)	114 (39.0)	22 (26.5)	108 (39.1)	187 (39.5)
Non-fatal overdose[c]	27 (45.0)	90 (56.3)	169 (57.9)	34 (41.0)	177 (64.1)	325 (68.6)
Methadone treatment	7 (11.7)	42 (26.3)	87 (29.8)	39 (47.0)	218 (79.0)	374 (78.9)
Emergency room visit[b]	23 (38.3)	58 (36.3)	131 (44.9)	16 (19.3)	82 (29.7)	151 (31.9)
Depression symptoms	26 (43.3)	87 (54.4)	160 (54.8)	40 (48.2)	155 (56.2)	241 (50.8)
Childhood trauma	35 (58.3)	97 (60.6)	195 (66.8)	48 (57.8)	183 (66.3)	313 (66.0)
Experience violence[b]	12 (20.0)	62 (38.8)	116 (39.7)	9 (10.8)	48 (17.4)	73 (15.4)
Incarceration	35 (58.3)	96 (60.0)	195 (66.8)	63 (75.9)	246 (89.1)	426 (89.9)
Regular employment[b]	27 (45.0)	74 (46.3)	133 (45.5)	24 (28.9)	71 (25.7)	133 (28.1)
Drug dealing[b]	10 (16.7)	55 (34.4)	95 (32.5)	6 (7.2)	73 (26.4)	110 (23.2)
Sex work	18 (30.0)	41 (25.6)	85 (29.1)	57 (68.7)	169 (61.2)	272 (57.4)

a. Comparison is yes vs. no unless otherwise specified.

b. Refers to activities, behaviours, and experiences in the last six months.

c. Includes injection and non-injection drug use.

d. Includes crack cocaine, cocaine, or crystal methamphetamine use.

e. Comparison is <median vs. ≥ median.

Table 10: Bivariate analyses investigating NMPOU before or after illegal street drug use (n=1,345)

Characteristic[a]	ARYS (n=512)				VIDUS (n=833)			
	NMPOU first (vs. never NMPOU)		Illegal Drugs First (vs. never NMPOU)		NMPOU first (vs. never NMPOU)		Illegal Drugs First (vs. never NMPOU)	
	Odds Ratio (95% CI)	*p*-value	Odds Ratio (95% CI)	*p*-value	Odds Ratio (95% CI)	*p*-value	Odds Ratio (95% CI)	*p*-value
Age per year older	0.91 (0.84 - 0.99)	0.033	0.94 (0.87 - 1.02)	0.122	0.98 (0.95 - 1.00)	0.080	0.98 (0.96 - 1.00)	0.083
Male sex	1.59 (0.85 - 2.96)	0.146	1.03 (0.57 - 1.81)	0.923	0.99 (0.59 - 1.63)	0.972	1.19 (0.73 - 1.91)	0.487
Caucasian/white	1.06 (0.57 - 1.93)	0.861	1.13 (0.64 - 2.00)	0.665	1.66 (1.02 - 2.74)	0.043	1.99 (1.25 - 3.21)	0.004
Homeless	1.99 (0.57 - 6.48)	0.257	1.47 (0.47 - 3.90)	0.467	2.48 (1.08 - 5.54)	0.028	2.26 (1.04 - 4.59)	0.029
High school incompletion	0.60 (0.33 - 1.12)	0.107	0.59 (0.33 - 1.05)	0.070	1.09 (0.66 - 1.80)	0.742	1.03 (0.64 - 1.66)	0.903
Daily heroin use[b,c]	4.30 (1.76 - 12.95)	0.003	4.82 (2.04 - 14.19)	0.001	2.82 (1.44 - 6.08)	0.004	2.61 (1.37 - 5.53)	0.006
Daily stimulant use[b,c,d]	0.63 (0.34 - 1.20)	0.158	0.93 (0.52 - 1.67)	0.798	1.25 (0.72 - 2.22)	0.437	1.23 (0.73 - 2.13)	0.455
Binge drug use[b,c]	2.39 (1.30 - 4.48)	0.006	3.06 (1.73 - 5.54)	0.000	1.60 (0.94 - 2.81)	0.091	1.63 (0.98 - 2.80)	0.067
$ spent on drugs/day[b,c,e]	1.18 (0.64 - 2.21)	0.594	1.13 (0.64 - 2.05)	0.669	1.77 (1.04 - 3.10)	0.041	1.80 (1.08 - 3.10)	0.027
Non-fatal overdose[c]	1.57 (0.87 - 2.87)	0.138	1.68 (0.96 - 2.95)	0.069	2.58 (1.57 - 4.28)	<0.001	3.14 (1.96 - 5.11)	<0.001
Methadone treatment	2.69 (1.20 - 6.91)	0.024	3.21 (1.49 - 8.00)	0.006	4.24 (2.53 - 7.16)	<0.001	4.22 (2.60 - 6.87)	<0.001
Emergency room visit[b]	0.91 (0.50 - 1.70)	0.775	1.31 (0.75 - 2.34)	0.354	1.77 (0.99 - 3.33)	0.064	1.96 (1.12 - 3.60)	0.023
Depression symptoms	1.61 (0.85 - 3.07)	0.145	1.55 (0.85 - 2.83)	0.148	1.35 (0.79 - 2.29)	0.271	1.15 (0.69 - 1.90)	0.593
Childhood trauma	1.08 (0.53 - 2.15)	0.825	1.17 (0.60 - 2.21)	0.630	1.58 (0.94 - 2.66)	0.083	1.61 (0.98 - 2.62)	0.059
Experience violence[b]	2.53 (1.28 - 5.34)	0.010	2.63 (1.38 - 5.38)	0.005	1.73 (0.85 - 3.92)	0.156	1.50 (0.75 - 3.33)	0.282
Incarceration	1.07 (0.58 - 1.95)	0.823	1.44 (0.81 - 2.53)	0.212	2.60 (1.37 - 4.87)	0.003	2.82 (1.54 - 5.00)	0.001
Regular employment[b]	1.05 (0.58 - 1.92)	0.868	1.02 (0.59 - 1.80)	0.938	0.85 (0.50 - 1.49)	0.564	0.96 (0.58 - 1.63)	0.873
Drug dealing[b]	2.62 (1.28 - 5.84)	0.012	2.41 (1.22 - 5.23)	0.017	4.61 (2.08 - 12.27)	0.001	3.88 (1.78 - 10.19)	0.002
Sex work	0.80 (0.42 - 1.57)	0.515	0.96 (0.53 - 1.79)	0.890	0.72 (0.42 - 1.21)	0.219	0.61 (0.37 - 1.00)	0.055

a. Comparison is yes vs. no unless otherwise specified.
b. Refers to activities, behaviours, and experiences in the last six months.
c. Includes injection and non-injection drug use.
d. Includes crack cocaine, cocaine, or crystal methamphetamine use.
e. Comparison is <median vs. ≥ median.

Table 11: Multivariate analyses investigating NMPOU before or after illegal street drug use (n=1,345)

Characteristic[a]	ARYS (n=512)					VIDUS (n=833)				
	NMPOU first (vs. never NMPOU)			Illegal Drugs First (vs. never NMPOU)		NMPOU first (vs. never NMPOU)			Illegal Drugs First (vs. never NMPOU)	
	Adjusted Odds Ratio (95% CI)	*p*-value		Adjusted Odds Ratio (95% CI)	*p*-value	Adjusted Odds Ratio (95% CI)	*p* - value		Adjusted Odds Ratio (95% CI)	*p*-value
Age per year older									0.98 (0.95 - 1.01)	0.128
Male sex										
Caucasian/white									2.39 (1.38 - 4.19)	0.002
Homeless										
High school incompletion										
Daily heroin use[b,c]	3.76 (1.33 – 13.52)	0.022		3.68 (1.37 – 12.79)	0.019					
Daily stimulant use[b,c,d]										
Binge drug use[b,c]	2.05 (1.08 – 3.95)	0.030		2.07 (1.12 – 3.90)	0.022					
$ spent on drugs/day[b,c,e]										
Non-fatal overdose[c]						1.81 (1.03 – 3.19)	0.038		2.43 (1.42 - 4.19)	0.001
Methadone treatment	2.22 (0.86 – 6.51)	0.118		3.13 (1.32 – 8.68)	0.016	4.43 (2.50 – 7.96)	<0.001		3.63 (2.12 - 6.24)	<0.001
Emergency room visit[b]										
Depression symptoms										
Childhood trauma						1.96 (1.10 – 3.53)	0.023		1.85 (1.05 - 3.24)	0.033
Experience violence[b]	2.42 (1.18 – 5.28)	0.020		2.74 (1.36 – 5.93)	0.007					
Incarceration						1.92 (0.93 – 3.90)	0.072		2.26 (1.11 - 4.50)	0.021
Regular employment[b]										

Characteristic[a]	ARYS (n=512)					VIDUS (n=833)				
	NMPOU first (vs. never NMPOU)			Illegal Drugs First (vs. never NMPOU)		NMPOU first (vs. never NMPOU)			Illegal Drugs First (vs. never NMPOU)	
	Adjusted Odds Ratio (95% CI)	*p*-value		Adjusted Odds Ratio (95% CI)	*p*-value	Adjusted Odds Ratio (95% CI)	*p* -value		Adjusted Odds Ratio (95% CI)	*p*-value
Drug dealing[b]				1.85 (0.87 – 4.32)	0.127	4.06 (1.72 – 11.31)	0.003		2.68 (1.17 - 7.29)	0.032
Sex work										

a. Comparison is yes vs. no unless otherwise specified.
b. Refers to activities, behaviours, and experiences in the last six months.
c. Includes injection and non-injection drug use.
d. Includes crack cocaine, cocaine, or crystal methamphetamine use.
e. Comparison is <median vs. ≥ median.

A total of 452 ARYS and 750 VIDUS participants reported ever engaging in NMPOU and were eligible for inclusion in the sub-analyses. The full results from the sub-analyses investigating transitions to and from NMPOU can be found in Table 12 and Table 13. In brief, the bivariate VIDUS analysis revealed no significant risk factors associated with transitioning from NMPOU to illegal street drug use (p>0.10); no multivariate analysis was performed. A multivariate analysis was performed for the ARYS participants with male sex, daily illegal street stimulant use, and emergency room use eligible for the final model (p<0.10); only male sex was significantly associated with transitioning from NMPOU to illegal street drugs in the final multivariate model (Adjusted Odds Ratio [AOR] = 1.57, 95% Confidence Interval: 1.04–2.41).

Table 12: Bivariate analyses of participants reporting NMPOU prior to illegal street drugs (n=1,202)

Characteristic[a]	ARYS (n=452)			VIDUS (n=750)	
	Odds Ratio (95% CI)	*p*-value		Odds Ratio (95% CI)	*p*-value
Age per year older	0.97 (0.92 - 1.02)	0.268		1.00 (0.99 - 1.01)	0.921
Male sex	1.54 (1.02 - 2.36)	0.042		0.84 (0.61 - 1.14)	0.252
Caucasian or white ethnicity	0.93 (0.63 - 1.39)	0.722		0.83 (0.62 - 1.13)	0.240
Homeless	1.35 (0.57 - 3.56)	0.513		1.10 (0.60 - 2.10)	0.770
High school incompletion	1.03 (0.68 - 1.54)	0.895		1.06 (0.78 - 1.43)	0.722
Daily heroin use[b,c]	0.89 (0.58 - 1.36)	0.600		1.08 (0.77 - 1.50)	0.649
Daily stimulant use[b,c,d]	0.68 (0.45 - 1.04)	0.080		1.02 (0.73 - 1.41)	0.911
Binge drug use[b,c]	0.78 (0.53 - 1.16)	0.217		0.98 (0.72 - 1.34)	0.912
$ spent on drugs/day[b,c,e]	1.04 (0.70 - 1.55)	0.837		0.98 (0.72 - 1.33)	0.892
Non-fatal overdose[c]	0.94 (0.63 - 1.38)	0.738		0.82 (0.60 - 1.12)	0.213
Methadone treatment	0.84 (0.54 - 1.29)	0.425		1.00 (0.70 - 1.45)	0.979
Emergency room visit[b]	0.70 (0.47 - 1.04)	0.076		0.90 (0.65 - 1.25)	0.540
Depression symptoms	1.04 (0.68 - 1.58)	0.865		1.17 (0.85 - 1.63)	0.332
Childhood trauma	0.92 (0.59 - 1.46)	0.725		0.99 (0.71 - 1.38)	0.940
Experience violence[b]	0.96 (0.65 - 1.43)	0.853		1.16 (0.77 - 1.72)	0.475
Incarceration	0.75 (0.50 - 1.11)	0.150		0.92 (0.57 - 1.51)	0.748
Regular employment[b]	1.03 (0.70 - 1.51)	0.886		0.89 (0.63 - 1.24)	0.489
Drug dealing[b]	1.09 (0.72 - 1.63)	0.691		1.19 (0.84 - 1.67)	0.319
Sex work	0.84 (0.54 - 1.29)	0.430		1.17 (0.87 - 1.59)	0.302

a. Comparison is yes vs. no unless otherwise specified.
b. Refers to activities, behaviours, and experiences in the last six months.
c. Includes injection and non-injection drug use.
d. Includes crack cocaine, cocaine, or crystal methamphetamine use.
e. Comparison is <median vs. ≥ median.

Table 13: Multivariate analysis of ARYS participants reporting NMPOU prior to illegal street drugs (n=452)

Characteristic[a]	Adjusted Odds Ratio (95% CI)	*p-value*
Male sex	1.57 (1.04 – 2.41)	0.036
Daily stimulant use[b,c,d]	0.71 (0.46 - 1.09)	0.119
Emergency room visit[b]	0.70 (0.47 – 1.05)	0.087
a. Comparison is yes vs. no. b. Refers to activities, behaviours, and experiences in the last six months. c. Includes injection and non-injection drug use. d. Includes crack cocaine, cocaine, or crystal methamphetamine use.		

4.4. Discussion

Among our sample of PWUD in Vancouver, BC, the prevalence of NMPOU was extremely high (88% among street youth and 90% among adults), and over one-third of those who reported engaging in NMPOU had initiated NMPOU before illegal street drug use (vs. transitioning from illegal street drugs to NMPOU). Participants who reported either transitioning from NMPOU to illegal street drugs or from illegal street drugs to NMPOU shared many risk factors when compared with those who reported never engaging in NMPOU. Regardless of their transition trajectory, youth who engaged in NMPOU were significantly more likely to engage in daily heroin use, binge drug use, and experience violence than those who never engaged in NMPOU. Adults who engaged in NMPOU were significantly more likely to report overdose, accessing methadone treatment, a higher score on the Childhood Trauma Questionnaire, and drug dealing regardless of transition trajectory. With the exception of our finding that males in the youth cohort were more likely to transition from NMPOU to illegal street drugs (vs. transition from illegal street drugs to NMPOU), overall our results indicate that the transition patterns between NMPOU and illegal street drugs were not meaningfully different with respect to socio-demographic, early life risk factors, substance use, income generation, or other socio-structural risk factors.

The results from this study indicate that youth and adults who engage in NMPOU (regardless of transition trajectory) have higher risk profiles than those who use illegal

street drugs but do not engage in NMPOU. Engaging in NMPOU before or after transitioning to illegal street drugs was linked with markers of higher intensity substance use among youth (e.g., daily heroin use, and binge drug use) and adult (e.g., non-fatal overdose, accessing methadone maintenance treatment, and drug dealing) participants. These findings are not consistent with previous research that found those who engage in NMPOU have lower risk profiles, such as better employment and education-related outcomes when compared with those who use heroin or cocaine (55, 91, 184, 361). Youth and adults in this setting who engage in NMPOU and illegal street drug use would likely benefit from harm reduction and addiction treatment services specifically designed to attract and retain those who use POs.

While the results from the primary analyses suggest that there are marked differences between those who engage in NMPOU versus illegal street drugs, the sub-analyses indicate that there may be fewer within-group differences among people who use illegal street drugs and engage in NMPOU in our setting. Given the similarities in risk factors associated with engaging in NMPOU regardless of trajectory (vs. those who did not engage in NMPOU) and few observed significant differences in outcomes associated with engaging in NMPOU before versus after initiating illegal street drugs, the results from this study suggest that initiation trajectory may not be a critical marker of risk among those who engage in NMPOU and illegal street drugs in our setting. It is noteworthy, however, that high proportions of participants in this study who engaged in NMPOU reported ever being homeless (94%) or ever incarcerated (79%), and a low proportion of participants reported recent regular employment (34%). These frequencies underscore that ongoing and intensified efforts to improve health-related outcomes for people who engage in NMPOU and illegal street drugs are needed.

This study did not include a sample based on random recruitment methods, although extensive street-based outreach efforts were undertaken to achieve a diverse sample. In addition, the survey responses in this study were subject to recall and socially desirable response biases; previous research, however, has found that self-reports of drug use and related behaviours are valid (325, 362).

Chapter 5.

The impact of physician prescriptions on NMPOU-related initiation and overdose

5.1. Initiating NMPOU with a Physician Prescription

5.1.1. Introduction

Alarming increases in iatrogenic addiction, PO dependence, NMPOU, and associated mortality (363-365) characterize what has become known as the PO epidemic in North America. Inappropriate PO prescribing has been identified as an important driver in the resulting public health crisis, and includes (i) prescribing higher than necessary dosages and/or quantities of POs, and (ii) prescribing POs without comprehensive patient assessments and/or monitoring (24, 366, 367). The rapid increase in opioid prescriptions and inappropriate prescribing practices in Canada and the United States of America has also been linked with increased attention to pain as a “fifth vital sign”, aggressive and misleading marketing of pain medications by pharmaceutical companies, poor curriculum coverage of pain management and substance use issues in medical schools, and systems-level factors unique to Canadian and American healthcare versus other global regions (368-370).

Studies report a high prevalence of pain that increases with age (up to 75%) among those who engage in NMPOU (371) as well as frequent reports that pain relief is a motivator for engaging in NMPOU (82, 140, 141, 144, 151). Other studies have found that injuries or pain frequently precede NMPOU initiation (127, 372), and some individuals are significantly more likely to initiate NMPOU than heroin due to pain (129). In addition, those who initiate NMPOU due to pain may change their motivations for engaging in NMPOU over time (144). Less is known, however, about the prevalence and impacts of initiating NMPOU with POs obtained from a physician prescription among PWUD. This is a critical gap in knowledge given the current policy focus on restricting opioid prescriptions as a means of responding to the opioid crisis (28, 373). As physician prescriptions have been described as a key driver of the PO crisis, it is important to investigate the prevalence and

related outcomes of initiating NMPOU with a physician prescription to inform remedial policies aimed at reducing future incidences of NMPOU initiation. Given the urgent need to expand the evidence base for understanding and addressing NMPOU, this study sought to identify the prevalence and correlates of initiating NMPOU with POs from a physician prescription among PWUD.

5.1.2. Methods

Data for this study were drawn from two linked prospective cohort studies: The At-Risk Youth Study (ARYS) and the Vancouver Injection Drug Users Study (VIDUS). ARYS and VIDUS have both been described in detail previously (97, 275). As noted previously, ARYS is a prospective open cohort study of youth and young adults recruited using snowball sampling and extensive street-based outreach methods (342). To be eligible, participants at recruitment must be aged 14–26 years, use substances other than cannabis in the past 30 days, provide written informed consent, and be ‘‘street-involved’’. In this cohort, ‘‘street-involved’’ was defined as being absolutely, periodically or temporarily homeless (e.g., having no fixed address, sleeping on the street, couch surfing, or staying in a shelter or hostel), and includes those who were not homeless but used services designated for street-youth in the last year. Youths’ street involvement and eligibility to participate was assessed during a semi-structured in-person interview with an ARYS staff member. VIDUS is a cohort of adult PWID who injected illegal street drugs at least once in the month prior to enrolment (275). Participants in the VIDUS cohort have been recruited through self-referral, snowball sampling, and street outreach since May 1996.

At enrolment and on a bi-annual basis, participants in ARYS and VIDUS completed a harmonized interviewer-administered questionnaire that included questions related to demographic and health information, drug use patterns, and socio-structural risk factors. At each study visit, participants were provided with a stipend ($30 CDN) for their time. The University of British Columbia/Providence Health Care Research Ethics Board approved the ARYS and VIDUS studies.

ARYS and VIDUS participants who reported ever engaging in injection or non-injection NMPOU, defined as using POs prescribed for others or only for the feeling they caused (yes vs. no), between 2013 and 2016 were eligible for these analyses. The primary outcome of this analysis was initiating NMPOU with POs from a physician prescription, versus other diverted sources (yes vs. no). To identify factors associated with initiating NMPOU with POs from a physician prescription, we considered a number of potential explanatory variables of interest. The following socio-demographic variables of interest were included: age (per year older); female sex (yes vs. no); Caucasian or white ethnicity (white vs. non-white); homelessness, defined as having no fixed address, sleeping on the street, couch surfing, or staying in a shelter or hostel in the last six months (yes vs. no). Multiple drug use variables were also included: any injection or non-injection heroin use (yes vs. no); any injection or non-injection crack cocaine use (yes vs. no); any injection or non-injection cocaine use (yes vs. no); any injection or non-injection crystal methamphetamine use (yes vs. no); binge drug use, defined as a period of using injection or non-injection drugs more often than usual (yes vs. no); experiencing a non-fatal drug overdose due to injection or non-injection drug use (yes vs. no); and younger age at NMPOU initiation, defined as initiating NMPOU below the median age of NMPOU initiation in either the ARYS or VIDUS samples (yes vs. no). A range of other risk factors hypothesized to be associated with the source of PO at NMPOU initiation were also included: current moderate to extreme pain, defined as reporting “I have moderate pain or discomfort” or “I have extreme pain or discomfort” based on the participant’s health state “today” (Euroqol-5D) (yes vs. no); regular employment, defined as having a regular job, temporary work, or being self-employed since the last study visit (yes vs. no); drug dealing, defined as selling drugs as a source of income (yes vs. no); engaging in sex work, defined as exchanging sex for money, drugs, gifts, food, clothes, shelter or favours (yes vs. no); and incarceration, defined as living in detention, prison or jail (yes vs. no). All variables referred to activities, behaviours, and experiences in the previous six months unless otherwise indicated.

Data for participants were drawn from the first study visit during the study period. First, a descriptive analysis of the study sample stratified by the cohorts was conducted. Second, to model factors associated with initiating NMPOU with a physician prescription, a generalized logistic model regression analysis was conducted separately for the youth

(ARYS) and adult (VIDUS) cohorts. As a first step, bivariate analyses were used to determine factors associated with initiating NMPOU with a physician prescription. To adjust for potential confounding variables and to identify factors that were independently associated with our outcome of interest, independent variables significant at the $p<0.10$ threshold in bivariate analyses were entered in a multivariate model. As a sub-analysis, a combined analysis with youth and adult participants was conducted, following the bivariate and multivariate procedure as above. All statistical analyses were performed using R software version 5.0 (360). All *p*-values are two sided.

5.1.3. Results

A total of 1,441 individuals were seen for a study visit between 2013 and 2016, and 1,284 (89%) of these individuals reported ever engaging in NMPOU and were eligible for this study. Of these 1,284 individuals, 511 (40%) were youth (ARYS) and 773 (60%) were adult (VIDUS) participants. Among youth participants, 178 (35%) were female, 308 (60%) were of Caucasian or white ethnicity, and the median age was 24 years at baseline (interquartile range [IQR]: 21-27). Similar proportions of adult participants were female (n=281, 36%) and of Caucasian or white ethnicity (n=463, 60%); the median age of adult participants was 47 years at baseline (IQR: 37-54).

A total of 57 (11%) youth participants reported initiating NMPOU with a physician prescription, and 125 (16%) adult participants also reported this outcome. Descriptive frequencies and bivariate analyses for youth and adult participants are presented in Table 14 and Table 15, respectively. Among youth participants, older age was significantly associated with initiating NMPOU using a physician prescription in the bivariate analysis (Odds Ratio=1.08; 95% Confidence Interval [CI]: 1.00-1.17). No other variables were significant in the bivariate analyses, therefore a final multivariate model was not constructed for the youth cohort. Several variables were significant in the bivariate analyses among adults, therefore a multivariate model was constructed. In the multivariate analysis (

Table 16), initiating NMPOU with a physician prescription was independently and positively associated with moderate to extreme pain (Adjusted Odds Ratio [AOR]=1.65; 95% CI: 1.11–2.47), and negatively associated with any heroin use (AOR=0.62; 95% CI: 0.41–0.94).

The multivariate sub-analyses combining the younger and older samples found that moderate to extreme pain (AOR=1.57, 95% CI: 1.13-2.19) was positively and significantly associated with initiating NMPOU with a physician prescription. (Table 17).

Table 14: Descriptive frequencies and bivariate logistic regression analyses of factors associated with initiating NMPOU from a physician prescription among at-risk youth in Vancouver (n=511)

Characteristic[a]	Total (%) (n=511)	Initiated NMPOU with a physician prescription		Unadjusted Odds Ratio (95% CI)	*p*-value
		Yes (%) (n=57)	No (%) (n=454)		
Age per year older [M (IQR)]	24 (21-27)	24 (22-28)	24 (21-26)	1.08 (1.00 - 1.17)	0.038
Female sex	178 (34.8)	16 (28.1)	162 (35.7)	0.70 (0.37 - 1.27)	0.257
Caucasian or white ethnicity	308 (60.3)	40 (70.2)	268 (59.0)	1.63 (0.91 - 3.04)	0.108
Homeless[b]	276 (54.0)	30 (52.6)	246 (54.2)	0.94 (0.54 - 1.64)	0.824
Any heroin use[b,c]	271 (53.0)	27 (47.4)	244 (53.7)	0.78 (0.44 - 1.35)	0.364
Any crack cocaine use[b,c]	177 (34.6)	23 (40.4)	154 (33.9)	1.32 (0.74 - 2.30)	0.337
Any cocaine use[b,c]	198 (38.7)	20 (35.1)	178 (39.2)	0.84 (0.46 - 1.48)	0.548
Any crystal meth use[b,c]	350 (68.5)	34 (59.6)	316 (69.6)	0.65 (0.37 - 1.15)	0.129
Binge drug use[b,c]	305 (59.7)	30 (52.6)	275 (60.6)	0.72 (0.41 - 1.26)	0.243
Any non-fatal overdose[b,c]	125 (24.5)	11 (19.3)	114 (25.1)	0.71 (0.34 - 1.38)	0.338
Initiate NMPOU at younger age[d]	293 (57.3)	30 (52.6)	263 (57.9)	0.63 (0.36 - 1.11)	0.109
Moderate to extreme pain	220 (43.1)	28 (49.1)	192 (42.3)	1.31 (0.75 - 2.27)	0.341
Regular employment[b]	233 (45.6)	26 (45.6)	207 (45.6)	1.00 (0.57 - 1.74)	0.998
Drug dealing[b]	170 (33.3)	18 (31.6)	152 (33.5)	0.92 (0.50 - 1.63)	0.774
Sex work[b]	56 (11.0)	6 (10.5)	50 (11.0)	0.95 (0.35 - 2.17)	0.912
Incarceration[b]	79 (15.5)	11 (19.3)	68 (15.0)	1.35 (0.64 - 2.65)	0.405

a. Comparison is yes versus no unless otherwise specified.
b. Refers to activities, behaviours, and experiences in the last six months.
c. Includes injection and non-injection drug use.
d. Defined as initiating NMPOU below the median age in this sample.

Table 15: Descriptive frequencies and bivariate logistic regression analyses of factors associated with initiating NMPOU from a physician prescription among adults who inject illegal street drugs in Vancouver (n=773)

Characteristic[a]	Total (%) (n=773)	Initiated NMPOU with a physician prescription		Unadjusted Odds Ratio (95% CI)	*p*-value
		Yes (%) (n=125)	No (%) (n=648)		
Age per year older [M (IQR)]	47 (37-54)	49 (43-54)	47 (37-54)	1.02 (1.00 - 1.04)	0.023
Female sex	281 (36.4)	45 (36.0)	236 (36.4)	0.98 (0.66 - 1.46)	0.929
Caucasian or white ethnicity	463 (59.9)	77 (61.6)	386 (59.6)	1.11 (0.75 - 1.66)	0.599
Homeless[b]	186 (24.1)	24 (19.2)	162 (25.0)	0.71 (0.43 - 1.14)	0.169
Any heroin use[b,c]	412 (53.3)	54 (43.2)	358 (55.2)	0.62 (0.42 - 0.91)	0.014
Any crack cocaine use[b,c]	355 (45.9)	59 (47.2)	296 (45.7)	1.06 (0.72 - 1.56)	0.755
Any cocaine use[b,c]	241 (31.2)	42 (33.6)	199 (30.7)	1.14 (0.76 - 1.71)	0.523
Any crystal meth use[b,c]	287 (37.1)	39 (31.2)	248 (38.3)	0.73 (0.48 - 1.10)	0.135
Binge drug use[b,c]	287 (37.1)	43 (34.4)	244 (37.7)	0.87 (0.58 - 1.29)	0.483
Any non-fatal overdose[b,c]	85 (11.0)	10 (8.0)	75 (11.6)	0.66 (0.32 - 1.27)	0.245
Initiate NMPOU at younger age[d]	254 (32.9)	38 (30.4)	216 (33.3)	0.84 (0.55 - 1.26)	0.405
Moderate to extreme pain	395 (51.1)	76 (60.8)	319 (49.2)	1.63 (1.10 - 2.42)	0.015
Regular employment[b]	211 (27.3)	34 (27.2)	177 (27.3)	0.99 (0.64 - 1.52)	0.979
Drug dealing[b]	189 (24.5)	28 (22.4)	161 (24.8)	0.87 (0.55 - 1.36)	0.560
Sex work[b]	102 (13.2)	11 (8.8)	91 (14.0)	0.59 (0.29 - 1.10)	0.116
Incarceration[b]	56 (7.2)	9 (7.2)	47 (7.3)	1.00 (0.45 - 2.00)	0.995

a. Comparison is yes versus no unless otherwise specified.

b. Refers to activities, behaviours, and experiences in the last six months.

c. Includes injection and non-injection drug use.

d. Defined as initiating NMPOU below the median age in this sample.

Table 16: Multivariate logistic regression analysis of factors associated with initiating NMPOU from a physician prescription among adults who inject illegal street drugs in Vancouver (n=773)

Characteristic	Adjusted Odds Ratio (95% CI)	*p*-value
Age per year older	1.01 (0.99 - 1.03)	0.216
Any heroin use[a,b] (yes vs. no)	0.62 (0.41 - 0.94)	0.024
Moderate to extreme pain (yes vs. no)	1.65 (1.11 - 2.47)	0.015
a. Includes injection and non-injection drug use b. Refers to activities, behaviours, and experiences in the last six months		

Table 17: Bivariate and multivariate analyses of factors associated with initiating NMPOU from a physician prescription among a combined sample of youth and adults who use illegal street drugs in Vancouver (n=1,284)

Characteristic[a]	Unadjusted Odds Ratio (95% CI)	*p*-value		Adjusted Odds Ratio (95% CI)	*p*-value
Age per year older	1.02 (1.01 -1.03)	<0.001		1.02 (1.01 - 1.02)	<0.001
Female sex	0.86 (0.68 -1.09)	0.208			
Caucasian or white ethnicity	1.35 (1.07 -1.70)	0.013		1.30 (1.03 - 1.64)	0.029
Homeless[b]	0.77 (0.61 - 0.98)	0.033		0.89 (0.68 - 1.15)	0.360
Any heroin use[b,c]	0.87 (0.71 - 1.07)	0.187			
Any crack cocaine use[b,c]	1.28 (1.05 - 1.56)	0.013		1.25 (1.03 - 1.53)	0.026
Any cocaine use[b,c]	0.97 (0.79 - 1.20)	0.804			
Any crystal meth use[b,c]	0.84 (0.68 - 1.03)	0.099		1.03 (0.81 - 1.30)	0.833
Binge drug use[b,c]	0.95 (0.79 - 1.13)	0.549			
Any non-fatal overdose[b,c]	0.77 (0.57 - 1.03)	0.081		0.83 (0.60 - 1.13)	0.229
Initiate NMPOU at younger age[d]	0.88 (0.70 - 1.10)	0.263			
Moderate to extreme pain	1.18 (0.98 - 1.42)	0.078		1.14 (0.95 - 1.36)	0.173
Regular employment[b]	1.01 (0.83 - 1.22)	0.920			
Drug dealing[b]	1.00 (0.81 - 1.23)	0.998			
Sex work[b]	1.02 (0.74 - 1.39)	0.926			
Incarceration[b]	1.19 (0.86 - 1.64)	0.306			
a. Comparison is yes versus no unless otherwise specified. b. Refers to activities, behaviours, and experiences in the last six months. c. Includes injection and non-injection drug use. d. Defined as initiating NMPOU below the median age in this sample.					

5.1.4. Discussion

This study found that 11% and 16% of youth and adult PWUD, respectively, initiated NMPOU with a physician prescription. Older age was the only risk factor associated with initiating NMPOU from a physician prescription in bivariate analyses among youth participants, whereas adult participants who reported this outcome were significantly more likely to report moderate to extreme pain, and significantly less likely to report heroin use. In the multivariate sub-analysis that combined both cohorts, moderate to extreme pain was positively and significantly associated with initiating NMPOU with a physician prescription.

Based on the findings from this study, initiating NMPOU with a physician prescription occurs infrequently among young participants, and is not a key marker of high intensity substance use or socio-structural vulnerability given that older age was the only independent variable associated with this outcome in the bivariate analyses. This statistical relationship may reflect more relaxed opioid prescribing practices through the 2000's that have recently been restricted in Canada and the United States of America (370, 374, 375). If this were true, however, we would expect that older age of NMPOU initiation would also be significantly associated with initiating NMPOU with a physician prescription, and this was not observed. Although directionality cannot be determined, these findings may indicate that pain, which is likely the only reason why someone would receive a prescription for POs, is less of an issue for younger PWUD, or perhaps that physicians are less likely to prescribe POs to younger patients.

Among adult participants, this study found a relatively low prevalence of initiating NMPOU with a physician prescription and those participants who reported the outcome were more likely to report moderate to extreme pain and less likely to use heroin; in the combined analysis, pain was the only variable significant in the multivariate model. Although a relatively low proportion of adult participants reported initiating NMPOU with a physician prescription (16%), the prevalence of moderate to extreme pain among adult participants who reported this outcome was 49%. One possible explanation for this relationship is iatrogenic addiction, where POs were initially prescribed for pain but the patient subsequently developed dependence and continued taking the physician-

prescribed POs only for the feeling they caused; however, it should be noted that the risks and prevalence of PO-related iatrogenic addiction are not well-understood (364).

Another possible interpretation of the relationship between initiating NMPOU with a physician prescription and pain is that these participants experienced the under-treatment of pain and thus self-medicated to relieve pain symptoms; however, the variable for pain is based on “current” symptoms and may not reflect pain symptoms at the time of initiating NMPOU. Given that directionality cannot be determined, caution is needed when interpreting these results. However, the relationship between pain, NMPOU, and physician prescribing is consistent with previous research from this study setting that has previously found 67% of PWUD who report moderate to extreme pain have been denied POs from physicians, leaving them with undertreated pain (272). The most frequently reported reason for being denied POs for pain was an accusation of drug-seeking by healthcare providers (272). These findings align with the existing literature which has consistently found that PWUD are often perceived as drug-seeking (72, 376) and manipulative (377). Most concerning, however, are the consequences of this stigmatization and discrimination towards PWUD. Being denied POs for pain has been associated with self-managing pain, and this is most frequently achieved by obtaining POs from diverted sources in illegal street drug markets (273), which carries substantive overdose risks given uncertainty regarding dosing and risk related to drugs of unknown purity and composition. Given the observed association between pain and initiating NMPOU with a physician prescription, appropriately responding to the PO crisis may require consideration of the prevalence, and poor medical management, of chronic physical pain among PWUD. Along with the previous literature, the results from this study may provide some support to indicate that limiting prescriptions to reduce NMPOU initiation and ongoing NMPOU contributes to untreated pain and have the inverse effect of increasing NMPOU for the purposes of self-managed pain relief.

Given that adult PWUD who initiated NMPOU with a physician prescription were significantly less likely to engage in heroin use, motivations to engage in NMPOU may have included pain relief and avoidance of the street drug supply, which is well-documented to be highly contaminated with fentanyl in this setting (283) and heavily implicated in elevated levels of fatal opioid overdose (349). Possible interpretations for this

result include (i) adult PWUD who engaged in heroin use may have already been engaged with social networks that enabled access to POs from diverted sources and facilitated NMPOU initiation, and (ii) these individuals may have had numerous markers of high-intensity substance use and been refused POs from a physician due to either stigma towards PWUD or safe prescribing practices.

Overall, our findings suggest that the circumstances of NMPOU initiation are complex and physician prescriptions do not appear to be implicated in the majority of initiations into NMPOU. Given the low prevalence of initiating NMPOU with a physician prescription (11% among youth and 16% among adults) and overall lack of risk factors associated with this initiation source, our study suggests that efforts to reduce opioid prescribing may not have a significant impact on NMPOU initiation among PWUD. Although beyond the scope this study, the unintended consequences of restricting opioid prescribing may include disrupting individuals' established linkages to care and result in increases in unmet health needs, as well as drug-related risks and harms as individuals turn to unregulated illegal street opioids to self-manage their pain. Future investigations into the circumstances of NMPOU initiation are needed to better inform potential policy responses.

A better understanding of the circumstances of NMPOU initiation is particularly important given that physician prescribing is currently thought to be a major driver of this "opioid crisis" (366, 367) and the primary response to this crisis has been to restrict opioid prescribing (28, 373). This is particularly important to investigate among PWUD because opioid prescribing has been linked with high rates of overdose deaths in the general population (364), but the results from this study indicate that younger and adult PWUD in Vancouver who initiated NMPOU with a physician prescription were not at significant risk for overdose. Given the enduring stigma and discrimination that PWUD have experienced when interacting with healthcare providers (377), and especially in relation to pain-related issues (72, 378), PWUD in this setting may not have been affected by the surge in opioid prescribing attributed to pain increasingly being recognized as the "fifth vital sign" and aggressive marketing campaigns by pharmaceutical companies. The findings from this study indicate that PWUD and the general population may have different initiation trajectories that includes significant differences in the source of POs used to initiate

NMPOU. Consequently, different strategies for addressing NMPOU among PWUD and the general population may be necessary to ensure that PWUD are not further marginalized in healthcare settings, and that their pain is appropriately and adequately treated.

There are limitations to this study. ARYS and VIDUS participants were recruited using nonprobability sampling techniques, therefore the resulting samples may not be representative of PWUD in Vancouver and the results may not be generalizable to other settings; however, study staff undertook extensive street-based and outreach efforts to achieve a diverse sample. In addition, this study was focusing on a drug-using population as opposed to the general chronic pain population, and the results may not be generalizable beyond PWUD; further investigation of the role of physician prescribing on initiating NMPOU among those with chronic pain is warranted. The ARYS and VIDUS cohorts also rely on self-report, which may be affected by social desirability and recall biases. This is especially relevant for this study, which relies on participants recalling the details of an event (the source of POs used when initiating NMPOU) that may have happened many years ago. Any recall issues would result in misclassification bias; however, any misclassification is likely to be non-differential as incorrect recall would not be expected to affect those who obtained POs from physicians differently than those who obtained POs from diverted sources. Previous research has also found that self-report of substance use and associated behaviours and experiences are valid and reliable (325, 362). This study used a cross-sectional approach as a first step to investigate the phenomenon of different sources at NMPOU initiation; however, a more robust longitudinal analysis of the long-term impacts associated with initiating NMPOU with a physician prescription would provide a better understanding of this initiation trajectory. Lastly, the analyses in this study included socio-demographic, substance use, socio-structural, and pain-related independent variables to identify key risk factors and adjust for confounding; despite these efforts, unmeasured confounding remains a limitation to this study. It is important to note, however, that unmeasured confounding is a limitation of all observational research and unlikely to be resolved without interventional studies that would be unethical in this field.

5.1.5. Conclusion

In conclusion, physician prescriptions do not appear to account for the majority of initiations into NMPOU among PWUD. Our stratified analyses suggest that initiating NMPOU with POs acquired from a physician was not a key indicator of substance use, overdose, or socio-structural risk among street-involved youth, but may indicate unresolved pain-related issues among adult PWUD. Overall this body of work suggests that policies restricting opioid prescribing may not have a substantive impact on NMPOU initiation among PWUD in this setting.

5.2. Acquiring POs with a physician prescription and risk of overdose

5.2.1. Introduction

Drastic increases in rates of overdose morbidity and mortality have been documented in numerous settings across Canada and the United States (114, 301). These alarming increases have been attributed to medical and nonmedical PO use, and prompted swift responses from policy-makers and health professionals. To date, a key focus of the response has been to reduce opioid prescribing by physicians (7, 116), as new national prescribing guidelines championed in Canada and the United States involve an emphasis on increased prescription monitoring programs to promote safe prescribing, restrictions on opioid dosages, and broadly increased caution regarding prescribing opioids (28, 373). While aimed at preventing individuals from developing opioid dependence, engaging in PO misuse, and experiencing harm, these policies and guidelines may reinforce existing stigma and discrimination towards PWUD; a group that already experiences challenges receiving appropriate medical care and pain relief (72, 377, 378). Despite these efforts, the impact of these policies and guidelines on overdose risk among PWUD is not well-understood.

In the context of swift and rapid action to address the acute public health overdose crisis, there is an urgent need to identify factors associated with NMPOU-related overdose and specifically investigate whether acquiring POs from physicians is associated with an

increased or decreased risk of experiencing an overdose. Given this knowledge gap and the urgent need to inform policy responses, this study sought to examine the relationship between physician-acquired POs and risk of non-fatal overdose among people who engage in NMPOU and use illegal street drugs.

5.2.2. Methods

The data for this study draw on two harmonized open prospective cohort studies: The At-Risk Youth Study (ARYS) and the Vancouver Injection Drug Users Study (VIDUS). Both cohorts use extensive snowball sampling, self-referral, and street outreach to recruit participants. Participants in the ARYS study must be between the ages of 14 and 26, have recently used a street drug other than or in addition to cannabis in the last month, and be "street-involved", defined as being recently homeless or having used services designated for street-youth (94, 96, 342, 379). Participants in the VIDUS cohort must have injected drugs at least once in the previous month and be 18 years of age at enrollment. All enrollees provided informed consent to participate and were given a stipend ($30 CDN) for their time. Participants in both cohorts completed a harmonized interviewer-administered questionnaire at their baseline study visit and every six months thereafter. The ARYS and VIDUS studies received ethical approval from the University of British Columbia/Providence Health Care Research Ethics Board.

Participants who reported ever engaging in injection or non-injection NMPOU (yes vs. no) were eligible for these analyses. Participants were specifically prompted about non-medical use of OxyNEO, Oxycontin, Percocet, Tylenol 3, Morphine, Dilaudid, Demerol, Methadone/Methadose, Fentanyl, Hydrocodone, Talwin, and Suboxone; the non-medical use of other POs was also accepted. The primary outcome of these analyses was experiencing a non-fatal drug overdose in the last six months (yes vs. no), defined as overdosing by accident or experiencing a negative reaction from using too much drugs. The key independent variable of interest was reporting acquiring POs exclusively from a physician for the purposes of NMPOU in the last six months (yes vs. no). Reports of acquiring POs from a single or multiple physician(s) were coded as "yes", while reports of acquiring POs from a physician and/or diverted sources (e.g., friends, family, street) were coded as "no". To test the relationship between non-fatal overdose and acquiring POs

exclusively from a physician, we considered secondary explanatory variables that we hypothesized as potentially confounding this relationship of interest. The following socio-demographic variables were included: younger age (per year younger); female sex (yes vs. no); Caucasian or white ethnicity (white vs. non-white); and homelessness, defined as having no fixed address, sleeping on the street, couch surfing, or staying in a shelter or hostel (yes vs. no). Substance use variables included: any injection or non-injection heroin use (yes vs. no); any injection or non-injection crack cocaine use (yes vs. no); any injection or non-injection cocaine use (yes vs. no); any injection or non-injection crystal methamphetamine use (yes vs. no); binge drug use, defined as a period of using injection or non-injection drugs more often than usual (yes vs. no); and immediate access to POs, defined as being able to acquire POs from any source within 10 minutes in the area where the participant typically obtains drugs (yes vs. no). The analyses also included the following risk factors: moderate to extreme pain, defined as reporting “I have moderate pain or discomfort” or “I have extreme pain or discomfort ” based on the participant’s health state “today” (Euroqol-5D) (yes vs. no); unemployment, defined as not having a regular job, temporary work, or being self-employed (yes vs. no); drug dealing, defined as selling drugs as a source of income (yes vs. no); ever engaging in sex work, defined as exchanging sex for money, drugs, gifts, food, clothes, shelter or favours (yes vs. no); incarceration, defined as being in detention, jail, or prison (yes vs. no); difficulty accessing services, defined as reporting difficulty accessing health and social services, based on responses to the question “‘In the last six months, was there a time you were in need of a service (e.g., housing, counselling) but could not obtain it?” (yes vs. no); and addiction treatment, defined as accessing any kind of addiction treatment (yes vs. no). All variables were time updated and refer to activities, behaviours, and experiences in the previous six months unless otherwise indicated.

To investigate whether acquiring POs exclusively from physicians was independently associated with non-fatal overdose, we conducted a series of analyses. First, a preliminary analysis was conducted to investigate correlates associated with acquiring POs exclusively from a physician using the above-mentioned independent variables. Baseline frequencies and bivariable analyses stratified by acquiring POs exclusively from a physician were conducted using Pearson’s chi-square test for categorical variables and the Mann-Whitney test for continuous variables. Characteristics

for participants who reported acquiring POs exclusively from physicians were measured at their first visit (during the study period: 2013–2016), which involved a report of acquiring POs exclusively from physicians. Characteristics for all other participants were measured from the first study visit during the study period.

Second, baseline frequencies and bivariable analyses stratified by non-fatal overdose were conducted using Pearson's chi-square test for categorical variables and the Mann-Whitney test for continuous variables. Baseline characteristics for participants who reported non-fatal overdose were measured at their first visit during the study period (2013–2016), which involved a report of non-fatal overdose. Characteristics for all other participants were measured from the first study visit during the study period.

Third, we conducted bivariate generalized estimating equations (GEE) analyses testing the relationship between each independent variable and the outcome, non-fatal overdose. Given that the key independent variable of interest (acquiring POs exclusively from physicians) was associated with non-fatal overdose in the bivariate analysis ($p<0.10$), we fit a series of confounding models. This step was based on an automated *a priori* approach (380, 381) where all potential confounders are included in a multivariate model and then removed one at a time in a stepwise manner. This process constructs a series of reduced models, and the relative coefficient of change for our primary explanatory variable of interest (acquiring POs exclusively from physicians) was calculated for these reduced models. Secondary explanatory independent variables that resulted in the smallest relative change in the coefficient for acquiring POs exclusively from physicians were removed iteratively. This process was continued until the smallest minimum relative change in the coefficient for the effect of acquiring POs exclusively from physicians and non-fatal overdose exceeded 5% of the value of the coefficient. Remaining variables were considered confounders and included in the final multivariate analysis. All statistical analyses were performed using SAS software version [9.3] (SAS, Cary, NC). All *p*-values are two sided.

5.2.3. Results

A total of 599 participants reported engaging in NMPOU between 2013 and 2016, and were eligible for this study. Among this sample, 211 (35%) were female, 364 (61%) were Caucasian or white, and the median age was 31 (Inter-Quartile Range: 24-48). At baseline, a total of 197 (33%) participants reported experiencing a recent non-fatal overdose, and 82 (14%) participants reported acquiring POs exclusively from physicians. A total of 268 (45%) of participants attended at least one study follow-up visit, with a median of 1 study visit (IQR: 1-2). The sample contributed a total of 1,069 observations, with 265 observations of non-fatal overdose and 147 observations of acquiring POs exclusively from a physician.

A number of independent variables were significantly associated with acquiring POs exclusively from a physician as shown in Table 18. Moderate to extreme pain (OR=1.65, 95% CI: 1.08-2.53) and unemployment (OR=1.59, 95% CI: 1.01-2.50) were positively and significantly associated with acquiring POs exclusively from a physician. Factors negatively associated with this outcome included younger age (OR=0.95, 95% CI: 0.93-0.97), homelessness (OR=0.44, 95% CI: 0.28-0.68), any crack cocaine use (OR=0.65, 95% CI: 0.43-0.99), any crystal methamphetamine use (OR=0.35, 95% CI: 0.23-0.53), and difficulty accessing services (OR=0.53, 95% CI: 0.34-0.83).

Table 18: Characteristics of participants stratified by acquiring POs exclusively from physicians among participants who engage in NMPOU at baseline, 2013-2016 (n=599)

Characteristic[a,b]	Total (%) (n=599)	Physician Prescription		Odds Ratio (95% CI)	*p*-value
		Yes (%) (n=114)	No (%) (n=485)		
Non-fatal overdose[c]	149 (24.9)	21 (18.4)	128 (26.4)	0.63 (0.38 - 1.05)	0.076
Younger age [Med (IQR)]	31 (24-48)	45 (29-54)	29 (23-44)	0.95 (0.93 - 0.97)	<0.001
Female sex	211 (35.2)	44 (38.6)	167 (34.4)	1.20 (0.79 - 1.82)	0.402
Caucasian/white	364 (60.8)	68 (59.6)	296 (61.0)	0.94 (0.62 - 1.42)	0.767
Homeless[c]	260 (43.4)	32 (28.1)	228 (47.0)	0.44 (0.28 - 0.68)	<0.001
Any heroin use[c,d]	440 (73.5)	77 (67.5)	363 (74.8)	0.70 (0.45 - 1.09)	0.112
Any crack cocaine use[c,d]	271 (45.2)	42 (36.8)	229 (47.2)	0.65 (0.43 - 0.99)	0.045
Any cocaine use[c,d]	244 (40.7)	42 (36.8)	202 (41.6)	0.82 (0.54 - 1.25)	0.347
Any crystal meth use[c,d]	365 (60.9)	46 (40.4)	319 (65.8)	0.35 (0.23 - 0.53)	<0.001
Binge drug use[c,d]	342 (57.1)	58 (50.9)	284 (58.6)	0.73 (0.48 - 1.09)	0.124
Immediate PO availability	378 (63.1)	71 (62.3)	307 (63.3)	0.91 (0.59 - 1.39)	0.659
Moderate to extreme pain	330 (55.1)	74 (64.9)	256 (52.8)	1.65 (1.08 - 2.53)	0.019
Unemployment[c]	200 (33.4)	29 (25.4)	171 (35.3)	1.59 (1.01 - 2.50)	0.045
Drug dealing[c]	225 (37.6)	35 (30.7)	190 (39.2)	0.69 (0.44 - 1.07)	0.093
Sex work[c]	98 (16.4)	17 (14.9)	81 (16.7)	0.87 (0.50 - 1.54)	0.642
Incarceration[c]	81 (13.5)	13 (11.4)	68 (14.0)	0.79 (0.42 - 1.48)	0.458
Difficulty accessing services[c]	238 (39.7)	32 (28.1)	206 (42.5)	0.53 (0.34 - 0.83)	0.005
Addiction treatment[c]	379 (63.3)	75 (65.8)	304 (62.7)	1.14 (0.75 - 1.76)	0.535

a. Characteristics for participants who reported acquiring POs exclusively from physicians were measured at their first visit (during the study period: 2013–2016), which involved a report of acquiring POs exclusively from physicians. Characteristics for all other participants were measured from the first study visit during the study period.

b. Comparison is yes versus no unless otherwise specified.

c. Refers to activities, behaviours, and experiences in the last six months.

d. Includes injection and non-injection drug use.

Baseline descriptive frequencies and bivariable analyses stratified by non-fatal overdose are displayed in Table 19 and the GEE bivariate analyses are displayed in Table 20. In bivariate analyses, acquiring POs exclusively from a physician was negatively and significantly associated with non-fatal overdose (Odds Ratio [OR]=0.60, 95% Confidence

Interval (CI): 0.39-0.94) ($p<0.05$). After extensive adjustment for confounding, acquiring POs exclusively from a physician was not independently associated with non-fatal overdose (Adjusted Odds Ratio [AOR]=0.87, 95% Confidence Interval [CI]: 0.52-1.47) ($p>0.05$) in the final multivariate model (Table 20). Factors that remained positively and independently significantly associated with non-fatal overdose included younger age (AOR=1.02, 95% CI: 1.00-1.04), homelessness (AOR=1.58, 95% CI: 1.08-2.29), any crystal methamphetamine use (AOR=2.28, 95% CI: 1.51-3.45), drug dealing (AOR=1.53, 95% CI: 1.12-2.10), and incarceration (AOR=1.93, 95% CI: 1.25-2.97).

Table 19: Characteristics of participants stratified by recent non-fatal overdose among participants who engage in NMPOU at baseline, 2013-2016 (n=599)

Characteristic[a,b]	Total (%) (n=599)	Overdose		Odds Ratio (95% CI)	*p*-value
		Yes (%) (n=197)	No (%) (n=402)		
Acquire POs exclusively from physicians[c]	82 (13.7)	19 (9.6)	63 (15.7)	0.57 (0.33 - 0.99)	0.044
Younger age [Med (IQR)]	31 (24-48)	28 (23-37)	34 (25-49)	1.04 (1.02 - 1.05)	<0.001
Female sex	211 (35.2)	69 (35.0)	142 (35.3)	0.99 (0.69 - 1.41)	0.943
Caucasian/white	364 (60.8)	129 (65.5)	235 (58.5)	1.34 (0.94 - 1.91)	0.105
Homeless[c]	257 (42.9)	116 (58.9)	141 (35.1)	2.68 (1.89 - 3.81)	<0.001
Any heroin use[c,d]	443 (74.0)	171 (86.8)	272 (67.7)	3.14 (1.98 - 4.99)	<0.001
Any crack cocaine use[c,d]	266 (44.4)	91 (46.2)	175 (43.5)	1.11 (0.79 - 1.57)	0.538
Any cocaine use[c,d]	248 (41.4)	98 (49.7)	150 (37.3)	1.66 (1.18 - 2.35)	0.004
Any crystal meth use[c,d]	369 (61.6)	156 (79.2)	213 (53.0)	3.38 (2.27 - 5.02)	<0.001
Binge drug use[c,d]	351 (58.6)	153 (77.7)	198 (49.3)	3.65 (2.47 - 5.39)	<0.001
Immediate PO availability	379 (63.3)	121 (61.4)	258 (64.2)	0.89 (0.62 - 1.27)	0.506
Moderate to extreme pain	328 (54.8)	107 (54.3)	221 (55.0)	0.97 (0.69 - 1.37)	0.879
Unemployment[c]	405 (67.6)	135 (68.5)	270 (67.2)	1.06 (0.74 - 1.54)	0.738
Drug dealing[c]	226 (37.7)	93 (47.2)	133 (33.1)	1.81 (1.28 - 2.56)	0.001
Sex work[c]	102 (17.0)	43 (21.8)	59 (14.7)	1.62 (1.05 - 2.51)	0.029
Incarceration[c]	80 (13.4)	47 (23.9)	33 (8.2)	3.49 (2.15 - 5.67)	<0.001
Difficulty accessing services[c]	235 (39.2)	94 (47.7)	141 (35.1)	1.69 (1.19 - 2.39)	0.003
Addiction treatment[c]	379 (63.3)	136 (69.0)	243 (60.4)	1.46 (1.02 - 2.10)	0.041

a. Characteristics for participants who reported non-fatal overdose were measured at their first visit (during the study period: 2013–2016), which involved a report of nonmedical prescription opioid use. Characteristics for all other participants were measured from the first study visit during the study period.

b. Comparison is yes versus no unless otherwise specified.

c. Refers to activities, behaviours, and experiences in the last six months.

d. Includes injection and non-injection drug use.

Table 20: Bivariate and multivariate analyses of factors associated with recent non-fatal overdose among participants who engage in NMPOU, 2013–2016 (n=599)

Characteristic[a]	Unadjusted			Adjusted	
	Odds Ratio (95% CI)	*p-value*		Odds Ratio (95% CI)	*p-value*
Acquire POs exclusively from physicians[b]	0.60 (0.39-0.94)	0.025		0.87 (0.53-1.44)	0.591
Younger age (per year younger)	1.04 (1.03-1.05)	<0.001		1.02 (1.00-1.04)	0.018
Female sex	1.07 (0.76-1.50)	0.693			
Caucasian/white	1.27 (0.91-1.77)	0.159			
Homeless[b]	2.60 (1.91-3.54)	<0.001		1.58 (1.08-2.29)	0.017
Any heroin use[b,c]	2.61 (1.76-3.86)	<0.001			
Any crack cocaine use[b,c]	1.21 (0.90-1.63)	0.211			
Any cocaine use[b,c]	1.45 (1.08-1.94)	0.012			
Any crystal meth use[b,c]	3.60 (2.52-5.14)	<0.001		2.28 (1.51-3.45)	<0.001
Binge drug use[b,c]	3.12 (2.28-4.25)	<0.001			
Immediate PO availability	0.91 (0.66 -1.24)	0.551		0.94 (0.66-1.35)	0.750
Moderate to extreme pain	0.82 (0.62-1.08)	0.156		0.80 (0.59-1.10)	0.173
Unemployment[b]	1.28 (0.94-1.75)	0.112		1.23 (0.87-1.75)	0.231
Drug dealing[b]	1.90 (1.43-2.53)	<0.001		1.53 (1.12-2.10)	0.008
Sex work[b]	1.73 (1.17-2.55)	0.006			
Incarceration[b]	2.78 (1.86-4.15)	<0.001		1.93 (1.25-2.97)	0.003
Difficulty accessing services[b]	1.52 (1.12-2.06)	0.007		1.15 (0.80-1.64)	0.457
Addiction treatment[b]	1.47 (1.07-2.02)	0.016			

a. Comparison is yes versus no unless otherwise specified.
b. Refers to activities, behaviours, and experiences in the last six months.
c. Includes injection and non-injection drug use.

5.2.4. Discussion

This study found that one-third of participants who engaged in NMPOU had experienced a recent non-fatal overdose. Participants who acquired POs exclusively from physicians were significantly less likely to be homeless, use crack cocaine, use crystal methamphetamine, receive income from regular employment, and report difficulty accessing services; these participants are also more likely to report moderate to extreme pain. In the primary analyses, acquiring POs exclusively from physicians was negatively

associated with non-fatal overdose in bivariate analyses but not in the multivariate analysis. The results indicate that the relationship between acquiring POs exclusively from physicians and non-fatal overdose was not statistically significant, and numerous other risk factors were associated with non-fatal overdose in the final multivariate model: younger age, homelessness, crystal methamphetamine use, drug dealing, and incarceration.

At baseline, a relatively small proportion of participants reported acquiring POs exclusively from physicians (14%), which is lower than a nationally-representative survey of Americans who engaged in NMPOU that found 20% of participants acquired their POs exclusively from physicians (158). Obtaining POs exclusively from a physician was not independently associated with reporting a recent non-fatal overdose in the final multivariate model, suggesting that the burden of NMPOU-related overdose may not be linked to opioid prescribing by physicians in this population. In addition, the protective effect observed between acquiring POs exclusively from a physician and non-fatal overdose in bivariate analyses may be linked to this population's higher likelihood of being housed and lower likelihood of crystal methamphetamine use. These results align with recent research from the BC Centre for Disease Control which found that POs were not driving the overdose crisis in BC (382). Previous research also found that obtaining POs from physicians was not associated with markers of higher intensity NMPOU that may be linked with risk for overdose (172). It should also be noted that counterfeit Oxycontin pills containing fentanyl were circulating in the street drug supply in 2014 (383), which may partly explain why participants who did not obtain POs exclusively from a physician were found to have a higher risk of non-fatal overdose.

While causation and directionality cannot be inferred from these results, the findings point to key insights related to NMPOU, the source of POs, and non-fatal overdose. Possible interpretations of the results include (i) physicians may be more likely to prescribe opioids to PWUD who are housed, less likely to use illegal street drugs, and already have a low risk of overdose, and (ii) a reliable and safe supply of POs from physicians may enable PWUD to maintain housing, use less illegal street drugs and/or avoid consumption of illegal street opioids (e.g., heroin, fentanyl) and POs sold in illicit markets, and thereby reduce overdose risk. Regardless of the directionality, our findings

point to an overall lower risk profile among PWUD who acquire POs exclusively from physicians, as these individuals were less likely to be homeless, use stimulants, or report difficulty accessing services. These results may indicate a certain adeptness at navigating services for PWUD among these individuals, such as housing, healthcare, and other social services. There may be a need, however, for healthcare that specializes in treating PWUD who experience pain, given the previously documented pervasive under-treatment of pain in this population (72, 272, 378). Further research investigating the relationship between acquiring POs from physicians and overdose is warranted in order to inform opioid prescribing policies and services for PWUD who engage in NMPOU. This is particularly important since 63% of participants in this study noted that POs were immediately available from any source within the area where they typically obtain drugs, and this was also not associated with overdose in the bivariate analyses or final multivariate model.

Given these findings, restrictions on opioid prescribing and policies to reduce the availability of POs may in fact push those who engage in NMPOU in this setting towards the illegal street drug supply, which is highly contaminated with fentanyl and resulted in the declaration of a public health emergency due to the surge in overdose deaths in the study setting (283, 384). It is important to note that the study period for these analyses ended in 2016, which is when the proportion of fatal overdoses involving fentanyl in the province of British Columbia more than doubled (from 29% to 67%) (283). Ongoing research to monitor the intersection of NMPOU, the contamination of the street drug supply, opioid prescribing practices, and overdose are needed to develop effective policies that reduce risk for overdose among those who engage in NMPOU and those who use street drugs. This is especially urgent given recent opioid prescribing guidelines that encourage low doses of opioids, titration down to low opioid doses, and avoiding the prescription of opioids altogether (28, 373).

This study has limitations. ARYS and VIDUS participants are recruited using nonprobability sampling techniques, therefore the generalizability of these findings may be limited. Data was collected using self-report that may be biased by recall and social desirability response biases. This may be particularly concerning for accurately measuring reports of NMPOU, however, study staff described POs using both the generic and brand names, and showed photographs of POs to clarify the question or assist participants. In

addition, self-report of substance use has previously been found to be both reliable and valid (325), and is often the only option for measuring non-fatal overdose as emergency services are not always present at overdoses (385). Lastly, the outcome for the main analysis was non-fatal overdose, which has previously been established as a key risk factor that predicts fatal overdose (386-388). Given the increasing contamination of the street drug supply with fentanyl and corresponding rise in overdoses, the risks for fatal overdose in this new era may be different than previously established. Therefore, the relationship between source of POs and fatal overdose may be markedly different than that between source of POs and non-fatal overdose.

5.2.5. Conclusion

The study found that acquiring POs exclusively from physicians for the purposes of engaging in NMPOU was not independently associated with non-fatal overdose among this sample of PWUD. Instead, these findings indicate that homelessness and crystal methamphetamine are key risk factors that increase the likelihood of non-fatal overdose among those engage in NMPOU. Although further research is needed to investigate NMPOU and overdose at a time when illicitly manufactured synthetic opioids such as fentanyl are contaminating the street drug supply, the results from this study indicate that a comprehensive strategy that includes safe opioid prescribing, overdose prevention and reversal services, and access to healthcare services equipped to treat pain among PWUD may provide the most benefit for those who engage in NMPOU.

Chapter 6.

Discussion

6.1. Summary of findings

The objective of this dissertation is to inform regional and national policy responses to NMPOU among PWUD by investigating NMPOU initiation, ongoing use, and PO acquisition patterns among PWUD in Vancouver. A summary of each empirical chapter is provided below.

Chapter 2 presented the results from a systematized review investigating NMPOU-related initiation, ongoing use, and harms among the general and hidden populations of six primarily English-speaking high-income countries. The majority of the studies included in the review were from the USA, and conducted population-level, observational, and quantitative research. The results from this review found that the circumstances and context of initiating and engaging in NMPOU are heterogeneous; however, younger age groups, female gender, lower socio-economic status, physical pain, mental health issues, and poly-substance use were most consistently linked with NMPOU and its initiation, ongoing use, and associated harms. The harms of NMPOU included non-fatal and fatal overdose, HCV and STIs, and intensifying drug-use trajectories, which clearly indicate serious negative consequences as a result of engaging in NMPOU. The high number of studies using data from nationally representative surveys or other population-level data sources increases the generalizability of this review's conclusions, but studies focusing on socio-economically marginalized groups were limited. In addition, there are specific gaps in the evidence base that include: few studies investigating the impacts of specific POs other than OxyContin, which is no longer manufactured (389); few studies investigating incarceration and HIV as potential harms associated with NMPOU; and a lack of research investigating potential protective effects of engaging in NMPOU versus street drugs. The findings from this review are limited by the search protocol that restricted eligible studies to the English language, a selection of countries, and peer-reviewed publications.

Chapter 3 investigated socio-demographic characteristics associated with NMPOU by conducting age-based and sex-based analyses among the full sample of ARYS and VIDUS participants. The prevalence of NMPOU did not differ substantially between age groups (younger vs. older) or sex (male vs. female). In both the age and sex analyses, those who engaged in NMPOU were significantly more likely to report heroin use, illegal street stimulant use, drug dealing, and difficulty accessing services. In addition, non-fatal overdose was significantly associated with NMPOU in the final model of both sex-based analyses as well as the older (VIDUS) sample in the age-based analyses. Overall, the results indicate that those who engaged in NMPOU had a higher risk profile regardless of age or sex; however, there are key differences between younger and older participants who engage in NMPOU which suggests that a two-track approach to addressing NMPOU based on age may be beneficial.

Chapter 4 examined the prevalence and impact of initiation trajectories, with a focus on whether initiating NMPOU before illegal street drug use (versus after) was associated with different substance use patterns or increased socio-structural risk factors. The results indicate that among our samples of PWUD, initiating illegal street drugs first was more common (57% among ARYS and VIDUS participants) than initiating NMPOU first (31% among ARYS and 33% among VIDUS participants). The primary study conducted two analyses for each cohort: (i) those who engaged in NMPOU before illegal street drugs, and (ii) those who engaged in illegal street drugs before NMPOU; the comparison group for both analyses was those who never engaged in NMPOU. ARYS participants shared numerous risk factors regardless of initiation trajectory, as any heroin use, binge drug use, and experiencing violence were all positively and significantly associated with both initiation trajectories; methadone treatment was positively associated with engaging in illegal street drugs first. VIDUS participants who engaged in NMPOU before or after illegal street drugs were significantly more likely to experience a non-fatal overdose, access methadone treatment, experience childhood trauma, and engage in drug dealing; those who engaged in illegal street drugs first were more likely to be male and be incarcerated. In a sub-analysis, there were few meaningful differences when restricting the sample to only those who engage in NMPOU and directly comparing those who engage in NMPOU before illegal street drugs versus after. Overall, these findings suggest that early NMPOU-related initiation trajectories do not appear to critically shape

future patterns and practices among our study population. Policies focused on using initiation trajectories as a marker for risk or modifying these trajectories will likely not have a meaningful impact on this population of PWUD. There were, however, key differences in the results for the ARYS versus VIDUS participants, which further suggests that a two-track approach for younger and older PWUD who engage in NMPOU may be beneficial.

Chapter 5 investigated the relationship between acquiring POs using a physician prescription and NMPOU-related initiation and harms. The first study identified the prevalence and correlates of initiating NMPOU using POs prescribed by a physician. A small proportion of ARYS and VIDUS participants reported initiating NMPOU using a physician prescription (11% in ARYS; 16% in VIDUS). Few risk factors were found to be associated with initiating NMPOU with a physician prescription among ARYS participants; however, VIDUS participants who reported this outcome were more likely to experience pain and less likely to engage in heroin use. These findings suggest that physician prescriptions do not account for the majority of initiations into NMPOU, and efforts to reduce opioid prescribing may not have a significant impact on NMPOU initiation among PWUD. The second study examined the relationship between reporting physician prescriptions as the exclusive source of POs and non-fatal overdose. In the bivariate analysis, participants who reported physician prescriptions as their exclusive source for PO were significantly less likely to report a non-fatal overdose; however, this relationship was confounded in the multivariate analysis by the following key risk factors: younger age, homelessness, crystal methamphetamine use, drug dealing, and incarceration. The results from these two studies suggest that the policy response of addressing NMPOU through restricting opioid prescribing is not expected to significantly reduce the initiation of NMPOU among PWUD, nor the prevalence of non-fatal overdose among those who engage in NMPOU. A two-track approach for younger and older PWUD who engage in NMPOU that focuses on well-known risk factors for engaging in, and experiencing harms associated with, illegal street drug use (e.g., homelessness, drug dealing, and incarceration), a pain treatment strategy for PWUD, and OAT may be more effective at addressing NMPOU among this population.

The studies in this dissertation indicate that NMPOU is not a wholly unique drug-related phenomenon, as key risk factors that have long been associated with illegal street

drugs are also associated with NMPOU. In particular, NMPOU-related initiation trajectories and acquisition source do not appear to be an especially meaningful target for policy solutions or interventions. These findings are consistent with previous research investigating NMPOU among youth in the American general population, which found that NMPOU was not a unique form of substance use and did not explain variances in negative outcomes associated with substance use (204). Given the prevalence of polysubstance use among this population, NMPOU also may be an important marker for substance use disorder(s). Although there were few substantive within-cohort differences associated with NMPOU-related initiation, ongoing use, and overdose, this dissertation found key between-cohort differences that indicate opportunities to tailor unique strategies to younger and older PWUD. Heroin use and drug dealing were most consistently associated with NMPOU-related initiation, ongoing use, and overdose, and suggest an important starting point for developing a targeted comprehensive strategy to address NMPOU among younger and older PWUD that includes OAT and income generation opportunities.

6.2. Study strengths and unique contributions

There are several strengths to this dissertation, which fills an important evidence gap in the existing literature and points to relevant policy implications for decision-makers and healthcare providers. The prevailing policy response to NMPOU has been to restrict opioid prescribing and generally reduce the supply of opioids. The studies in this dissertation contribute to a better understanding of how acquiring POs from physicians impacts NMPOU initiation and related non-fatal overdose, as well as initiation trajectories and correlates associated with ongoing NMPOU. While this dissertation did not seek to formally evaluate the policy response to NMPOU, the results point to key indicators of how the policy response may impact PWUD who engage in NMPOU. In particular, the findings from Chapter 5 provide insight into how PO supply reduction may impact NMPOU initiation and non-fatal overdose among those who engage in NMPOU. These analyses found that POs acquired from a physician do not account for the majority of initiations into NMPOU and that the relationship between acquiring POs from a physician for the purposes of NMPOU and non-fatal overdose is confounded by predominantly socio-structural risk factors. Age, homelessness, crystal methamphetamine use, pain, drug dealing, and

incarceration were stronger predictors of initiating NMPOU and NMPOU-related non-fatal overdose than physician-acquired POs, indicating that services tailored for these groups (e.g., age, people who use crystal methamphetamine, and people who are in pain) and reducing exposure to socio-structural risk factors (e.g., homelessness, drug dealing, and incarceration) may increase the impact of the existing policy response to address NMPOU among PWUD. These findings may also translate to changes in physician practice, where regimen non-compliance or NMPOU triggers an intensification of services that may include alternative options for pain relief and OAT, rather than punitive measures (390).

The socio-demographic analyses in Chapter 3 point to minimal differences between men and women who engaged in NMPOU, and is consistent with the findings from Chapters 4 and 5 that consistently found age and socio-structural risk factors, such as drug dealing and access to health and social services, were stronger determinants of NMPOU-related trajectories and harms than biological sex. These results align with previous research that found few gender differences among American youth in the general population who engage in NMPOU (204); however, this contrasts with what is known about women and substance use more generally. The extant literature investigating gender and substance use has found an overall higher risk profile among women who engage in drug use, who are historically more socio-economically vulnerable and experience unique drug-related harms when compared with men (331, 335, 336). Indeed, opioid use disorder has been increasing among American women who are pregnant (391). Given these few sex-related differences, there remains strong evidence for a two-track approach to addressing NMPOU that tailors the design, location, and capacity of services to younger and older PWUD.

Another unique contribution of this dissertation is the use of the Risk Environment Framework to examine NMPOU-related risks and harms. Focusing on socio-structural and environmental factors to inform policy responses is an important approach that is needed in addition to the supply-reduction strategy currently implemented by policy-makers and healthcare providers. The studies in this dissertation investigated the role of key socio-structural and environmental variables such as incarceration, housing status, income generation, and access to health and social services, in addition to individual-level socio-demographic categories, substance use behaviours, and moderate to extreme pain. While

the prevailing policy response to restrict POs and improve patient compliance is an important strategy, the findings from this dissertation suggest that reducing the supply of POs may not have a significant impact on reducing opioid related harms among PWUD in this sample. This is especially likely given that physician prescribing did not directly account for the majority of initiations into NMPOU and was not significantly associated with non-fatal overdose.

The results from this dissertation do, however, support the need for much broader policy solutions that include continuously improving the availability and accessibility of health and social services, expanding overdose prevention and reversal services, implementing innovative treatments for heroin and NMPOU that may include injectable opioids such as diacetylmorphine and hydromorphone, and creating safe low-barrier opportunities for PWUD to generate income. In addition to opioid agonist therapies such as Methadone/Methadose and Suboxone that have been available in the study setting for some time, diacetylmorphine and hydromorphone have a strong evidence base (288-290) and may provide healthcare professionals with additional evidence-based tools for treating opioid use disorder among those who engage in NMPOU. It is worth noting that the study setting for this dissertation recently scaled up overdose prevention and reversal services, however, that was largely in response to the illicitly manufactured synthetic opioid crisis rather than overdoses stemming from NMPOU.

While there is an urgent need to characterize and investigate the illicitly manufactured synthetic opioid crisis, this dissertation aims to clarify the risks and harms of NMPOU among a sample of PWUD by focusing on key risk factors and outcomes such as age, sex, initiation trajectories, overdose, and acquiring POs from physicians. Future research is needed investigating the independent risks and harms of the illicitly manufactured synthetic opioid crisis as well as the combined effects of these two opioid crises. Separating the independent effects of these crises is important because the healthcare needs for those engaging in NMPOU may be quite different from those who use illicitly manufactured synthetic opioids. There may also be unique sub-groups that are at-risk for experiencing harms associated with NMPOU versus illicitly manufactured synthetic opioids that may enable policy-makers to target interventions for optimal outreach and effectiveness. This is particularly important given that engaging in NMPOU

using POs of known purity and dosage with a prescribed regimen may be an effective harm reduction option for those who are using illegal street drugs and are at risk of exposure to toxic adulterants such as fentanyl (392). While this dissertation does not investigate the illicitly manufactured synthetic opioid crisis, the results and implications from this research highlight the public health and public safety tensions between simultaneous opioid crises that involve a constellation of intersecting issues: physician prescribing patterns, availability and accessibility of various pain treatment options, scaling up harm reduction services such as supervised consumption sites, and traditional supply-reduction approaches to “problematic” substance use.

Lastly, these analyses use unique longitudinal data from hard-to-reach populations. There are few ongoing cohorts of PWUD with similarly robust research infrastructure that are able to longitudinally track this hidden population and gather data on a comprehensive range of variables associated with engaging in NMPOU as well as numerous variables to adjust for confounding; these include extensive data related to socio-demographic information, illegal street drug use, interactions with police and the criminal justice system, income generation activities, social service use, and health status. Where possible, this dissertation used high-quality longitudinal data with multiple participant follow-ups and conducted rigorous statistical analyses to account for within and between participant differences over time. The studies in Chapters 4 and 5 that did not use longitudinal data investigated NMPOU initiation, and were designed to provide a first step towards further research in these areas.

6.3. Limitations

This section presents the limitations that are common to all data-driven analyses in this dissertation. Participants in the ARYS and VIDUS studies were recruited using nonprobability sampling techniques, which may have resulted in samples that are not representative of PWUD in Vancouver and findings that are not generalizable to PWUD outside of Vancouver. Respondent-driven sampling is a probabilistic sampling technique often used to recruit hidden populations; however, nonprobability sampling is an appropriate, and the most common, method for recruiting participants from hidden populations such as PWUD (393). In addition, extensive street-based outreach efforts

were undertaken to recruit a representative sample of PWUD in Vancouver, such that the demographic composition of the ARYS cohort is similar to other studies of street-youth in Vancouver (315, 316).

As with any research using survey methodology, there are numerous biases that may arise during data collection. First, data were collected using self-report which may result in social desirability bias, especially since the study instrument contained sensitive questions. This bias was mitigated as much as possible by placing sensitive questions towards the end of the questionnaire to build rapport throughout the study visit. In addition, sensitive health-related questions were asked by the study nurse (rather than lay study staff) during the portion of each study visit where participants undergo phlebotomy for serologic testing. Previous research has also found that self-reported substance use is generally reliable and valid (325, 362), and any under-reporting of sensitive experiences or behaviours would bias our results to the null and result in underestimations. Second, recall response biases may have affected the validity of participant responses and resulted in misclassification bias; however, we are unaware of any reason why misclassification in participant responses would be differential. Any response biases associated with whether a participant engaged in NMPOU were mitigated as much as possible by using the brand and generic name of POs as well as showing pictures of POs to enable accurate recall. Despite these efforts, participants who acquired POs from diverted sources (e.g., friends, family, street) may have unwittingly received illicitly manufactured POs that were indistinguishable from pharmaceutical-grade POs and resulted in misclassification of NMPOU. For example, counterfeit Oxycontin pills were known to be circulating in the street drug supply in Vancouver (383).

This research is observational and subject to limitations that apply to all observational research. First, causation cannot be determined from the analyses. Second, unmeasured confounding is an important limitation of all observational research and may potentially affect the study results. To mitigate this issue of unmeasured confounding, the analyses in this dissertation were adjusted extensively using a wide range of variables available from the study questionnaire. With some variations in individual studies, the analyses in this dissertation were adjusted for relevant socio-demographic and other individual-level variables (e.g., pain), illegal substance use, income generation activities,

incarceration, accessing addiction treatment, and accessing health and social services. The most effective method to reduce or eliminate unmeasured confounding is randomized controlled trials; however, these trials would be unethical to conduct when investigating substance use among street-entrenched populations.

Lastly, biological sex at birth was used as a proxy for gender throughout the statistical analyses. Self-identified gender would have been ideal for the analyses, however, there were issues aligning data collection timelines. This is an important limitation given that gender is a key social determinant of health and often drives experiences of inequality, rather than biological sex at birth (394).

6.4. Recommendations and Implications

The NMPOU-related risks and harms identified in this dissertation are largely consistent with what is known about illegal street drug use through research using the Risk Environment Framework, and support continued efforts to reduce exposure to harmful socio-structural factors such as incarceration, drug dealing, sex work, and barriers to accessing health and social services. These risk factors have long been associated with drug injecting and HIV risk (100), and reflect a consistent pattern of unaddressed issues related to the criminal justice system, labour market participation, and access to healthcare and services among PWUD in this setting and elsewhere. The results indicate that improvements to these socio-structural factors are still needed in this setting, and that PWUD who engage in NMPOU are not a substantially different population than other PWUD who only use illegal street drugs. NMPOU itself may serve as a marker of substance use disorder(s), and may also provide a potential pathway for developing a new treatment modality as a strategy for safer opioid use among this population. Given that another more lethal drug crisis has already emerged with the contamination of the street drug supply with illicitly manufactured highly potent synthetic opioids, there is a renewed urgency to implement the most effective policy options based on the available evidence. The results from this dissertation support what has been known for decades about illegal street drug use, and a drug strategy informed by this long-standing and extensive knowledge base is needed now more than ever.

This dissertation found that younger and older age groups shared many risk factors for engaging in NMPOU, including heroin, illegal street stimulant use, engaging in drug dealing, and reporting difficulty accessing services; however, younger participants were more likely to binge on drugs, and older participants were more likely to report a non-fatal overdose and sex work. More focused analyses found that regardless of initiating NMPOU before or after illegal street drugs, younger participants were more likely use heroin, binge on drugs, and experience violence; conversely, older participants were more likely to report a non-fatal overdose, childhood trauma, drug dealing, and accessing methadone treatment regardless of initiation trajectory. In the second analysis focused on initiating NMPOU, a multivariate model was built only for the VIDUS sample, and the results indicate that initiating NMPOU with a physician prescription is positively associated with pain and negatively associated with heroin use. In the final study of this dissertation, younger age confounded the relationship between non-fatal overdose and acquiring POs exclusively from physicians.

Collectively, these findings suggest that similar low-barrier services and supports are needed for younger and older age groups, such as harm reduction services for ongoing substance use (e.g., needle exchange programs, Naloxone distribution, supervised consumption facilities) and income generation opportunities that are safe, meaningful, and legal. Although these results point to similar risk factors and policy implications, a two-track approach for designing and delivering these services would specifically benefit youth who often find that services designed for adults do not meet their needs (304, 395, 396). Indeed, previous research investigating at-risk and street-entrenched youths' unique needs found numerous service-related factors that are important to youth, such as fewer rules (304, 397, 398); locations where youth feel safe (397, 399); respectful and non-judgmental staff (397, 398); adequate capacity to provide on-demand support rather than wait lists (397, 400); comprehensive and integrated services (401); and access to "higher-level" services such as addiction treatment, housing, and case management (399, 402).

Given the higher risk profile associated with engaging in NMPOU and, in particular, the consistent relationship between heroin and NMPOU, the results from Chapters 3-5 indicate the importance of improving access to evidence-based OAT to treat those who

engage in NMPOU and heroin use. In addition to opioid agonist therapies such as Methadone/Methadose and Suboxone, this may include diacetylmorphine, hydromorphone, and medicinal cannabis. Emerging research has indicated that cannabis may have important benefits for those who engage in NMPOU, as cannabis has been associated with fewer opioid-related hospitalizations and overdose among the American general population (403) and may be willingly substituted for POs, based on findings from a sample of Canadians who use cannabis medicinally (404). As the illicitly manufactured synthetic opioid crisis has continued, guidelines have been developed in the current study setting for injectable opioid treatment such as diacetylmorphine and hydromorphone (405) and there is interest in supplying PWUD in Vancouver who would regularly obtain contaminated street drugs with pharmaceutical-grade POs of known purity and dosage (392). For those who are not ready to enter treatment, harm reduction services remain a critical intervention for those who engage in opioid use. Harm reduction services typically include supervised consumption sites, drug testing services, access to sterile syringes for those who inject, and widespread Naloxone distribution. Despite the large evidence base supporting harm reduction services as effective interventions to prevent overdose, reverse overdose, and connect PWUD to healthcare services (406-408), scaling up and improving access to these services remains an urgent priority in Canada and in many settings around the world (409, 410).

6.5. Future Research

Research to disentangle the risks and associated harms of NMPOU from the proliferation of illicitly manufactured synthetic opioids in the illegal street drug supply in Vancouver is urgently needed. Although Vancouver policy-makers and healthcare providers have been aware of the increasing contamination of the street drug supply for years (10, 11), this awareness is relatively new in other settings (12). While Canadian and American physicians over-prescribed opioids for many years (370), there have been noteworthy declines in opioid prescribing across Canada since 2011 (27, 374). Although NMPOU and illegal street drug use were found to share many commonalities, further research investigating the unique harms of NMPOU versus illicitly manufactured synthetic opioids is needed in order to inform policies to provide tailored services and supports for

PWUD and also improve access to treatments that are most likely to benefit PWUD. This research would also likely include examinations of temporal trends related to NMPOU, causal research investigating the impact of restricted PO prescribing among PWUD, and the impact of polysubstance use. These findings would provide valuable insight into how PWUD respond to the supply reduction of a legal and therapeutic substance, as there has been some debate over whether restrictive opioid prescribing policies caused people who engage in NMPOU to substitute with illegal street opioids (411, 412). This is especially pertinent to investigate given that the findings from Chapter 5 indicate that physician prescribing does not appear to significantly impact NMPOU initiation or NMPOU-related non-fatal overdose among PWUD. Other possible sequelae associated with restricted opioid prescribing may include fewer visits to healthcare providers, greater mistrust between patients and healthcare providers, and lower likelihood of accessing and/or adhering to addiction treatment.

The results from Chapter 5 point to important areas for future research related to pain and overdose. The first analysis in Chapter 5 found that moderate to extreme pain is associated with initiating NMPOU using opioids acquired from a physician. Although this dissertation did not conduct a comprehensive examination of pain and its relationship to NMPOU among PWUD in Vancouver, these investigations are critical for moving forward with an effective plan to address NMPOU without increasing untreated pain and reducing rapport between patients and physicians. The second analysis in Chapter 5 found that the relationship between physician-prescribed POs and non-fatal overdose is confounded by younger age, homelessness, crystal methamphetamine use, drug dealing, and incarceration. Homelessness, drug dealing, and incarceration are known risk factors for overdose (243, 348, 413, 414); however, the study period for this analysis ended as the prevalence of fentanyl-related overdoses doubled in the study setting (283). The high toxicity and potency of illicitly manufactured synthetic opioids in the street drug supply increased the lethality of overdoses (415) and may result in a different set of risk factors associated with overdose; future research is urgently needed to track whether there are any changes in overdose risk.

6.6. Conclusion

This dissertation examined the initiation, ongoing use, and associated harms of NMPOU among PWUD with an emphasis on the impact of acquiring POs from physicians. The studies in this dissertation found that a range of risk factors that includes illegal substance use, illegal and quasi-legal income generating activities, and difficulty accessing services were most consistently associated with NMPOU initiation trajectories and ongoing use. Most noteworthy, the findings also suggest that acquiring POs from physicians is not implicated in the majority of initiations into NMPOU and not significantly associated with non-fatal overdose among PWUD who are street-entrenched. In addition to the continued need for safe opioid prescribing and in particular, ethical advertisement of pharmaceuticals, the results from this dissertation point to a suite of policy options that may reduce the harms of NMPOU and are also recognized as long-standing solutions to addressing illegal substance use, such as harm reduction services, overdose prevention and reversal supports, safe and stable housing, legal income generation opportunities, and a spectrum of OAT therapies. A two-track approach to designing and delivering these services based on age may be an effective approach to optimize uptake and effectiveness of supports for PWUD who engage in NMPOU, along with a longer-term strategy to move away from harmful drug policies and anti-drug strategies.

The NMPOU crisis offers another opportunity for the media, the public, and politicians to approach substance use as a medical condition and learn from past failed approaches to managing successive drug crises, especially among youth (416). An evidence-based approach is particularly important given the increasing overdose rates associated with illicitly manufactured synthetic opioids in the drug supply, and lethality of this current drug crisis (12). The data presented in this dissertation suggests that NMPOU may be a marker for dependence in this population of people who use illegal drugs, and aligns with the extensive body of research investigating substance use. Collectively, these findings provide further support for the need to address socio-structural risk factors as part of a comprehensive substance use strategy that also includes supply-reduction, patient compliance, and strict advertising regulations. In addition to benefiting those who already engage in NMPOU, implementing a more comprehensive strategy may also serve as a template for effectively managing the illicitly manufactured synthetic opioid crisis and

reduce the considerable mortality rates that threaten communities of PWUD across Canada and the USA.

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Appendix.

Tables for Chapter 2: Systematized Review

Table A1: MEDLINE Search Strategy

Search 1	(MH "Adolescent") OR (MH "Middle Aged") OR (MH "Young Adult") OR adult
Search 2	(MH "OpioidRelated Disorders") OR ((“prescri*” OR “pharmaceutical”) AND (“opioid” OR “opiate” OR “pain relie*” OR “analgesi*” OR “dependen*” OR “narcotic”) AND (“*use” OR “*medical” OR “illicit” OR “aberrant” OR “addict*” OR “disorder*”))
Search 3	(MH “antibacterial agents”) OR (MH “palliative care”) OR (MH “pain, postoperative”) OR (MH “pharmaceutical preparations”) OR (MH “migraine disorders”) OR (MH “apoptosis”) OR (MH “pregnancy complications”) OR (MH “antineoplastic agents”) OR (MH “neoplasms”)
Search 4	1 AND 2 NOT 3

Limiters: full text, date of publication: 19990101-20141231; English language; human

Table A2: Summary table of included studies (n=154)

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
1	Dertadian 2014 (87). Australia	Qualitative	1 youth and 1 young adult from the general population	N/A	Change in drug use	One participant reported transitioning from nonmedical prescription opioid use (NMPOU) to heroin after being unable to purchase prescription opioids (POs) from a dealer.
2	Nielsen 2011 (129). Australia	Cross-sectional	192 participants in addiction treatment	Those primarily entering treatment due to NMPOU vs. heroin	Overdose, initiating NMPOU	Those entering treatment primarily due to NMPOU were less likely to report an overdose history (Adjusted Odds Ratio [AOR]=0.90, 95% Confidence Interval [CI]: 0.81–0.99), and were more likely to initiate opioid use for pain (AOR=2.52; 95% CI: 1.04–6.12) than those with a primary heroin problem.
3	Arora 2013 (49). Australia	Cross-sectional	902 people who inject drugs (PWID)	Recently exceeded recommended dose vs. did not exceed recommended dose	Pain	Those exceeding the recommended dose of over the counter codeine were more likely experience moderate to very severe pain (AOR=2.54, 95% CI: 1.76–3.69).
4	Roxburgh 2013 (250). Australia	Longitudinal	136 decedents where Fentanyl was a contributory cause of death (Nationally representative sample [NRS])	Decedents with a prescription for Fentanyl vs. no prescription for Fentanyl	Overdose and mortality	The majority of deaths involved the not-as-prescribed use of Fentanyl (62%); Fentanyl was prescribed for only 36% of decedents at the time of death.
5	Buykx 2010 (241). Australia	Cross-sectional	452 attendees at emergency departments	Engaging NMPOU vs. other drugs causing overdose	Overdose and mortality	POs were implicated in 4% of medication misuse or overdose presentations to emergency departments in the general Australian population.

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
6	Nielsen 2013 (208). Australia	Cross-sectional	141 participants with a history of substance use	Pain vs. no pain	Pain, NMPOU	There was no association with pain and illicit use of POs (Odds Ratio [OR]=1.17, 95% CI: 0.60-2.29) or reporting of greater frequencies of aberrant opioid-related behaviours (β=-0.014, 95% CI: −1.05-1.02).
7	Wilkins, 2011 (48). New Zealand	Longitudinal	PWID participating in the Illicit Drug Monitoring System (IDMS)	Availability of street/illicit morphine vs. street/illicit methadone	PO acquisition	In 2009, street/illicit morphine was more easily available than street/illicit methadone (90% vs. 77%, p=0.044), and street/illicit methadone was easier to obtain than heroin (77% vs. 49%, p=0.007).
8	Brands, 2010 (168). Canada	Cross-sectional	2,914 secondary students (NRS)	Engaging in NMPOU vs. not	PO acquisition, poly-substance use	Those who engaged in NMPOU had higher past-year prevalence of alcohol use (76%, 95% CI: 70.8–80.2), daily smoking (10%, 95% CI: 7.1–13.1), hallucinogens (17%, 95% CI: 13.7–21.3), cocaine or crack (10%, 95% CI: 7.3–13.5), and heroin (2%, 95% CI: 1.2–4.8). Among those who engaged in NMPOU, 72% reported obtaining POs from home and 6% reported obtaining POs from friends.
9	Roy, 2011 (181). Canada	Qualitative	60 street-involved youth	N/A	Route of administration, infectious disease	Injection was the main route of administration observed among those who engage in NMPOU. PO-specific injection practices such as “doing a wash” could pose new challenges for preventing infections.
10	Shield, 2013 (149). Canada	Cross-sectional	13,032 participants who obtained POs from a pharmacy (NRS)	Those who engage in NMPOU to get high vs. other motivations	Motivations	In Canada, the prevalence of engaging in NMPOU to get high was 0.4% (95% CI: 0.1% to 0.8%) in 2009.

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
11	Nosyk, 2012 (166). Canada	Longitudinal	1,871 street-involved youth and PWID	Perceived availability of POs: not available, delayed availability (≥10 min), and immediate availability (<10 min)	PO availability	The availability of POs increased over time, regardless of changes in the characteristics of cohort entrants. Controlling for other covariates, the odds of delayed availability was between 34% (for hydromorphone) and 71% (for acetaminophen/codeine) greater in each given calendar year, compared to being unavailable.
12	Firestone, 2009 (253). Canada	Qualitative	25 illicit drug users	N/A	Infectious disease	Fentanyl matrix patches are often purchased and used among 4–6 street users, which contributes to high-risk conditions for the transmission of infectious diseases, such as HCV and HIV.
13	Roy, 2012 (182). Canada	Mixed methods	451 street-based crack cocaine users	Engaging in NMPOU intravenously vs. other routes of administration	Route of administration	According to the survey, 88% of participants who used opioids did so intravenously.
14	Shield, 2011 (154). Canada	Cross-sectional	2,030 adults in the general population	Engage in NMPOU vs. not	Socio-demographic characteristics, poly-substance use, mental health	There were no significant differences between men and women for either PO use or NMPOU. Males who engage in NMPOU are more likely to be younger (OR=3.27, 95% CI: 1.27-16.58) and use cannabis (OR=4.64, 95% CI: 1.60-13.48). Both males (OR=7.55; 95% CI: 2.87- 19.88) and females (OR=4.21; 95% CI: 1.61-11.00) who engage in NMPOU were more likely to report psychological distress.
15	Fischer, 2013 (197). Canada	Longitudinal	4,023 adults in the general population	2010 survey respondents vs. 2011 survey respondents	Socio-demographic characteristics	Reductions in NMPOU from 2010 to 2011 occurred among older age groups but not among those aged 18-29 (7% to 7%; p=0.987).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
16	Bruneau, 2012 (51). Canada	Longitudinal	246 adults who currently inject drugs	Hepatitis C (HCV)-positive vs. HCV-negative	Route of administration, infectious disease	The proportion of PWID who inject POs increased from 21% in 2004 to 75% in 2009 ($p<0.001$). Participants who injected POs were more likely to become infected with HCV (Adjusted Hazard Ratio [AHR]=1.87; 95% CI: 1.16-3.03), and >30 injections in the past month was associated with risk of HCV infection (AHR=2.72, 95% CI: 1.58-4.70).
17	Sproule, 2009 (159). Canada	Cross-sectional	571 people admitted to detoxification	N/A	PO acquisition, poly-substance use, pain, mental health	A moderate proportion of participants obtained POs from physician prescriptions (37%) and reported comorbid substance use problems (43% used benzodiazepines, 30% used cocaine), pain (31% reported back pain), and psychiatric symptoms (53% reported depressive symptoms).
18	Fischer, 2004 (243). Canada	Longitudinal	651 illicit opioid users	Non-intravenous hydromorphone users vs. intravenous hydromorphone use	Overdose and mortality	Compared with no hydromorphone use, non-intravenous hydromorphone use (oral, nasal, smoking) was associated with non-fatal drug overdose (AOR=2.37, 95% CI: 1.20-4.71); however, intravenous hydromorphone use was not associated with non-fatal drug overdose (AOR=0.87, 95% CI: 0.46-1.64).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
19	Fischer, 2008 (55). Canada	Cross-sectional	484 illicit opioid users	Those who use heroin only vs. PO-only	Socio-demographic characteristics, poly-substance use, route of administration, infectious disease, overdose	PO-only users were more likely to be older (OR=1.06, 95%CI: 1.01-1.10), white ethnicity (OR=3.49, 95% CI: 1.21-10.07), receive income from paid work (OR=6.59, 95% CI: 2.28-19.03), use cocaine (OR=2.13, 95% CI: 1.02-4.43) and benzodiazepines (OR=13.32, 95% CI: 4.62-38.41); PO-only users were less likely to engage in intravenous drug use (OR=0.14, 95% CI: 0.06-0.35). Syringe sharing (OR=1.33, 95% CI: 0.36-4.91) and non-fatal overdose (OR=1.16, 95% CI: 0.32-4.18) were not significantly associated with PO-only use.
20	Kolajova, 2014 (186). Canada	Cross-sectional	92 people in addiction treatment	N/A	Route of administration, poly-substance use	58% of participants reported using an opioid substance as the first-ever drug injected; hydromorphone was the most commonly injected opioid for first-time injections. Among those who engaged in NMPOU, 13% co-administered either crack cocaine or powder cocaine.
21	Fischer, 2010 (191). Canada	Longitudinal	500,217 people in addiction treatment	Those in treatment due to NMPOU vs. other drugs use	Socio-demographic characteristics, poly-substance use	Among participants in treatment due to NMPOU, a large proportion were <35 years old (~60%), unemployed (~75%), and engaged in poly-substance use (75%).
22	Sinyor, 2012 (246). Canada	Cross-sectional	397 decedents due to overdose (suicide)	Death due to NMPOU vs. other drugs	Overdose and mortality	Opioid analgesics were the most frequently detected class of lethal substances (28%).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
23	Currie, 2012 (142). Canada	Cross-sectional	44,344 secondary students (NRS)	Engage in NMPOU vs. not	Motivations	Participants engaging in NMPOU to get high were more likely to be older (OR=2.30, 95% CI: 2.27-2.33), and identify as First Nations (OR=2.56, 95% CI: 2.50-2.61), Metis (OR=1.69, 95% CI: 1.64-1.75), or Inuit (OR=5.05, 95% CI: 4.80-5.31); males were less likely to engage in NMPOU to get high (OR=0.87, 95% CI: 0.86-0.88).
24	Fischer, 2013 (110). Canada	Cross-sectional	7,289 secondary students and adults from the general population	Engage in NMPOU vs. not	Socio-demographic characteristics, poly-substance use, mental health	Males who engaged in NMPOU were more likely to engage in other drug use (students: AOR=6.02, 95% CI: 3.12-11.60) and cannabis use (adults: AOR=2.03, 95% CI: 1.11-3.72). Females who engaged in NMPOU were more likely to live in a rural residence (AOR=1.95, 95% CI: 1.24–3.06), engage in other drug use (AOR=2.70, 95% CI: 1.48–4.91), and experience suicidal ideation (AOR=2.13, 95% CI: 1.12–4.06); female adults were more likely to engage in binge drinking (AOR=3.32, 95% CI: 1.14=9.66).
25	Apantaku-Olajide, 2013 (43). Ireland	Cross-sectional	63 youth with substance use disorders	N/A	Motivations	Participants reported the following motives for engaging in NMPOU: “seeking high or buzz” (79%), “having good time” (63%), and “relief from boredom” (56%).
27	Lind 2003 (192). UK	Cross-sectional	408 hospital patients	Engaging in NMPOU vs. other drugs	Socio-demographic characteristic, poly-substance use	Those who recently engaged in NMPOU were more likely to be unemployed (versus invalid, sick or retired) (Fisher’s exact test: $p<0.01$). All nine patients dependent on POs were misusing more than one substance.

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
28	Schepis, 2008 (188). USA	Cross-sectional	18,678 youth in the general population (NRS)	Engaging in NMPOU vs. not	Socio-demographic characteristics, mental health	Youth who engage in NMPOU are more likely to be older (OR=2.75, 95% CI: 2.32–3.27), female (OR=1.18, 95% CI: 1.02–1.37), have poorer academic performance (OR=2.84, 95% CI: 2.29–3.51), and experience a major depressive episode in the past year (OR=2.91, 95% CI: 2.41–3.52).
29	Havens, 2011 (195). USA	Cross-sectional	17,842 youth in the general population (NRS)	Engaging in NMPOU vs. not	Socio-demographic characteristics	Youth who engage in NMPOU are more likely to live in a rural/ nonmetro area (12%, 95% CI: 10.1-12.9) rather than an urban/large metro area (9%, 95% CI: 7.76-9.47) (p=0.004).
30	Vaughn, 2012 (227). USA	Cross-sectional	1,783 youth in the general population who engage in NMPOU (NRS)	Membership in one of four latent risk classes differentiated by poly-substance use and delinquency	Socio-demographic characteristics, mental health	Membership in higher risk classes was associated with male gender (OR=3.23, 95% CI: 1.20–8.70), lower income households (OR=2.31, 95% CI: 1.80–2.97), and experiencing lifetime anxiety (OR=11.06, 95% CI: 1.97–62.16).
31	Sung, 2005 (190). USA	Longitudinal	17,709 youth in the general population (NRS)	Engaging in NMPOU vs. not	Socio-demographic characteristics, poly-substance use	Youth who engage in NMPOU are more likely to live in a lower-income household (OR=0.99, 95% CI: 0.95-1.03). Participants' use of other prescription drugs were the strongest predictors of NMPOU, such that the odds of NMPOU were higher for those who used stimulants (OR=4.25, 95% CI: 3.3-5.5), tranquilizers (OR=11.1, 95% CI: 8.2-14.9), and sedatives (OR=2.2, 95% CI: 1.1-4.4).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
32	Boyd, 2006 (140). USA	Cross-sectional	1,086 youth in the general population	Each additional motivation for engaging in NMPOU	Motivations	Youth in this study endorsed the following motivations for engaging in NMPOU: pain relief and at least one other motivation (79%), pain relief solely (69%), getting high (11%). Each additional motivation for engaging in NMPOU increased the odds of a positive Drug Abuse Screening Test score by a factor of 1.8.
33	Deandrea, 2013 (198). USA	Longitudinal	135,552 youth in the general population who engage in not-as-prescribed OxyContin use (NRS)	Age of participants	Socio-demographic characteristics	From 2004–2008, the estimated risk of not-as-prescribed OxyContin use increased at age 12 years, peaked in mid-adolescence at roughly five newly incident users per 1000 persons per year (95% CI: 0.3-0.7%), and then declined.
34	Meier, 2012 (136). USA	Longitudinal	138,729 youth in the general population (NRS)	Age of participants	Socio-demographic characteristics	The estimated peak risk of initiating NMPOU occurred in mid-adolescence, at approximately age 16 (meta-analysis summary estimate: 3%).
35	McCabe, 2007 (216). USA	Cross-sectional	1,086 secondary students	Engaging in NMPOU vs. other drugs	Poly-substance use	Students who engaged in both as-prescribed and not-as-prescribed PO use were more likely to use marijuana (AOR=2.6, 95% CI: 1.6–4.1), and use an illicit drug other than marijuana (AOR=5.9, 95% CI: 2.8–12.4).
36	Suryaprasad, 2014 (134). USA	Longitudinal	1,202 youth in the general population (NRS)	Age of participants	Initiation, trajectories	On average, participants initiated NMPOU at age 17.7 (range 10–28 years), and oxycodone, specifically, at age 17.9 (range 10–28 years). Participants initiated heroin use on average 2.0 years after initiating NMPOU.

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
37	Paulozzi, 2012 (249). USA	Longitudinal	6,293 members of general population	Decedents of unintentional overdose (cases) vs. patients with a PO prescriptions (controls)	Mortality	Death due to overdose is associated with male gender (AOR=2.4, 95% CI: 1.8–3.1), older age (AOR=1.3, 95% CI: 1.2–1.4), and a prescription for buprenorphine (AOR=9.5, 95% CI: 3.0–30.0), fentanyl (AOR=3.5, 95% CI: 1.7–7.0), hydromorphone (AOR=3.3, 95% CI: 1.4–7.5), methadone (AOR=4.9, 95% CI: 2.5–9.6), or oxycodone (AOR=1.9, 95% CI: 1.4–2.6).
38	Veliz, 2013 (193). USA	Cross-sectional	21,135 secondary students (NRS)	Engaging in NMPOU vs. not; sports participants vs. non-sports participants	Socio-demographic characteristics	Students who engaged in NMPOU were more likely to be female (AOR=1.29, 99% CI: 1.05-1.59), older adolescents (AOR=2.37, 99% CI: 1.89-2.97), receive a suspension from school (AOR=3.69, 99% CI: 2.94-4.62), and live in an urban environment (AOR=1.29, 99% CI: 1.02-1.64). The odds of engaging in NMPOU increased 50% among adolescent students who participated in “high-injury” sports.
39	Rice, 2012 (203). USA	Longitudinal	821,916 people in the general population who made at least insurance claim for a PO during 2007-2009	Those diagnosed with opioid abuse during 1999–2009 vs. those without a diagnosis for opioid abuse	Socio-demographic characteristics, poly-substance use, mental health, infectious disease	Participants diagnosed with PO abuse were more likely to be male (OR=1.35, 95% CI: 1.08-1.68), and a diagnosis of abusing at least one non-opioid drug (OR=9.89, 95% CI: 7.47–13.09), mental illness (OR=2.45, 95% CI: 2.28–2.64), and hepatitis C (OR=2.36, 95% CI: 1.97–2.83).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
40	Momper, 2011 (148). USA	Qualitative	49 people of Aboriginal ancestry living on a reserve	N/A	PO acquisition, motivations, findings related to specific POs	Participants reported numerous strategies to obtain POs, which included doctor shopping and obtaining POs from elderly or disabled tribe members who sold their pills as a form of income. Participants reported using OxyContin to relieve boredom or unhappiness, or escape; however, a range of negative outcomes were associated with not-as-prescribed OxyContin use, such as losing employment, inability to care for family members, decreasing community safety, and dropping out of college.
41	Gonzales, 2011 (226). USA	Cross-sectional	6,841 people in addiction treatment	Engaging in NMPOU vs. other drugs	Socio-demographic characteristics	A large proportion of adults (aged 18+) were admitted to treatment due to NMPOU (89%), as compared to adolescents (aged 12-17) who were admitted mostly for prescription stimulant use (45%) and OTC drugs (32%).
42	Dowling, 2006 (131). USA	Cross-sectional	109,309 people in the general population (NRS)	Initiate NMPOU vs. not	Socio-demographic characteristics, mental health, poly-substance use	Recent initiation of NMPOU (≤2 years ago) was associated with multiple age groups younger than 35 years old (OR range: 3.61-14.90), having a serious mental health indicator (AOR=2.42, 95% CI: 1.96-2.99), and lifetime marijuana (AOR=6.86, 95% CI: 5.86, 8.03), cocaine (AOR=5.36, 95% CI: 4.53, 6.33), and heroin use (AOR=3.87, 95% CI: 2.51, 5.97).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
43	Back, 2010 (84). USA	Cross-sectional	55,279 people in the general population (NRS)	Engaging in NMPOU vs. not; males vs. females	Socio-demographic characteristics, PO acquisition, poly-substance use, mental health	Engaging in NMPOU was associated with male gender (AOR=1.30, 95% CI: 1.12–1.52), younger age (AOR=2.23, 95% CI: 1.86–2.67), serious psychological distress (AOR=1.42, 95% CI: 1.11–1.81), and other substance use including heroin (AOR=3.95, 95% CI: 1.34–11.66), cocaine (AOR=1.95, 95% CI: 1.41–2.69), hallucinogens (AOR=1.59, 95% CI: 1.20–2.10), stimulants (AOR=2.76, 95% CI: 2.01–3.78) and tranquilizers or sedatives (AOR=15.75, 95% CI: 11.22–22.11). Men were more likely to purchase POs from a dealer (2% vs. 0.5%, p=0.001) and obtain POs for free from family and friends, and experience serious psychological distress (15% vs. 11%, p<0.001).
44	Simoni-Wastila, 2004 (79). USA	Cross-sectional	3,185 people in the general population (NRS)	Engaging in NMPOU vs. not	Socio-demographic characteristics, poly-substance use	Engaging in NMPOU was associated with female gender (OR=1.41, 95% CI: 1.12–1.72), Caucasian ethnicity (OR=1.75, 95% CI: 1.47–2.08), and past-year illicit drug use (OR=6.67, 95% CI: 5.56–8.33). Younger age groups (versus middle age) were associated with NMPOU (12–17 years: OR=1.96, 95% CI: 1.43–2.63; 18–34 years: OR=1.92, 95% CI: 1.35–2.70, 25–34 years: OR=1.43, 95% CI: 1.05–1.96); however, elderly participants (vs. middle aged) were 31% more likely to engage in NMPOU (95% CI: 0.14–0.68).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
45	Simoni-Wastila, 2004 (76). USA	Cross-sectional	4,049 people in the general population (NRS)	Engaging in NMPOU vs. other drug use	Socio-demographic characteristics, poly-substance use	Engaging in NMPOU was associated with female gender (AOR=2.00, 95% CI: 1.10-3.70). Younger age groups (versus >25 years) (12-17 years: AOR=0.37, 95% CI: 0.16-0.88; 18-24 years: AOR=0.29, 95% CI: 0.15-0.58) and illicit drug use (AOR=0.56, 95% CI: 0.35-0.90) were negatively associated with NMPOU.
46	Smith, 2007 (222). USA	Cross-sectional	5,167 people in the general population (NRS)	People who engage in non-medical use of hydromorphone (Dilaudid) vs. non-medical use of hydrocodone (Vicodin)	Poly-substance use	Dilaudid users were three times more likely to have used heroin (OR=3.11, 95% CI: 1.69-5.70), cocaine (OR=4.94, 95% CI: 1.91-12.75), and have used ≥2 POs (in addition to Dilaudid) nonmedically (OR=4.65, 95% CI: 2.26-9.58) compared to nonmedical hydrocodone users.

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
47	Tetrault, 2008 (206). USA	Cross-sectional	55,023 people in the general population (NRS)	Males vs. females	Socio-demographic characteristics, poly-substance use, mental health	Women who engage in NMPOU were more likely to experience a serious mental illness (AOR=1.67, 95% CI: 1.29–2.17). Men who engage in NMPOU were significantly more likely to use Percocet (46% vs. 31%), codeine (31% vs. 22%), Oxycontin (19% vs. 12%), Demerol (14% vs. 8%), morphine (12% vs. 7%), Methadone (7% vs. 4%) (all p<0.05). Men and women who engaged in NMPOU were both significantly more likely to report past-year use of cocaine (women: AOR=1.72, 95% CI: 1.19–2.50; men: AOR=1.81, 95% CI: 1.28–2.54), non-medical stimulant use (women: AOR=4.07, 95% CI: 2.79–5.94; men: AOR=2.48, 95% CI: 1.68–3.65), and non-medical tranquilizer or sedative user (women: AOR=10.38, 95% CI: 7.32–14.63; men: AOR=14.88, 95% CI: 10.59–20.90).
48	Tetrault, 2010 (254). USA	Cross-sectional	54,623 people in the general population (NRS)	Sexually transmitted infection (STI) vs. not	Infectious disease	Engaging in NMPOU was not associated with STIs (OR=1.4, 95% CI: 0.9–2.2).
49	Ford, 2011 (172). USA	Cross-sectional	68,736 people in the general population (NRS)	Engaging in NMPOU vs. other prescription drug use	PO acquisition	Engaging in NMPOU more frequently was associated with purchasing POs from a friend or relative (b=26.648, p<0.01), a drug dealer or other stranger (b=67.959, p<0.001), or obtaining diverted POs in some other way (b=49.546, p<0.001).
50	Kuramoto, 2012 (232). USA	Cross-sectional	2,021 people in the general population (NRS)	Engaging in NMPOU vs. not	Mental health	Engaging in NMPOU was associated with suicidal ideation among former users (AOR=1.42, 95% CI: 1.11-1.81) and current users (AOR=1.52, 95% CI: 1.10-2.10).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
51	Sees, 2005 (237). USA	Longitudinal	18,329 people in the general population (NRS)	Engaging in not-as-prescribed OxyContin use vs. other NMPOU	Poly-substance use, trajectories	Participants engaged in not-as-prescribed OxyContin use were more likely to use cocaine or heroin (78% vs. 43%, p<0.01), and report poly-substance use involving other POs and illicit substances (non-medical use of >2 POs and use of cocaine or heroin) (75% vs. 28%, p<0.01). A large proportion of not-as-prescribed OxyContin users reported having used illicit drugs or other prescription medications non-medically prior to initiating NMPOU (82% vs. 64%, p<0.01)
52	Jones, 2013 (218). USA	Longitudinal	334,295 people who engage in NMPOU (NRS)	Engaging in NMPOU and heroin use vs. only NMPOU	Poly-substance use, trajectories	Between 2002–2004 and 2008–2010, past year heroin use increased among people engaging in NMPOU (p<0.01). The proportion of participants who reported engaging in NMPOU prior to initiating heroin use increased from 64% in 2002-2004 to 83% in 2008-2010.
53	Couto, 2009 (161). USA	Cross-sectional	938,586 people who use POs as pain treatment	Complying with PO treatment regimen vs. not complying	PO acquisition	Urine test results indicated that a large proportion of participants were not consistently adhering to their PO treatment regimen for pain (75%): 38% had no detectable level of their prescribed medication, 29% had a non-prescribed medication present, 27% had a drug level higher than expected, and 15% had a drug level lower than expected.

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
54	Subramaniam, 2009 (184). USA	Cross-sectional	94 youth admitted to treatment	Participants in treatment due to NMPOU vs. heroin use	Socio-demographic characteristics, route of administration, poly-substance use, mental health	Participants in treatment due to NMPOU were more likely to meet criteria for ≥3 substance use disorders (83% vs. 55%, p=0.004), have a current diagnosis of ADHD (47% vs. 21%, p=0.012), report prior psychiatric treatment (68% vs. 41%), be in school or have graduated from high school (65% vs. 35%, p=0.004). A large proportion of participants engaging in heroin use did so intravenously (73%) as compared to 0% of those in treatment for NMPOU. Participants from either group were not more likely to be female (39% vs. 49%, p=0.332).
55	Whiteside, 2013 (160). USA	Cross-sectional	2,135 youth who attended emergency rooms	Engaging in NMPOU in the past year vs. not engaging in NMPOU in the past year	PO acquisition, socio-demographic characteristics, poly-substance use	Among participants who engaged in NMPOU, 15% had a current home prescription for an opioid. Engaging in NMPOU was associated with failing grades or dropping out of school (AOR=2.26, 95% CI: 1.42–3.61), being on public assistance or parents living on public assistance (AOR=1.60, 95% CI: 1.11–2.32), marijuana use (AOR=1.92, 95% CI: 1.31–2.83), and nonprescription cough or cold medicine misuse (AOR=3.50, 95% CI: 2.43–5.02).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
56	Miech, 2013 (75). USA	Cross-sectional	762,330 people in the general population (NRS)	Younger birth cohorts vs. older	Socio-demographic characteristics, PO availability	Participants born in 1980-1984 (female: OR=1.35; male: OR=1.40), 1985-1989 (female: OR=1.52; male: OR=1.49), or 1990-1994 (female: OR=1.41; male: OR=1.30) had higher odds of engaging in NMPOU than previous birth cohorts (all $p<0.05$). Compared to all age groups combined, females in the youngest age category (15-19 years) were approximately twice as likely to engage in NMPOU (OR=1.99), and males in the same age category were more likely to engage in NMPOU (OR=1.87). The authors attribute these findings to the increasing availability of POs.
57	Young, 2012 (82). USA	Cross-sectional	2,597 middle and secondary school students	Engaging in NMPOU due to sensation-seeking vs. not (includes medical PO users and non-PO users)	Socio-demographic characteristics, poly-substance use, mental health	A large proportion of participants who engaged in NMPOU were female (62-70%). Sensation seekers were significantly more likely to also engage in illicit substance use (Mean [M]=0.31, Standard Deviation [SD]=0.47), marijuana use (M=0.51, SD=0.50), report anxiety or depression (M=7.50, SD=5.65), and report feeling withdrawn or depressed (M=5.22, SD=3.13) when compared with nonusers or medical PO users (all $p<0.05$).
58	McCabe, 2011 (150). USA	Cross-sectional	2,597 middle and secondary school students	N/A	Motivations	A low proportion engaged in NMPOU in order to get high or increase the effects of other drugs or alcohol (9.2%).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
59	Osgood, 2012 (137). USA	Cross-sectional	24 youth who are either attending a substance abuse recovery secondary school or are alumni	N/A	NMPOU initiation, route of administration	On average, participants first used oxycodone for not-as-prescribed uses at the age of 15 (range 13–18).
60	Fibbi, 2012 (214). USA	Mixed methods	150 youth in the general population who engage in NMPOU	Ever denied a prescription for opioids vs. never denied	Pain	A moderate proportion of participants reported being denied POs for the treatment of a painful condition (23%). A higher proportion of those who were denied POs reported a current pain problem (65% vs. 32%).
61	Wong, 2013 (236). USA	Cross-sectional	560 youth who engage in NMPOU	Membership in one of four typologies related to NMPOU: suppressor, others-reliant copers, self-reliant copers, active copers	Mental health	Participants who initiated NMPOU at a younger age were more likely to be classified as “suppressors”, characterized by the overall highest endorsement of suppression among all the coping or emotion regulation strategies.
62	Lankenau, 2012 (53). USA	Qualitative	50 youth who inject drugs	N/A	NMPOU initiation; trajectories	Participants reported easy access to POs from friends, family, and their own prescriptions, and this facilitated initiation into NMPOU. A moderate proportion of participants transitioned from NMPOU to heroin use (30%), and 22% of participants initiated intravenous drug use with POs.

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
63	Silva, 2013 (240). USA	Cross-sectional	596 youth across various socio-demographic strata who engage in NMPOU	N/A	Overdose and mortality	A high proportion of participants who ever experienced an overdose reported overdosing with POs (42%).
64	Cleland, 2011 (225). USA	Cross-sectional	29,114 youth and adults enrolled in opioid treatment	NMPOU and heroin use vs. only heroin use	Poly-substance use	Participants entering treatment below the average age (i.e. younger participants) were more likely to engage in both NMPOU and heroin use, versus only heroin use (OR=0.93, 95% CI: 0.92-0.94); the authors note, however, that this relationship is weak.
65	Madden, 2011 (238). USA	Longitudinal	76 people who died due to methadone-related causes from 2001-2006	N/A	Overdose and mortality	The number of methadone-related deaths increased 2-fold between 2002 and 2006 (1.7% vs. 3.4% of reported deaths; 17% vs. 37% of overdose deaths). A large proportion of decedents obtained methadone through illegal diversion (67%).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
66	Grau, 2007 (46). USA	Cross-sectional	237 people who engage in NMPOU	Not-as-prescribed OxyContin use vs. other NMPOU or heroin use	Route of administration, findings related to specific POs, trajectories	A larger proportion of participants had injected heroin recently as compared to OxyContin (85% vs. 52%). Participants who engaged in polyopioid use (including at least one PO) versus only not-as-prescribed OxyContin use were at increased risk of transitioning to heroin use within two years of initiating NMPOU (Hazard Ratio=0.74, p=0.615). Engaging in not-as-prescribed OxyContin use as compared to other opioid use was not significantly associated with gender, employment status, or years of opioid abuse (p>0.05); however participants who engaged in heroin use as compared to not-as-prescribed OxyContin use had significantly lower Addiction Severity Index psychiatric composite scores (p<0.05).
67	McCabe, 2009 (151). USA	Cross-sectional	12,441 secondary school seniors (NRS)	NMPOU motivated by pain relief vs. NMPOU due to other motivations	Motivations, pain	45% of those who engaged in NMPOU reported pain alleviation as an important motivation. Participants who engaged in NMPOU only for pain relief (vs. non-pain related motives) had lower odds of alcohol use and other substance use (p<0.01).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
68	Daniulaityte, 2012 (130). USA	Longitudinal	396 youth who engage in NMPOU	Not-as-prescribed buprenorphine use vs. other NMPOU	NMPOU initiation, route of administration, findings related to specific POs	Qualitative data indicates that experienced drug users initiated not-as-prescribed buprenorphine use after being introduced to it by their peers. Participants reported administering buprenorphine (with or without naloxone) orally, intranasally, and intravenously. Not-as-prescribed buprenorphine use was associated with using a greater number of POs over the lifetime (OR=1.38, 95% CI: 1.07-1.78).
69	Carlson, 2014 (156). USA	Cross-sectional	390 youth who engage in NMPOU	White vs. non-white ancestry	Motivations	There were no statistical differences between whites and non-whites who engage in NMPOU to get high only, self-medicate only, or both ($p>0.05$).
70	Fiellin, 2013 (132). USA	Longitudinal	55,215 youth in the general population (NRS)	Engaging in NMPOU vs. not	NMPOU initiation	Participants who reported marijuana use were more likely to initiate NMPOU (males: OR=2.44, 95% CI: 2.22-2.67; females: OR=1.92, 95% CI: 1.74-2.11). Males who used alcohol were more likely to initiate NMPOU (OR=1.23, 95% CI: 1.11-1.36), however, this relationship was not significant for females (OR=0.78, 95% CI: 0.73–0.84).
71	Quintero, 2009 (145). USA	Qualitative	91 post-secondary students	N/A	Motivations	Participants described their motivations for engaging in NMPOU as including getting high, having a good time, and experimenting.

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
72	Zullig, 2012 (231). USA	Cross-sectional	22,783 post-secondary students (NRS)	Engaging in NMPOU vs. not	Mental health	Participants who engaged in NMPOU were more likely to report feeling hopeless, sad, or depressed (AOR range=1.18–1.43, p<0.05). Males who engaged in NMPOU (vs. males who did not) were more likely to report suicidal ideation (AOR=1.31, 95% CI: 1.01-1.71); females who engaged in NMPOU (vs. females who did not) were more likely to report attempting suicide (AOR=1.32, 95% CI: 1.06-1.65).
73	Kelly, 2007 (81). USA	Longitudinal	400 club-going youth	Engaging in NMPOU vs. not	Socio-demographic characteristics	A larger proportion of females (85%) reported lifetime use of NMPOU than males (75%).
74	Daniulaityte, 2009 (42). USA	Cross-sectional	402 youth who report lifetime MDMA/ecstasy use	Engaging in NMPOU vs. not	Poly-substance use, mental health	Participants who engaged in NMPOU were more likely to report not-as-prescribed use of pharmaceutical tranquilizers (OR=6.43, 95% CI: 3.36-12.31), pharmaceutical stimulants (OR=2.90, 95% CI: 1.33-6.32), hallucinogens (OR=2.02, 95% CI: 1.03-3.94), inhalants (OR=2.26, 95% CI: 1.01-5.06), and higher levels of depression (OR=2.15, 95% CI: 1.04-4.44).
75	Siegal, 2003 (256). USA	Qualitative	10 adults who recently initiated heroin use	N/A	Trajectories	Five participants reported initiating NMPOU before heroin use, and attributed their transition to heroin due its ready availability and lower costs. These participants also reported that they would have never used heroin if they were not first addicted to OxyContin.
76	Hermos, 2008 (220). USA	Cross-sectional	12,958 adults in the general population (NRS)	Engaging in NMPOU vs. not	Poly-substance use	The prevalence of NMPOU among participants who use alcohol is 9.4% (95% CI: 8.4-10.4).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
77	Pollini, 2011 (91). USA	Cross-sectional	123 PWID	Transition from NMPOU to heroin vs. transition from heroin to NMPOU	Trajectories	A large proportion of participants transitioned from NMPOU to heroin use (40%). Participants who transitioned from NMPOU to heroin were more likely to perceive themselves to be at lower risk for HIV than other PWID (AOR=4.32; 95% CI: 1.26–14.77) and were less likely to have ever been tested for HIV (AOR=0.25; 95% CI: 0.08–0.80).
78	Rigg, 2013 (128). USA	Qualitative	90 adults in treatment for NMPOU	N/A	NMPOU initiation	Participants reported multiple pathways of NMPOU initiation: (i) a high proportion of females (42%) reported initiating NMPOU within the context of a romantic heterosexual relationship; (ii) participants who also engaged in cocaine use reported initiating NMPOU in order to manage the effects of cocaine, and (iii) initiating NMPOU after experiencing an injury requiring treatment.
79	Hall, 2008 (248). USA	Cross-sectional	295 decedents of unintentional overdose	N/A	Overdose and mortality	Among decedents of PO overdose, only 44% had ever been prescribed a PO and 79% used multiple licit and illicit substances.
80	Beaudoin, 2014 (167). USA	Longitudinal	85 emergency department patients discharged with a prescription for opioids	Engaging in NMPOU vs. not	PO acquisition, socio-demographic characteristics, pain	A moderate proportion of participants who engaged in NMPOU did not have a doctor's prescription (39%), and a high proportion reported engaging in NMPOU due to pain (64%). Participants who engaged in NMPOU did not differ significantly based on various socio-demographic characteristics (gender, marital status, income level, ancestry, or education level), or pain scores (all p>0.05).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
81	Martins, 2010 (83). USA	Longitudinal	62,243 adults in the general population (NRS)	Younger birth cohort vs. older birth cohort	Socio-demographic characteristics	Younger (more recent) birth cohorts have a higher prevalence of past-year NMPOU-related disorder (0.6%, 95% CI: 0.4-0.9) and among those who report lifetime NMPOU (16%, 95% CI: 10.0-21.7). The prevalence of past-year NMPOU-related disorder in the general population increased among participants in the 1954-1963 birth cohort (488% increase, $p<0.001$), which suggests an age effect for NMPOU and related dependence disorders.
82	Meade, 2009 (185). USA	Cross-sectional	50 adults in addiction treatment due to opioid dependence	Engaging in not-as-prescribed oxycodone use vs. heroin	Route of administration, infectious disease	Participants who engaged in not-as-prescribed oxycodone use did not report any injection drug use, whereas 89% of heroin users did so. Participants who engaged in not-as-prescribed oxycodone use were more likely to engage in high-risk sexual behaviour than those who engaged in heroin use (AOR=4.05, 95% CI: 1.11–14.81).
83	Rigg, 2010 (141). USA	Mixed methods	684 adults who engage in not-as-prescribed pharmaceutical drug use	N/A	Motivations	Participants reported the following motivations for engaging in NMPOU: pain relief, getting high, coping with stress and anxiety, avoiding withdrawal, moderating the effects of other drugs, and feeling “normal”.
84	Dollar, 2013 (85). USA	Cross-sectional	38,067 adults in the general population (NRS)	Engaging in NMPOU vs. other not-as-prescribed pharmaceutical drug use	Socio-demographic characteristics	Engaging in NMPOU was negatively associated with female gender (OR=0.87) and employment (OR=0.89) (both $p<0.05$).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
85	Young, 2012 (257). USA	Cross-sectional	503 adults who live in rural areas and use drugs	N/A	Trajectories, health-related harms	Participants transitioned from non-intravenous to intravenous OxyContin use after a median of 3 years.
86	Green, 2011 (242). USA	Longitudinal	26,314 adults in addiction treatment	N/A	Overdose and mortality, infectious disease	A high proportion of participants exhibited high risk factors for PO-related overdose (81%), and 18% of participants were at risk for infectious diseases.
87	Wilsey, 2008 (235). USA	Cross-sectional	113 emergency department patients with an ongoing pain condition	Experience mental health issues vs. not	Mental health	Various mental health conditions (panic attacks, trait anxiety and the presence of a personality disorder) account for 38% of the variance in the potential for NMPOU.
88	Cicero, 2012 (207). USA	Cross-sectional	2573 adults in addiction treatment primarily due to NMPOU	Female vs. male; older age groups vs. younger	Mental health, pain	Large proportions of participants in all age groups reported bodily pain and were assessed as having a psychiatric disorder (≥40%). Females were more likely than males to report any psychiatric disorder (OR=2.11, 95% CI: 1.80-2.47). Older participants were more likely to report moderate to severe pain than younger age groups (age 35-44: OR=1.34, 95% CI: 1.11-1.64; age ≥45: OR=2.12, 95% CI: 1.70-2.64).
89	Meade, 2014 (255). USA	Cross-sectional	653 adults in addiction treatment for opioid dependence	Engaging in sexual risk behaviours vs. not	Initiating NMPOU	Participants who initiated NMPOU for recreational motivations were not significantly more likely to have unprotected sex (OR=1.43, 95% CI: 0.94-2.18) or have multiple sexual partners (OR=0.70, 95% CI: 0.40-1.23).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
90	Carise, 2007 (146). USA	Cross-sectional	27,816 adults entering addiction treatment	Engaging in not-as-prescribed OxyContin use vs. not	Motivations, routes of administration, poly-substance use	A large proportion of participants reported using OxyContin to get high (86%). Various proportions of participants reported using POs orally (72%), intranasally (11%), and intravenously (17%). Participants who had not used heroin ($\chi 2=16.36$, df=1, $p<0.0001$) or other illicit drugs such as cocaine, sedatives, or amphetamines (all $\chi 2$ values>19; all *p*-values<0.0001) had lower odds of not-as-prescribed OxyContin use.
91	Ward, 2011 (169). USA	Cross-sectional	641 patients at an urban medical centre	N/A	PO acquisition	Participants who borrowed medication most commonly borrowed pills to relieve pain (usually opioids) from a family member (49%) or friend (38%).
92	Momper, 2013 (143). USA	Cross-sectional	400 Aboriginal adults living on-reserve	N/A	Motivations, socio-demographic characteristics	Younger participants (aged 18-25) were more likely to use OxyContin for not-as-prescribed purposes. The majority of participants who engaged in not-as-prescribed OxyContin use did so to relieve pain (59%) and get high (52%).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
93	Green, 2009 (163). USA	Cross-sectional	29,906 adults seeking addiction treatment	Female vs. male	Socio-demographic characteristics, PO acquisition, poly-substance use, pain, mental health	Female participants were more likely to report recent NMPOU than males (15.4% females vs. 11.1% males, p< 0.001). Females who engaged in NMPOU were also more likely to report problem drinking (AOR=1.41, 95% CI: 1.12-1.79), and inhalant use (AOR=3.52, 95% CI: 1.48-8.37), and less likely to report a recent pain problem (AOR=0.63, 95% CI: 0.50-0.78). Males who engaged in NMPOU were more likely to report hallucinogen use (AOR=2.17, 95% CI: 1.38-3.42), and depression (AOR=1.29, 95% CI: 1.09-1.53). Both males and females were more likely to report taking prescribed medication for pain (female: AOR=6.16, 95% CI: 5.00-7.60; males: AOR=5.93, 95% CI: 4.90-7.19).
94	Cicero, 2013 (175). USA	Mixed methods	3,520 opioid-dependent adults seeking treatment	Not-as-prescribed hydrocodone use vs. not-as-prescribed oxycodone use	PO acquisition, route of administration, socio-demographic characteristics, findings related to specific POs,	Those who engaged in not-as-prescribed hydrocodone use were more likely to be women (OR=1.33, 95% CI: 1.12-1.57), >34 years old (35-44 yrs: OR=1.39, 95% CI: 1.13-1.71; ≥45 years: OR=2.09, 95% CI: 1.68-2.61), use oral routes of administration (OR=8.09, 95% CI: 5.90-11.10), and were less likely to acquire POs from drug dealers (vs. other sources) (OR=0.33, 95% CI: 0.28-0.40).
95	Paulozzi, 2009 (245). USA	Longitudinal	250 decedents of PO or methadone overdose	Methadone-related fatal overdose vs. other opioid-related fatal overdose	Overdose and mortality	Decedents of methadone overdose were more likely to be younger than decedents of overdose due to other opioids (28% vs. 10%, p=0.001).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
96	Blanco, 2013 (210). USA	Cross-sectional	43,093 adults in the general population (NRS)	NMPOU vs. other nonmedical prescription drug use	Pain	Participants who engaged in NMPOU reported the numerically highest levels of pain (2.01).
97	Wu, 2010 (228). USA	Cross-sectional	43,093 adults in the general population (NRS)	Engaging in NMPOU vs. not	Poly-substance use	Males who engage in NMPOU (vs. females) were more likely to engage in polydrug use across multiple drug classes (AOR range=1.96-2.25); females who engaged in NMPOU and other substance use had higher rates of mood/anxiety disorders than men across multiple subtypes of polydrug use.
98	Wang, 2013 (196). USA	Cross-sectional	75,964 adults in the general population (NRS)	Engaging in NMPOU vs. not	Socio-demographic characteristics, poly-substance use, mental health	There was no significant difference in the prevalence of NMPOU among residents in urban and rural counties (4.7% vs. 4.3%, p=0.15). Participants who engaged in NMPOU were more likely to report severe psychological distress (urban: AOR=1.64, 95% CI: 1.41–1.89; rural: AOR=1.63, 95% CI: 1.23–2.17), nonmedical use of other prescription medications (urban: AOR=9.97, 95% CI: 8.34–11.92; rural: AOR=10.09, 95% CI: 6.87–14.82), and any illicit drug use (urban: AOR=2.77, 95% CI: 2.37–3.24; rural: AOR=3.10, 95% CI: 2.20–4.38).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
99	McCabe, 2007 (135). USA	Cross-sectional	43,093 adults in the general population (NRS)	Early initiation of NMPOU vs. late	Initiating NMPOU; trajectories	The estimated mean age for initiating NMPOU was 23.19 years, (Standard Error=0.31), and the median age for NMPOU initiation was 20.00 (range=5-88 years). The estimated percentage of those who initiated NMPOU before the age of 21 was 55%, and the estimated percentage of those who engaged in NMPOU and progressed to abuse of opioids during their lifetimes was 24% (95% CI: 21.4%, 26.4%). Earlier age of NMPOU initiation was associated with the development of lifetime prescription drug dependence ($p<0.05$).
100	Boyd, 2009 (224). USA	Longitudinal	34,653 adults in the general population (NRS)	Wave 1 of survey vs. Wave 2	Poly-substance use	Participants who engaged in NMPOU during Wave 1 of the survey were more likely to report a general substance or opioid use disorder at Wave 2 (AOR=3.42, 95% CI: 1.45-8.07).
101	Martins, 2012 (233). USA	Longitudinal	34,653 adults in the general population (NRS)	Wave 1 of survey vs. Wave 2	Mental health	Lifetime NMPOU was associated with the incidence of any mood disorder (AOR=1.8, 95% CI: 1.4-2.3) and any anxiety disorder (AOR=1.4, 95% CI: 1.1-1.8) at Wave 2. Conversely, lifetime reports of any mood disorders (AOR=1.6, 95% CI: 1.3-2.0) and generalized anxiety disorder (AOR=1.6, 95% CI: 1.1-2.1) at Wave 1 were associated with incident NMPOU at Wave 2. Lifetime reports of any mood disorders (AOR=2.1, 95% CI: 1.5-3.0) at Wave 1 were associated with incident opioid disorder due to NMPOU at Wave 2.

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
102	McCabe, 2008 (223). USA	Longitudinal	85,955 adults in the general population (NRS)	Wave 1 of survey vs. Wave 2	Poly-substance use	Nearly three-quarters (74%) of participants with prescription opioid related disorders also met the DSM-IV criteria for an additional recent substance use disorder. The past-year co-occurrence of prescription opioid use disorder and any substance use disorder increased ($p<0.01$).
103	Havens, 2013 (180). USA	Cross-sectional	392 adult IDUs	HCV-positive vs. HCV-negative; Lifetime NMPOU vs. not	Route of administration, infectious diseases	The majority of participants had injected POs at some point during their lifetime (89%) and 68% injected POs in the past six months. Most participants initiated intravenous drug use with POs (62%). Injecting POs was associated with HCV seropositivity (AOR =2.22; 95% CI: 1.13-4.35) and syringe sharing (AOR=6.87, 95% CI: 1.61-29.4).
104	Gwin Mitchell, 2009 (177). USA	Mixed methods	515 adults who use illicit opioids	Participants using diverted methadone vs. not	PO acquisition, poly-substance use	Participants who used diverted methadone (vs. those who did not) were less likely to use heroin ($t[513]=6.54$, $p<0.01$) and cocaine ($t[513]=3.14$, $p<0.01$) prior to treatment admission. The qualitative data found that the two most common reasons for using diverted methadone or buprenorphine were to avoid withdrawal symptoms from heroin or methadone, and to stop using heroin.

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
105	Becker, 2011 (158). USA	Cross-sectional	3,238 adults who engage in NMPOU (NRS)	Obtaining POs from a physician for not-as-prescribed uses vs. other source for NMPOU	PO acquisition	Participants who engaged in NMPOU most frequently obtained POs from physicians (31%); among these participants, 20% obtained POs solely from physicians and 36% reported at least one other source involving friends or family. A physician source for POs was associated with past-year PO abuse or dependence (AOR=2.0; 95% CI: 1.5-2.7).
106	Cicero, 2012 (152). USA	Cross-sectional	445 adults who use POs	Participants who obtain Tramadol via doctor-patient-pharmacy model ("traditional") vs. obtain Tramadol via the internet without a prescription ("nontraditional")	Motivations; PO acquisition	Nontraditional Tramadol users overwhelming reported using Tramadol to treat pain (95%), and 55% of nontraditional users reported using internet pharmacies because they did not receive sufficient doses of Tramadol to relieve their pain. Over one-third of the nontraditional users reported that internet pharmacies were a cheaper alternative than paying for a physician visit and paying the noninsured rate for POs at a pharmacy (37%); however, nontraditional users also reported a significantly greater mean number of adverse events than traditional users ($p<0.001$).
107	Hall, 2013 (138). USA	Cross-sectional	503 rural adults who use methadone	Illicit methadone use vs. prescribed methadone use	Initiating NMPOU; PO acquisition	Participants who initiated illicit methadone use at a younger age were more likely to use illicit methadone at a high frequency (vs. low frequency). Illicit methadone was most commonly obtained from friends (46%), dealers (29%), and family members (12%).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
108	Inciardi, 2007 (164). USA	Qualitative	74 adults with a history of street or club drug use	N/A	PO acquisition	Participants described formal and informal schemes to sell POs as a source of income. No street-based participants obtained POs from the internet due, in part, to costs.
109	Sigmon, 2006 (183). USA	Cross-sectional	75 adults in addiction treatment	In treatment primarily for NMPOU vs. heroin use	Route of administration	NMPOU was associated with a lower proportion of lifetime injecting drug use (60%) as compared to heroin use (92%) ($p=0.01$), and significantly fewer reports of injecting as the primary route of administration (41% vs. 92%, $p<0.0001$).
110	Bonar, 2014 (209). USA	Cross-sectional	326 adults in addiction treatment	Heavy NMPOU vs. not; lifetime overdose vs. not	Pain; overdose and mortality	Heavy NMPOU was associated with past-week pain (AOR=1.31, 95% CI: 1.16–1.48), and in a separate model, was associated with lifetime overdose (AOR=2.99, 95% CI: 1.53–5.84). Only 3% of participants who experienced an overdose reported a "past-week pain level". A moderate proportion of participants who experienced an overdose reported taking someone else's POs (20%) or borrowing POs from someone else (26%).
111	Passik, 2006 (170). USA	Cross-sectional	109 opioid dependent adults in addiction treatment	N/A (descriptive)	PO acquisition, mental health	Nearly all participants had obtained POs from a street-based dealer at least once (91%), and 68% had used someone else's POs with permission. All participants in this study met the criteria for current opioid abuse or dependence.
112	Moore, 2007 (199). USA	Cross-sectional	200 opioid dependent adults in addiction treatment	Engage in NMPOU only vs. heroin only	Socio-demographic characteristics	Participants who only engaged in NMPOU were younger (≤35 years) than those who only used heroin ($p=0.02$).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
113	Wu, 2011 (217). USA	Cross-sectional	43,093 adults who use drugs	Engage in NMPOU vs. other drugs	Poly-substance use	Participants who engage in NMPOU are more likely than those who use other drugs to report the following past-year psychiatric disorders: alcohol use (AOR=1.46, 95% CI: 1.16–1.84), any drug use (AOR=1.31, 95% CI: 1.02–1.69), sedative use (AOR=2.10, 95% CI: 1.14–3.86), amphetamine use (AOR=2.00, 95% CI: 1.12–3.57), and tranquilizer use (AOR=4.03, 95% CI: 1.93–8.41).
114	Young, 2013 (251). USA	Cross-sectional	81 Hepatitis C-positive rural adults who engage in NMPOU	PWID vs. non-PWID	Infectious disease	Participants who reported recent injecting drug use were more likely to be Hepatitis C RNA-positive (AOR=4.06, 95% CI: 1.04 – 15.83) in the multivariable model including egocentric social network variables, but not in the model including sociometric and socio-demographic variables.
115	Havens, 2009 (77). USA	Cross-sectional	714 rural adult stimulant users	Engage in NMPOU vs. not	Socio-demographic characteristics, pain, poly-substance use, mental health	Participants who engage in NMPOU were more likely to be younger (AOR=0.97, 95% CI: 0.95–0.99), use heroin (AOR=5.76, 95% CI: 2.12–15.6), and report anxiety (AOR=2.04, 95% CI: 1.60-2.59); chronic pain was not associated with NMPOU after adjustment (no statistics reported).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
116	Grattan, 2012 (174). USA	Cross-sectional	1,334 adults on chronic opioid therapy	Depression vs. not	PO acquisition, mental health	Participants with moderate or severe depression were more likely to engage in NMPOU by not adhering to their prescribed PO regimen (AOR range: 2.86-3.13, both $p<0.001$) and for non-pain reasons (AOR range: 1.75-2.42, both $p<0.05$). Depression was not significantly associated with borrowing or sharing POs with others (no statistics reported).
117	Han, 2014 (165). USA	Longitudinal	All adults with a recorded prescription for POs	Doctor shopping for POs vs. not	Socio-demographic characteristics, overdose and mortality	Participants who acquired POs via doctor shopping obtained between 3-6 times higher cumulative morphine-equivalent amounts of opioids than among the general population. Approximately 1.4% of participants aged 64 and younger engaged in doctor shopping, while only 0.5% of those aged 65 and older engaged in doctor shopping.
118	Ashrafioun, 2014 (173). USA	Experimental	277 college students in the general population	Craving POs vs. not	PO acquisition	After exposure to a cue related to PO use, participants who acquired POs from non-medical sources were significantly more likely to report higher cravings for POs, as indicated by higher scores on the Drug Desires Questionnaire Overall, ($t[146]=2.26$, $p<0.05$), and Desire and Intention subscale, ($t[146]=2.52$, $p<0.05$).
119	Surratt, 2011 (179). USA	Cross-sectional	791 adults who engage in NMPOU	N/A	Route of administration	Participants most commonly used POs orally (91%), followed by intranasal use (53%), injection (24%), and smoking (15%).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
120	Vivian, 2005 (189). USA	Cross-sectional	242 street-based adults who use drugs	Actively engaging in NMPOU vs. not	Socio-demographic characteristics, poly-substance use, mental health, infectious disease, overdose and mortality	Participants who actively engaged in NMPOU were more likely to have completed high school or beyond (60% vs. 44%, p<0.04), inject crack (12% vs. 2%, p=0.001) and use benzodiazepines (48% vs. 11%, p=0.001). These participants were significantly more likely to have ever received mental health treatment (52% vs. 28%, p<0.001), and have Hepatitis C (OR=3.23; 95% CI: 1.34-7.78). Mortality related to POs rose from 11% in 1999 to 24% in 2002.
121	McCabe, 2012 (153). USA	Longitudinal	12,431 secondary students (NRS)	Membership in one of five motivational subtypes	Motivations, route of administration, trajectories	Among participants who engaged in NMPOU, 77% endorsed more than one motive. Females who engaged in NMPOU were more likely to be motivated by alleviating pain and relaxing (no statistics reported), and those who used POs to get high were more likely to use non-oral routes of administration (no statistics reported). Participants who engaged in NMPOU to relieve pain were more likely to engage in NMPOU before medical PO use and after medical PO use, and those who use POs to get high, relax, and regulate their affect were all more likely to engage in NMPOU before medical PO use (no statistics reported).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
122	Garnier, 2009 (221). USA	Longitudinal	1,118 postsecondary students	Alcohol-only vs. non-concurrent users of alcohol and POs vs. concurrent users of alcohol and POs	Poly-substance use	Among all participants who engaged in NMPOU, 58% used alcohol concurrently. The odds of engaging in concurrent NMPOU and alcohol use were increased with each additional drink per drinking day (AOR=1.18, 95% CI: 1.03-1.35), and each additional drinking day (AOR=1.03, 95% CI: 1.02-1.04).
123	Young, 2012 (139). USA	Cross-sectional	212 adults who use drugs	Rural residence vs. urban residence	Initiating NMPOU; socio-demographic characteristics	Rural participants initiated the not-as-prescribed use of two POs (out of three) at a significantly younger median age than urban participants: oxycodone (median=20, IQR: 17-27), hydrocodone (median=18, IQR: 15.5–26) (both p<0.001). Rural drug users were also more likely to report lifetime use of illicit methadone (AOR=31.09, 95% CI: 7.72–125.19), OxyContin (AOR=5.69, 95% CI: 1.81–17.84), and other oxycodone (AOR=-4.23, 95% CI: 1.16–15.43).
124	Katz, 2013 (78). USA	Longitudinal	34,653 adults in the general population (NRS)	Wave 1 vs. Wave 2	Socio-demographic characteristics; mental health	Participants who reported engaging in NAPU at Wave 2 were less likely to be older (AOR=0.97, 95% CI: 0.97–0.98) and female (AOR=0.82, 95% CI: 0.68–1.00). Incident NMPOU at Wave 2 was positively associated with AXIS I and II mental disorders (with the exception of any anxiety disorder) at Wave 1 (AOR range=1.72–3.02).
125	McCabe, 2007 (219). USA	Cross-sectional	14,000 post-secondary students (NRS)	DSM-IV alcohol dependence vs. not	Poly-substance use	The unadjusted prevalence estimate of recent NMPOU and DSM-IV alcohol dependence is approximately 14%.

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
126	Jones, 2011 (187). USA	Cross-sectional	50 adults in the general population who engaged in not-as-prescribed oxycodone use	Intranasal vs. intravenous oxycodone users	Route of administration, socio-demographic characteristics, poly-substance use	Participants who used oxycodone intranasally were (marginally) more likely to be motivated by pain (52% vs. 28%, p=0.07), and employed (72% vs. 36%, p=0.004) than those who injected oxycodone; there were no significant gender differences between those who used intransasally or intravenously. High proportions of intravenous (100%) and intranasal (88%) users reported also engaging in the recreational use of another drug aside from tobacco.
127	Caviness, 2013 (171). USA	Cross-sectional	315 adult Methadone patients with intentions to quit smoking	Share POs or receive POs from non-healthcare source vs. not	PO acquisition, socio-demographic characteristics	Among participants prescribed POs, 12% shared them with others; however, sleeping medications, sedatives, and attention deficit hyperactivity disorder medications were also commonly shared (11-14%). Sharing and receiving mediations were significantly associated with younger age (sharing: OR=0.92, 95% CI: 0.88- 0.96; receiving: OR=0.94, 95% CI: 0.92-0.97).
128	Pletcher, 2006 (133). USA	Longitudinal	3,163 adults in the general population	Engage in NMPOU vs. not	Initiating NMPOU, pain, mental health, trajectories	Engaging in NMPOU was significantly associated with initiating PO use for pain (OR=8.6; 95% CI: 2.5–30) and previous reports of illicit drug use (1.0%, exact 95% CI: 0.7–1.5%, p<0.001); NMPOU was not associated with depressive symptoms (AOR=1.1, 95% CI: 0.3-3.4). Among illicit drugs, amphetamines were the best predictor of future NMPOU (sensitivity 87%, specificity 79%).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
129	Gagajewski, 2003 (244). USA	Longitudinal	96 adults who use methadone	Not-as-prescribed methadone users vs. prescribed	Overdose and mortality	The majority of decedents with detectable methadone in their blood were not participating in a methadone treatment program (65%).
130	Lineberry, 2004 (178). USA	Case report	4 adults in the general population	N/A	PO acquisition	In Cases 2, 3, and 4, patients purchased POs through the internet and some purposefully avoided internet pharmacies that required a physician evaluation or prescription for POs.
131	Cicero, 2014 (86). USA	Mixed methods	2,851 adults seeking treatment for heroin dependence	Initiating opioid use (heroin or NMPOU) in the 1960's vs. the 1980's	Trajectories	In the 1960's, 80% of people who initiated opioid use did so with heroin. In the 1980's, 75% of people initiated opioid use with POs. Many participants reported using heroin instead of POs because of the limited availability of POs.
132	Havens, 2011 (252). USA	Cross-sectional	800 felony probationers	PO injection vs. not	Infectious diseases	Injecting POs was positively associated with risky injection behaviours (receptive syringe sharing or sharing other injection equipment) (AOR=14.7, 95% CI: 7.7-28.1).
133	Cicero, 2008 (157). USA	Cross-sectional	1,116 adults in addiction treatment	Male vs. female	PO acquisition	Approximately 49% of males and 59% of females reported obtaining POs from a physician prescription. A small proportion of participants reported obtaining POs from the internet (6%).
134	Boscarino, 2010 (229). USA	Cross-sectional	705 patients with a history of PO prescriptions	History of major depression vs. not	Mental health	Current NMPOU was positively associated with a history of major depression (AOR=1.29, 95% CI: 1.05–1.60).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
135	Jamison, 2010 (211). USA	Longitudinal	622 pain patients	Male vs. female	Pain; mental health	NMPOU was positively associated with being disabled because of pain ($\chi 2=11.14$, $p<0.001$). Females received higher scores on the Prescription Drug Use Questionnaire (PDUQ) ($\chi 2=17.93$, $p<0.001$) and were more likely to report psychological issues ($t=2.31$, $p<0.05$); males were more like to report a history of being arrested as a result of NMPOU ($t=3.51$, $p<0.001$).
136	Havens, 2007 (194). USA	Cross-sectional	1,525 felony probationers	Rural vs. urban	Socio-demographic characteristics	NMPOU was positively associated with rural residence (AOR=4.92, 95% CI: 2.70-8.97).
137	Lanier, 2012 (247). USA	Cross-sectional	1,562 alive and deceased people who use POs	Cases (decedents with at least one PO causing death) vs. controls (people who use POs)	Overdose and mortality	Decedents were more likely to have obtained POs from diverted sources (Exposure Prevalence Ratio=4.8; 95% CI: 3.6–6.0).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
138	Edlund, 2007 (234). USA	Cross-sectional	9,279 people in the general population (NRS)	Engage in NMPOU vs. not	Mental health	When analyzed together in multiple logistic regression models, frequent PO use and depression were both positively associated with any NMPOU (AOR=3.98, 95% CI: 2.96-5.35 and AOR=3.51, 95% CI: 2.78-4.46, respectively) and problematic NMPOU (AOR=7.89, 95% CI: 3.45-18.05 and AOR=8.82, 95% CI: 6.04-12.89, respectively). The prevalence of depression (9%), however, was substantially higher than the prevalence of NMPOU (3%) which suggests that the population-attributable risk for NMPOU due to mental health disorders is likely much greater than the risk for NMPOU resulting from prescribed opioid use.
139	McCabe, 2006 (202). USA	Cross-sectional	9,161 postsecondary students	NMPOU vs. other nonmedical prescription drug use	Socio-demographic characteristics	A significantly higher proportion of males (10%) reported engaging in NMPOU than females (9%) ($p<0.001$).
140	Mitchell, 2011 (176). USA	Qualitative	6 people on opioid agonist treatment	N/A	PO acquisition	One participant did not want to use heroin but did not have enough money for methadone treatment. His friends helped him obtain diverted (illicit) methadone, but when he could not obtain any he returned to heroin use because it was cheaper.
141	Barry, 2009 (213). USA	Cross-sectional	293 people seeking methadone treatment	Lifetime history of chronic pain vs. not	Pain	Participants with a lifetime history of chronic pain were not significantly more likely to take more of their own prescribed POs (40% vs. 37%, $\chi2=0.25$), somebody else's POs (40% vs. 32%, $\chi2=1.21$), or street methadone (35% vs. 27%, $\chi2=1.54$).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
142	Barry, 2013 (212). USA	Cross-sectional	244 adults seeking office-based buprenorphine-naloxone treatment	Chronic pain vs. some pain	Pain	Participants reporting chronic pain were not significantly more likely to take more of their own prescribed POs (AOR=1.5, 95% CI: 0.6–3.4, p=0.35), somebody else's POs (AOR=1.6, 95% CI: 0.8–3.3, p=0.19), use heroin ($\chi 2$=1.1, 95% CI: 0.5–2.2, p=0.88), or street methadone (AOR=1.1, 95% CI: 0.4–3.2, p=0.89).
143	Schumann, 2008 (239). USA	Longitudinal	221 people with a history of illicit opioid use	N/A	Overdose and mortality	The majority of decedents were African American (51%), and the deaths occurred in non-residential settings (51%). Fentanyl-related deaths peaked in the spring of 2006.
144	Cepeda, 2012 (201). USA	Longitudinal	25 million people with at least one dispensing record for any PO	Doctor shopping vs. not	Socio-demographic characteristics	Doctor shopping was more common among participants between 25 and 64 years old (0.25%) as compared to those 65 years and older (0.07%).
145	Levy, 2007 (147). USA	Cross-sectional	422 people in treatment for substance use	N/A	Motivations, PO acquisition, route of administration, trajectories	The majority of participants reported using OxyContin to get high (59%), and 70% acquired POs from their friends. Intranasal use was the most frequent route of administration among participants (37%). Nearly three-quarters (73%) of OxyContin users subsequently initiated heroin use, and 77% of OxyContin users had a history of prior opiate use.

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
146	Catalano, 2011 (204). USA	Longitudinal	912 young adults in the general population	Frequency of NMPOU	Socio-demographic characteristics; poly-substance use	The mean frequency of NMPOU was not significantly different between females and males in grade 10 or 12, or aged 19 or 20; however, males in grade 11 engaged in NMPOU significantly more frequently ($p<0.05$). A large proportion of participants who reported light or heavy lifetime NMPOU also used one other illicit drug (95% and 96%, respectively).
147	Veliz, 2014 (200). USA	Longitudinal	1,540 adolescents in the general population	Participation in organized sports vs. not	Socio-demographic characteristics	Past year receipt of a prescription for POs was common among males (22%) and females (35%). Male students who participated in organized sports (vs. those who did not participate) were more likely to receive a recent PO prescription (AOR=1.86, 95% CI: 1.23–2.82), and recently engage in NMPOU to get high (AOR=4.01, 95% CI: 1.13–14.2).
148	Zosel, 2013 (44). USA	Longitudinal	16,209 teenagers with a record in a poison centre database	N/A	Overdose and mortality	Only 0.1% of intentional exposures to prescription drugs (including POs, depressants, and stimulants) resulted in death, however, oxycodone and methadone were linked with the most deaths (both, 35%).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
149	McHugh, 2013 (162). USA	Cross-sectional	653 adults with PO dependence	Female vs. male	PO acquisition; socio-demographic characteristics; pain; poly-substance use; mental health	Female participants were more likely to have first obtained POs through a physician prescription ($\chi 2=14.91$, $p<0.001$), use hydrocodone ($F[1,651]=16.7$, $p<0.001$), and engage in NMPOU to cope with pain ($t[651]=4.31$, $p<0.001$) or interpersonal stress ($t[651]=5.11$, $p<0.001$). Males were more likely than females to use long-acting oxycodone ($F[1,651]=29.73$, $p<0.001$) and report greater alcohol use severity ($t[620]=-3.65$, $p<0.001$).
150	Back, 2011 (127). USA	Qualitative	24 adults seeking treatment for PO dependence	N/A	Motivations; Initiating NMPOU; route of administration; mental health	Significantly more females engaged in NMPOU to cope with stress and anxiety than males (73% women vs. 27% men, $p=0.04$). The majority of males (58%) and females (83%) reported initiating PO use after receiving a PO prescription to treat injuries or pain. Females initiated NMPOU nearly six years later than males but reported engaging in regular NMPOU only three years later than males. The majority of participants chewed POs (62%) and 46% crushed or snorted POs; male participants were more likely than females to crush and snort POs (75% vs. 17%, $p=0.01$).

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
151	Barth, 2013 (144). USA	Cross-sectional	127 adults in the general population	Engage in NMPOU vs. not	Motivations, PO acquisition, socio-demographic characteristics, pain, mental health	The majority of participants reported initiating NMPOU to relieve pain (70%). Participants reported the following subsequent motivations for engaging in NMPOU: pain relief (81%), to get high (74%), to increase energy (71%), to decrease anxiety (51%), and to improve sleep (36%). Participants who engaged in NMPOU reported the following sources for acquiring POs: doctor (91%), friend (81%), and parent (18%). NMPOU was significantly associated with less education ($\chi 2=24.7$, $p<0$ .001), a lower likelihood of being employed ($\chi 2=29.7$, $p<0$ .001), and current pain ($\chi 2=26.6$, $p<0.001$).
152	Lord, 2011 (155). USA	Cross-sectional	412 postsecondary students	Engage in NMPOU regularly vs. infrequently	Motivations, PO acquisition, poly-substance use	Females were more likely to report engaging in NMPOU to get high (63% vs. 37%, $p<0$ .05) and to manage chronic pain (57% vs. 43%, $p<0$ .001). Participants who engaged in NMPOU obtained POs from the following sources: friends (85%), "other" sources (48%), parents (18%), and other family members (12%). Participants who regularly engaged in NMPOU were more likely to also report recent cocaine ($\chi 2[1,411]=4.84$, $p<0$ .05), methamphetamine ($\chi 2[1,411]=6.58$, $p<0$ .01), and heroin ($\chi 2[1,411]=9.46$, $p<0$ .01) use.

	Study	Study design	Sample characteristics	Comparison group or condition	Outcome(s)	Relevant findings
153	Gros, 2013 (230). USA	Cross-sectional	90 individuals with PO dependence	NMPOU with comorbid mood and anxiety disorders vs. NMPOU without comorbid mood and anxiety disorders	Mental health	Nearly half of participants (47%) met DSM-IV-TR criteria for a mood or anxiety disorder. Participants with PO dependence and a comorbid mood or anxiety disorder diagnosis scored higher (i.e. reported more severe symptoms) on the Addiction Severity Index (ASI) Alcohol ($t=2.28$, $p<0.05$) and Psychiatric subscale ($t=2.97$, $p<0.01$).
154	Lawson, 2013 (361). USA	Cross-sectional	201 individuals in the general population	Engage in NMPOU vs. not	Socio-demographic characteristics	Participants who engaged in NMPOU were more likely to be younger (mean difference=5.2 years, $p=0.040$) and had more education (49% vs. 45%, $p<0.001$)) than those who used cocaine.

Abbreviations:

- AHR: Adjusted hazard ratio
- AOR: Adjusted odds ratio
- CI: Confidence interval
- HR: Hazard ratio
- M: Mean
- NMPOU: nonmedical prescription opioid use
- NRS: Nationally-representative sample
- OR: Odds ratio
- POs: Prescription opioids
- PWID: People who inject drugs
- SD: Standard deviation
- SE: Standard error