POLYSUBSTANCE USE PATTERNS AMONG PEOPLE WITH OPIOID USE DISORDER IN VANCOUVER, CANADA

by

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Abstract

Background: A growing body of evidence suggests that people with opioid use disorder (OUD) engage in polysubstance use (PSU). However, most studies are variable-centred and cross-sectional, and as a result, several aspects of longitudinal PSU patterns amongst people with OUD remain understudied. This thesis investigated longitudinal PSU classes among people with OUD by pursuing these specific objectives: systematically review the evidence on PSU classes among people with OUD; describe people with OUD's substance use patterns after a national supply-level reduction intervention (i.e., reformulation of OxyContin); identify person-centred longitudinal patterns of PSU among them; and assess the longitudinal association between membership in different classes of PSU and non-fatal overdose events.

Methods: To summarize the literature on PSU amongst people with OUD, a literature search was conducted following standard systematic review guidelines. Empirical data were obtained from three prospective cohorts of people who use drugs in Vancouver, Canada. Interrupted time-series (ITS) analysis was used to assess how people with OUD's substance use patterns changed after the reformulation of OxyContin in Canada. Repeated measures latent class analysis (RMLCA) and longitudinal multivariable generalized estimating equations models were applied to identify distinct longitudinal classes of PSU and their associated odds of non-fatal overdose.

Results: The systematic review identified 30 eligible studies and documented numerous PSU patterns among people with OUD and several methodological limitations in the literature. The ITS analysis showed that reducing access to OxyContin was not associated with reductions in illicit opioid use among people with OUD. The RMLCA analysis found five distinct longitudinal PSU

patterns, including low/infrequent use, primarily opioid and methamphetamine use, primarily cannabis use, primarily opioid and crack use, and persistent PSU. Those in higher-intensity PSU classes were at higher odds of non-fatal overdose.

Conclusion: This research underscored the heterogeneous nature of people with OUD in terms of both longitudinal substance use patterns and long-term odds for non-fatal overdose. It also highlighted the limited capacity of supply-level interventions in reducing opioid use among people with OUD. The high frequency of polysubstance use and heterogeneities among people with OUD should be reflected in OUD-related research, policy, and clinical practice developments.

Lay Summary

The opioid epidemic in British Columbia (BC) continues to account for high economic, social, and human costs. Life expectancy in BC has declined due to unintentional opioid-related toxicity deaths among people who use drugs, and several overdose events involve polysubstance use (PSU). While PSU practices are common and have been associated with several mental and physical harms among people with opioid use disorder (OUD), the understanding of PSU patterns remains limited. This thesis research aimed to describe different patterns of PSU among people with OUD over time and shed light on predictors and harms associated with membership in different classes of PSU. The findings highlighted the diverse characteristics of people with OUD as well as the increased risk of overdose among certain groups of people with OUD. Altogether, these findings provide practical implications for measuring and addressing PSU in substance use research, clinical decision-making, and policy development.

Preface

I was responsible for conceptualizing, designing, analyzing, and writing the work presented in this thesis under the guidance of my committee (Drs. Thomas Kerr, Jane Buxton, Kanna Hayashi, and Ekaterina Nosova), and with support from the statistical team at the BC Centre on Substance Use. All empirical analyses in the thesis were approved by the University of British Columbia/Providence Health Care research ethics boards (H14-01396, H05-50233, H05-50234, and H04-50160).

Chapter 1 is original, unpublished work. I conducted the literature review and background research and drafted the Introduction chapter with guidance from members of my supervisory committee.

Chapter 2 is original, unpublished work. A version of the systematic review presented in this chapter is under review for publication. I conceptualized and conducted all steps of the systematic review under the guidance of my supervisory committee. The second reviewer for this chapter was Andreas Pilarinos (PhD Candidate at UBC) who was responsible for screening the titles, abstracts, and fill-texts of the studies retrieved through the literature search, independently. The original version of the systematic review was drafted by me and revised based on feedback from my supervisory committee.

Chapter 3 is original, unpublished work. A version of this chapter is currently being prepared for submission to a peer-reviewed journal. I conceptualized and wrote this study with input from my supervisory committee. I also prepared the data and completed the data analysis with guidance from Dr. Ekaterina Nosova using R software.

Chapter 4 is original, unpublished work. A version of this chapter is currently being prepared for submission to a peer-reviewed journal. I conceptualized and wrote this study with

input from my supervisory committee. I also prepared the data and completed the data analysis with support from Dr. Ekaterina Nosova and the statistical team (Zishan Cui) in British Columbia Centre on Substance Use (BCCSU) using R and SAS software.

Chapter 5 is original, unpublished work. A version of this chapter is currently being prepared for submission to a peer-reviewed journal. I conceptualized and wrote this study with input from my supervisory committee. I also prepared the data and completed the data analysis with support from Dr. Ekaterina Nosova and BCCSU's statistical team (Zishan Cui and JinCheol Choi) using R and SAS software.

Chapter 6 is original, unpublished work. I conducted the literature review and background research and drafted the Conclusion chapter with guidance from members of my supervisory committee.

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List of Abbreviations

95% CI	95% Confidence interval
(A)OR	(Adjusted) odds ratio
AB	Alberta
ACCESS	AIDS Care Cohort to evaluate Exposure to Survival Services
ACF	Autocorrelation function
AIC	Akaike information criterion
ARYS	At-Risk Youth Study
BC	British Columbia
BIC	Bayesian information criterion
CNS	Central nervous system
DSM (III, IV, 5)	Diagnostic and Statistical Manual of Mental Disorders (Version III, IV, or 5)
DTES	Downtown Eastside
GEE	Generalized estimating equations
GMM	Growth mixture modeling
GRoLTS	Guidelines for Reporting on Latent Trajectory Studies
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IDU	Injection drug use
IQR	Interquartile range
ITS	Interrupted time series
L6M	Last six months
LCA	Latent class analysis

LLC	Longitudinal latent class analysis
LPA	Latent profile analyses
LTA	Latent transition analysis
Non-IDU	Non-injection drug use
OAT	Opioid agonist treatment
OD	Overdose
ON	Ontario
OUD	Opioid use disorder
PO	Prescription opioids
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSU	Polysubstance use
PTSD	Post-traumatic stress disorder
PWID	People who inject drugs
PWUD	People who use drugs
Q1, Q3	First quartile, third quartile
QIC	Quasi-information criterion
RMLCA	Repeated measure latent class analysis
SD	Standard deviation
SUD	Substance use disorders
U.S.	United States
VIDUS	Vancouver Injection Drug Users Study

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I could not have completed this thesis research without the support of many mentors, colleagues, and friends. I would like to sincerely thank my supervisors Dr. Thomas Kerr and Dr. Jane Buxton, for believing in me and providing invaluable mentorship throughout my PhD training. You showed me the way and held my hand throughout this journey. Your support and confidence have continually motivated me to set higher goals for myself and grow both personally and professionally. I am also really grateful to my supervisory committee, Drs. Kanna Hayashi and Ekaterina Nosova for their generosity, support, and guidance. During my days at BCCSU, I was also fortunate to receive support and mentorship from Drs. Kora Debeck, Rod Knight, Ryan McNeil, M-J Milloy, and Lindsey Richardson.

I acknowledge that this PhD research was undertaken on the traditional unceded territories of the Coast Salish People, including the Sḵwx̱wú7mesh (Squamish), səl̓ilwətaʔɬ (Tsleil-Waututh), and xʷməθkʷəy̓əm (Musqueam) Nations. I would not have been able to complete this research without the contributions of the study participants, interviewers, as well as clinical and administrative staff of VIDUS, ACCESS, and ARYS cohorts. I cannot thank the statistical team at BCCSU enough for their generosity and patience with me. Thank you Zishan Cui and JinCheol Choi.

I would also like to thank my colleagues and friends at the BCCSU. You enriched my graduate training experience in many ways. I am grateful for your friendship, helpful feedback, fun coffee breaks, and sharing laughs or frustrations. Thank you Dr. Mary Clare Kennedy, Dr. Brittany Barker, Dr. Stephanie Lake, Dr. Pierre-julien Coulaud, Dr. Jano Klimas, Andreas Pilarinos, Pauline Voon, Dr. Huiru Dong, Sanjana Mitra, Michelle Olding, Tara Beaulieu, and Dr. Kate Jaffe.

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Dedication

To my family; Thanks for being a constant source of love, support, and encouragement.

Chapter 1: Introduction

1.1 Opioid epidemic in Canada

Canada is in the midst of a drug overdose (OD) epidemic, characterized by unintentional opioid-related toxicity deaths (1, 2). Opioids may be derived naturally from the opium poppy plant (e.g., opium, morphine) or manufactured synthetically (e.g., fentanyl and its analogues). Opioids can be an effective pharmacotherapy for managing pain; however, they could also be misused for pleasure and experiencing euphoria (3, 4). Among some people who use opioids, chronic opioid use may lead to the development of opioid use disorder (OUD). For example, a recent systematic review and meta-analysis of 12 studies corresponding to observations from over 300,000 pain patients, reported a pooled estimate of 4.7% for incidence of opioid dependence or 'abuse' among those exposed to opioid analgesic therapy (5). Moreover, data from over 800,000 participants (2002-2016) in the National Survey on Drug Use and Health in the United States (U.S.) suggested that among 1021 people who had initiated using heroin (i.e., newly incident cases), about 30% had developed heroin dependence a year after their heroin use onset (6). Based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), OUD symptoms include, but are not limited to, at least two of the following conditions: strong craving for opioids, inability to control or reduce opioid use (e.g., showing withdrawal symptoms), persistent use of opioids over time, and regular opioid use despite adverse social, mental, and physical outcomes (7, 8). In addition to developing OUD, people who use opioids may be at risk of opioid-related poisoning, given that opioids could act as respiratory depressants and lead to fatal and non-fatal OD events.

The number of opioid-related OD deaths in Canada has been surging in the past few years and surpass motor vehicle incidents and homicide deaths combined (9, 10). Between January 2016 and December 2020, an estimated 21,174 apparent opioid toxicity deaths and 24,671 opioid-related poisoning hospitalizations have been recorded in Canada (11). While Western Canada (e.g., British Columbia [BC], Alberta [AB]) is the most impacted region in the country, rates of opioid toxicity deaths and opioid-related hospitalizations have also surged in other provinces, including Ontario (ON) (11). Indeed, during the past four years (2016-2020), 85% of all opioid toxicity deaths and 90% of opioid-related hospitalizations across Canada have occurred in BC, AB, and ON (11). In BC, in particular, the unprecedented surge of drug-related OD deaths led to the declaration of a public health emergency on April 14, 2016 (12). Most opioid-related toxicity deaths and hospitalizations have occurred among males and those aged between 29 to 49 years old (11). In response to the opioid epidemic, an array of federal and provincial efforts has been implemented: guidelines for opioid prescribing have been published (13), interventions to prevent opioid misuse (14) and OD have been implemented (15), and treatment options for OUD have been expanded (16-18). Despite these efforts, the rate of opioid toxicity deaths continues to increase.

Canada's unprecedented OD epidemic, however, is not a recent public health problem and could be characterized as a chronic public health emergency that has evolved over the past few decades. The recent rise in opioid toxicity deaths in Canada can be conceptualized in a few distinctive waves: i) a rapid surge in heroin-related ODs and outbreaks of human immunodeficiency virus (HIV) and hepatitis infections in the 1990s in Vancouver, which led to the declaration of a public health emergency for hepatitis, HIV, syphilis, and OD deaths in 1997 (19), ii) increased opioid prescribing practices starting in the late 1990s, which led to a

rise in OD-related deaths involving prescription opioids (PO) in the subsequent years (20-22), and iii) significant surges in OD-related deaths involving synthetic opioids since 2014, particularly those involving illicit fentanyl and its analogues, which were involved in 82% of accidental opioid toxicity deaths from January to September 2020 (11, 23, 24).

While most research studies have focused on the involvement of opioids in drug-related mortality and morbidity (25), a growing body of clinical and epidemiological studies indicate that both opioid- and stimulant-related poisoning hospitalizations and deaths often involve multiple substances (26-28). In Canada, from January to September 2020, 33% of opioid-related poisoning hospitalizations also involved non-opioid polysubstance use (PSU), and 61% of stimulant-related poisoning hospitalizations also involved non-stimulant PSU (11). Moreover, in BC, during the past four years, the most commonly detected drugs in illicit drug-related deaths were fentanyl (83%), cocaine (50%), amphetamines (33%), and heroin (16%) (29). Similar patterns were observed in the U.S., where data from the National Vital Statistics System suggested that cocaine OD deaths involving opioids have increased from 29% to 63% between 2000 and 2015 (30).

1.2 Polysubstance use

There is little consensus over the definition of PSU, but it is often used as a broad term to describe the use of ≥2 different substances or classes of substances either simultaneously or separately over a defined period of time (26). The introduction of the notion of PSU, however, goes back to a few decades ago and a historical review of the medical literature provides some insight into how this terminology has evolved and fallen in and out of favour throughout the years (31). PSU was first discussed in detail in the DSM-III in 1980, where the diagnostic

category of “mixed substance abuse” was introduced (32). This categorization, however, was quite imprecise and subjective; it referred to clinical conditions where the substances used could not be fully identified or the behaviour involved “so many substances that the clinician prefers” to treat a combination of substance use disorders (SUD) and not a particular one (31, 32). The notion of “polysubstance dependence”, which was later introduced in the DSM-III-R in 1987, tried to address some of the ambiguities in the previous definition and defined polysubstance dependence as regular use of at least three substances (excluding nicotine and caffeine) while not meeting dependence criteria for any particular substance (31, 33).

The DSM-IV published in 1994 helped improve the specificity of this definition further by limiting it to three or more classes of drugs frequently used in the previous year, while no dependence on a single drug is diagnosed (34). Such narrow definitions suggesting polysubstance dependence to be an infrequent disorder among people who use drugs (PWUD) were often misunderstood, deemed disconnected from the reality of substance use, and therefore, were not commonly used by addiction researchers or healthcare providers (31, 35, 36). Lastly, the DSM-5 published in 2013, made drastic changes with regards to the concept of SUD and distanced itself from the problematic binary classification approach opted for detecting different SUD in DSM-III and DSM-IV (7, 37-39). DSM-5 combined the criteria for dependence and abuse into a single non-binary diagnosis of SUD ranging from mild to severe (7).

Although “polysubstance dependence” is no longer diagnosed in clinical assessments, its clinical significance is quite relevant and requires attention in substance use research and practice. Several studies have reported PSU to be a common practice among PWUD who may engage in such substance use practices for several recreational or therapeutic reasons (27, 28,

31). For example, mixing alcohol and benzodiazepines that have similar sedative effects on the central nervous system (CNS) can boost their euphoric effects (40, 41). Moreover, combining opioids and benzodiazepines or stimulants and opioids that have different impacts on CNS could magnify their effects (28, 42, 43). Certain substances may be used concurrently or consecutively to reduce cravings or withdrawal symptoms (26). PSU could also be driven by substance availability in the illicit drug supply. For example, the reduced availability of heroin in 2000 in Australia was associated with a decrease in the population size of people who injected heroin and an increase in amphetamine injection initiators (45). More recently in the North American context, the shortages in heroin and PO supplies (e.g., OxyContin) may have contributed to people engaging in PSU involving synthetic opioids (27, 46-48).

As PSU has been associated with several adverse mental and physical health outcomes (26, 49-55), it is essential to improve the understanding of its patterns and the unique characteristics of people who engage in this behaviour. However, measuring PSU remains statistically and methodologically challenging (44). Most studies have assessed PSU using variable-centred approaches, such as contingency tables of several drugs, which lead to small cell sizes or highly skewed distributions and, therefore, limited analyses or interpretations (26, 56, 57). Given the wide range of substances available, it is unclear what polysubstance patterns are prevalent. Considering the importance of characterizing the distribution and correlates of PSU for OD prevention programs and harm reduction interventions, methodological developments have been made to help identify and uncover subpopulations with distinct PSU patterns through person-centred methods (57-60). Latent class analysis (LCA) and latent profile analysis (LPA) are cross-sectional methods that examine the data using an inductive lens and could reveal unobserved typologies or classes of polysubstance. These methods

analyze participants' response patterns to certain individual variables that measure specific substance use practices (57-60). The changing nature of substance use patterns over time, however, requires longitudinal person-centred statistical methods, three of which are briefly discussed in the next section.

1.3 Person-centred and variable-centred approaches to longitudinal data

With the increasing availability of longitudinal data, several analytical approaches have been developed. Overall, these methods could be conceptualized as variable-centred or person-centred (61). Although the notion of person-centred approaches can be traced back to early to mid-1900s (61), Jack Block is one of the first to introduce the lexicon focusing on variables and persons and defined them as follow: "Variable-centred analyses are useful for understanding the differences between people and what characteristics go with what characteristics in a group of individuals. But as well, and ultimately, psychology will need to seek understanding of the configuration and systematic connection of personality variables as these dynamically operate within a particular person" (62). The revival of person-centred approaches could be attributed to the research works of Bob Cairns in the late 1990s, who focused on the person-centred nature of life trajectories and highlighted the need for applying a holistic lens to human development (63, 64).

These concepts were further elaborated upon by David Magnusson (65) and Lars Bergman (66) in 2003. They argued that variable-centred approaches focus on the relationship between individual variables and assume homogeneity among the population of interest with regards to how predictors impact the outcome of interest (65, 66). Typical statistical analyses for variable-centred approaches include correlation and regression analyses (61). In contrast,

person-centred approaches focus on identifying groups of people who share certain attributes (65, 66). In other words, person-centred approaches assume heterogeneity among the population of interest with regards to how outcomes of interest are influenced by predictors. Typical statistical analyses for person-centred approaches include cluster, latent class, and latent profile analyses. Variable-centred approaches can be used to identify correlates of class membership (61).

While person-centred approaches are not recent and have been around for over a century, these methods seem to have lost their popularity to variable-centred approaches when behaviourism became attractive to researchers who wanted to focus on identifying universal behavioural patterns rather than understanding individual differences among people (61). In addition, statistical software packages were heavily focused on variable-centred methods and gave little attention to person-centred approaches. Indeed, most software are still ill-equipped to conduct advanced longitudinal person-centred analyses (61, 67).

Although person-centred approaches are regaining their credibility among the research community, they are still not favoured by the majority of traditional researchers due to three major misconceptions. First, traditional statistical approaches assume that the notion of person-centred techniques is unnecessary and could be simply addressed by introducing interaction terms into variable-centred analyses. However, a considerable body of literature has highlighted that interaction terms based on a few variables have numerous methodological and conceptual limitations and often fail to detect meaningful groups of people with similar attributes (61, 66, 68). Second, there are arguments that reporting styles of person-centred analyses lack consistency and standard guidelines are unavailable, making it hard to conduct reproducible analyses. However, the field of person-centred statistical approaches is rapidly

evolving and great progress has been made in recent years. Several clear recommendations for both cross-sectional and longitudinal assessments using a person-centred lens are now available (57-60). Third, some researchers have surprisingly equated person-centred techniques with qualitative data analysis. While person-centred approaches could be perceived as techniques that use a cluster of individual variables to detect qualitatively different groups of people, all measurements are purely quantitative. Indeed, latent classes are identified based on a set of variables guided by *a priori*-defined statistical procedures, and not the researchers' subjective perspectives (61).

Recent arguments concerning this research area, however, have suggested that discussions about person-centred approaches versus variable-centred ones are rooted in a "false dichotomy" and that these methods are complementary and not competing (61). While variable-centred approaches for longitudinal data view variables as agents that help shed light on the principles of change over time, person-centred methods help identify different trajectories of certain groups of individuals in comparison with others (61). Therefore, both approaches are helpful in longitudinal data analysis and are used in chapters four and five of this thesis.

As explained earlier, person-centred approaches are not focused on quantifying the impact of certain variables on an outcome in a research study. Instead, they aim to identify a set of mutually exclusive subgroups of analogous individuals characterized by their response patterns to certain variables. Longitudinal person-centred approaches are often interested in assessing some form of change over time. The latent indicators of latent classes are similar but measured repeatedly over the course of the study. Overall, there are three popular techniques

for person-centred approaches for longitudinal data analysis: Repeated measure latent class analysis (RMLCA), growth mixture modeling (GMM), and latent transition analysis (LTA).

RMLCA or longitudinal latent class analysis (LLC) is an extension of LCA but for longitudinal data structures (57, 69). RMLCA allows identifying the emerging latent patterns of a particular behaviour (e.g., PSU patterns, binge drinking behaviours) as well as their prevalence over all time points. Change over time can be discontinuous in RLMCA. GMM is another popular person-centred approach in developmental research that is similar to RMLCA in nature. However, GMM aims to describe the heterogeneity in people's growth trajectories and identify population subgroups based on typical trajectory shapes or growth patterns over time. To identify longitudinal trajectories, GMM assumes a functional form (e.g., linear, quadratic) for time while RMLCA assumes no particular function for time, and the trend over time could have any form that fits the data best. Moreover, GMM cannot account for discontinuous behavioural patterns over time (70). LTA is another extension of LCA that can be applied to studies with repeated measurements of certain indicators (69). This approach, which is similar to latent Markov modeling, allows an estimation of transition probabilities between latent classes over time. LTA measures latent classes at each time point and is most appropriate when the adjacent time points have highly similar latent classes. In contrast to RMLCA, LTA provides more specific information about transitions across classes over time but is feasible when fewer numbers of repeated measurements of particular indicators are available (57).

1.4 Rationale

PSU is often challenging to measure, and people's substance use practices often change over time (26). PSU has been associated with several adverse mental and physical health outcomes (26, 60) and is particularly high among individuals with OUD (26, 71-73). However, PSU among people with OUD is not fully understood and is limited to small-scale cross-sectional studies that often suffer from methodological restrictions. Moreover, the illicit drug market across North America has changed drastically in the past few years (46-48). Considering the recent opioid OD epidemic and the surge in fatal and non-fatal opioid-related ODs, identifying the characteristics of the PSU among people with OUD requires special attention and likely tailored intervention. The overall objective of the proposed research is to longitudinally examine the natural history of PSU classes among people with OUD over their drug use career in Vancouver, BC, Canada.

Using person-centred approaches and statistically transparent, inductive, and reproducible methods, the proposed research seeks to address current knowledge gaps related to PSU among people with OUD in Vancouver, BC, Canada. To my knowledge, this study will be the first to draw on a cohort study that has followed people with OUD for over twelve years and characterized classes of PSU and their associated OD risks. Identifying PSU patterns, predictors, classes, and associated health outcomes among people with OUD is critical to facilitating the implementation of evidence-based policies and interventions aimed at addressing the OD epidemic in BC and elsewhere.

1.5 Study setting and context

Data for the empirical analyses conducted in my thesis were based on three open,

prospective cohort studies of over 2000 PWUD in Vancouver, BC, Canada. These cohorts are funded by the National Institutes of Health and include the Vancouver Injection Drug Users Study (VIDUS)(74), the AIDS Care Cohort to Evaluate Access to Survival Services (ACCESS)(75), and the At-Risk Youth Study (ARYS)(76). All participants of these cohorts have been recruited using snowball sampling and street outreach, have used drugs aside from or in addition to cannabis, reside in Vancouver, and have provided written informed consent upon enrolment. VIDUS was established in 1996 and has recruited over 2700 adult people who inject drugs (PWID) to date (74). VIDUS includes PWID who are HIV-negative and self-report having injected drugs during the month before enrolment in the cohort (74). ACCESS includes PWUD who are living with HIV. VIDUS participants that sero-convert to HIV-positive during the study period are also transferred to ACCESS, which involves approximately 1000 adult PWUD who are HIV-positive (74, 75). ARYS is the youngest of the three cohorts and was established in 2005. ARYS participants include over 900 street-entrenched youth who are between 14-26 years old (76). All cohort participants complete a comprehensive, interviewer-administered risk-assessment questionnaire at baseline and semi-annual follow-up visits. The questionnaires are harmonized across all three cohorts and collect a wide range of data on participants' socio-demographics (e.g., age, gender, ethnicity, education, and income), sexual behaviours (e.g., number of sexual partners, condom use frequency in sexual encounters, and involvement in sex work), substance use practices (e.g., frequency and patterns of injection drug use [IDU], history of OD), history of encounters with law enforcement (e.g., incarceration, experiences with the police), and history of receiving services at harm reduction (e.g., access to sterile needles, take-home naloxone kits) and healthcare facilities (e.g., hospitalization, access to drug and alcohol treatment services). Participants also provide a blood sample at each visit

which is tested for HIV and hepatitis C virus (HCV) sero-positivity. All participants receive a $40 stipend at each study visit to compensate for their time.

1.6 Conceptual framework

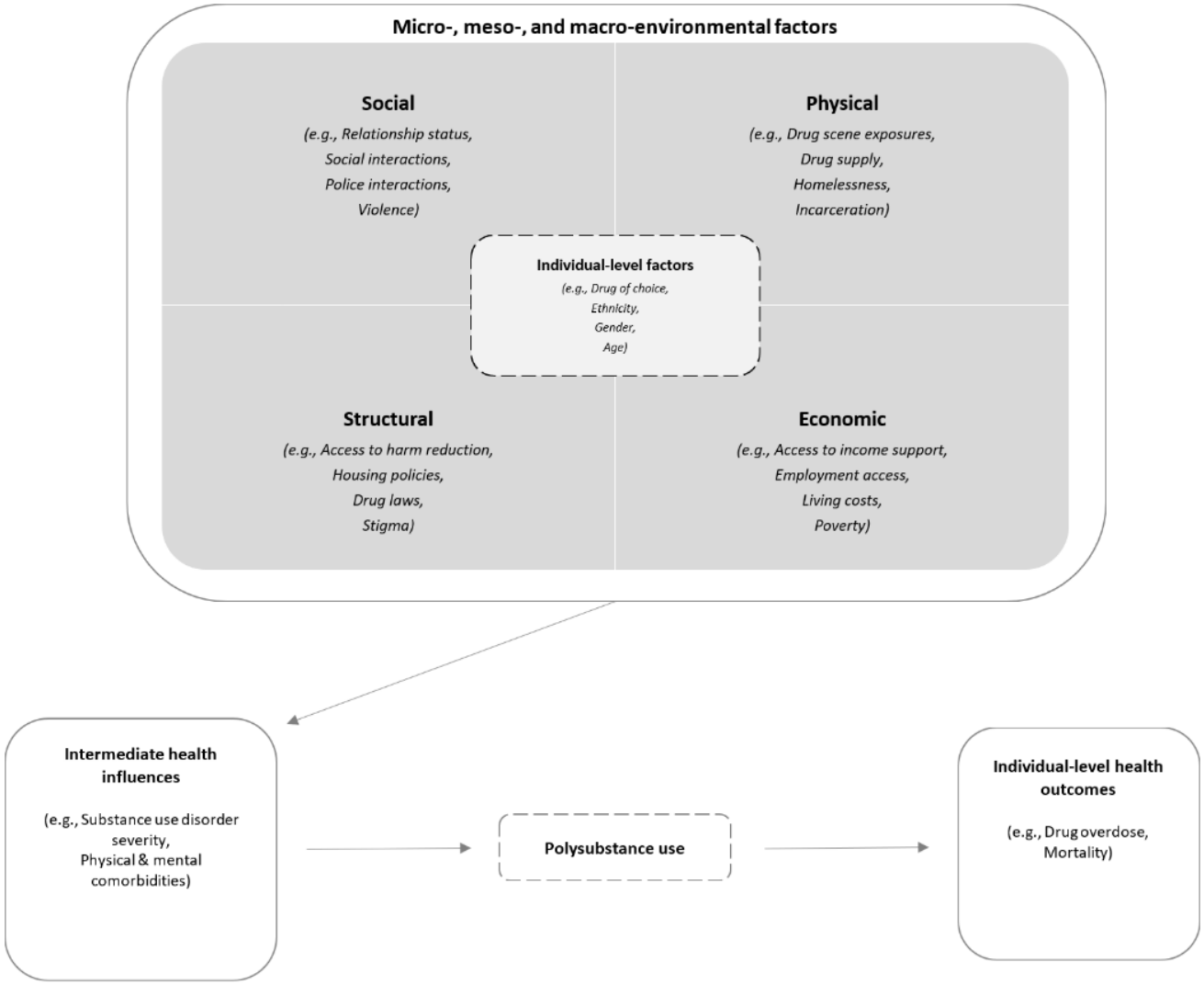
The proposed research is informed by Rhodes' Risk Environment Framework (77-79). Traditionally, research on substance use-related harms has primarily focused on individual-level risks and behaviour change. A growing body of evidence has highlighted the limitations of such conceptual frameworks (e.g., health belief model) that underscore individual-level decision-making interventions as a remedy to reducing substance use-related harms and adverse health outcomes (77, 80). Rhodes' framework takes on a more contextual approach towards identifying factors that affect PWUD's health (77, 78). It conceptualizes that a group of micro-, meso-, and macro-level influences within economic, physical, structural, and social environments interact with individual-level factors and impact substance use-related harms. In other words, Rhodes' framework views individual-level behaviours and outcomes as consequences or products of the interaction of individual-level factors with several influences within the economic (e.g., access to licit employment), physical (e.g., homelessness), structural (e.g., drug laws), and social (e.g., relationship status) environments. Through the lens of Risk Environment Framework applied in this research, PSU could be conceptualized as a behaviour that is impacted and influenced by a range of individual- (e.g., drug of choice), micro- (e.g., availability of harm reduction services), meso- (e.g., policing intensity), and macro-level influences (e.g., toxic drug supply). Identifying the role of these factors in shaping PSU practices among people with OUD could provide insights to help understand the heterogeneities among people with OUD and identify their specific needs. Figure 1.1 provides

a schematic overview of the conceptual framework used to inform this thesis research.

1.7 Study objectives

The current thesis aims to characterize longitudinal PSU patterns among a cohort of people with OUD in Vancouver, BC, Canada. The specific objectives of this research and an overview of the methodologies used are presented here. Chapter one provides a current picture of the opioid epidemic in Canada, presents a historical overview of PSU in the literature, and reviews the commonly used person-centred statistical methods used in longitudinal studies. Chapter one also provides information about the study context, data sources, and conceptual framework informing the research studies included in the thesis. Chapter two presents a systematic review of the literature that summarizes the published literature that has utilized person-centred statistical approaches on identifying PSU classes among people with OUD. Chapter three assesses how substance use patterns of people with OUD changed after a supply-level intervention (i.e., delisting Oxycontin from public drug formularies) was implemented in BC in 2012. Chapter four identifies the longitudinal patterns of PSU among people with OUD and characterizes different factors associated with participants' membership in each PSU class. Chapter five characterizes non-fatal OD risks among different sub-classes of PSU over time. Lastly, Chapter six presents a summary of the main findings of the research, discusses study limitations and implications for future research, practice, and policy developments.

Figure 1.1. Modified risk environment framework



Adapted from Rhodes (2002, 2009)

Chapter 2: Patterns of polysubstance use among people with opioid use disorder: A systematic review

2.1 Introduction

There is little consensus when it comes to defining PSU; it is often used as a broad term to describe the use of ≥2 different substances or classes of substances either simultaneously or separately over a defined period (26, 60, 81). Nonetheless, a growing body of international evidence suggests that PSU is particularly frequent among people with OUD (73, 82-85). Moreover, drug OD deaths often involve several drugs in addition to opioids (28). For example, in the Canadian province of BC, which has been hit hard by the OD epidemic, the most commonly detected drugs in illicit drug toxicity deaths during the past four years were fentanyl (83%), cocaine (50%), amphetamines (34%), and heroin (15%) (86). Similar patterns are observed in the U.S., where National Vital Statistics System reported that cocaine OD deaths involving opioids to have increased from 29% to 63% between 2000 and 2015 (30).

Given the wide range of substances available, it is unclear what types of PSU are prevalent among people with OUD and how they can be measured or predicted in a clinically meaningful way. Indeed, measuring PSU is statistically and methodologically challenging. Most studies have assessed PSU using contingency tables of several single drugs, leading to small cell sizes or highly skewed distributions and, therefore, limited or biased analyses or interpretations (26, 28, 87). Despite inconsistencies over what constitutes PSU, studies have consistently associated PSU with an increased risk of various poor health outcomes (88-93).

Considering the importance of characterizing the distribution and correlates of PSU for OD prevention programs and harm reduction interventions, methodological developments

have been undertaken to help better identify and uncover subpopulations with distinct PSU patterns through person-centred methods (57, 60, 94, 95). These approaches (e.g., LCA, LTA, LPA, GMM) examine the data using an inductive lens, analyze participants' response patterns to certain individual variables that measure specific substance use practices, and reveal unobserved typologies or classes of PSU via statistically transparent and reproducible methods (57, 95). This systematic review aims to classify, characterize, and summarize the latent patterns of PSU among people with OUD. Identifying PSU classes and associated determinants among people with OUD is critical to facilitating and informing the implementation of evidence-based interventions aimed at addressing the ongoing OD epidemic.

2.2 Methods

2.2.1 Databases and search strategy

Following the Peer Review of Electronic Search Strategies (PRESS) guidelines (96) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (97), I searched for empirical peer-reviewed studies or grey literature on latent classes of PSU among people with OUD from inception, through to June 15, 2020 (See Appendix A for PRISMA checklist). The search concepts, databases searched, and information about the review's protocol registration are presented in Table 2.1, and a sample search strategy is available in Appendix B.

2.2.2 Inclusion criteria

Empirical studies of any design (i.e., observational, experimental, cross-sectional, and cohort) were considered for inclusion if they identified latent classes of substance use among people with OUD. OUD was assessed based on the following criteria: i) participants had regular opioid use; ii) were clinically assessed as having OUD based on DSM or other validated tools (7); or iii) participants were receiving treatment for OUD. Studies with mixed populations of OUD and people with other SUD were considered if they provided separate analyses for participants with OUD or if more than 50% of the participants had OUD. Studies were included if they had reported categorical or continuous measures of substance use during any time interval (e.g., last year, last six months, last month, current). Studies were only included if they reported latent classes of substance use through various latent class analytical approaches (e.g., LCA, LTA, LPA, GMM). Eligible studies had to report details about latent classes identified and variables used as item response indicators. Studies were excluded if they used latent class analyses for variables other than substance use characteristics (e.g., HIV or OD risk).

2.2.3 Study selection

Two independent reviewers (MK and AP) completed the title and abstract screening. Studies that met the inclusion criteria or were unclear were retained for full-text screening, which was also done by two independent reviewers (MK and AP). Disagreements over the inclusion of studies were resolved through discussion throughout the screening process. Duplicate studies were identified and excluded.

2.2.4 Data extraction and analysis

I developed a data extraction sheet and pilot-tested it by two independent authors (MK and AP). Data extraction was completed independently by two reviewers (MK and AP), and discrepancies were resolved through discussion. Data were extracted on study characteristics, participant characteristics, and outcome characteristics. Given the considerable conceptual heterogeneity of covariates (e.g., the inclusion of a range of sociodemographic or behavioural variables in the multivariable analyses) and outcomes included in the analyses across the studies (e.g., PSU operationalization using different self-reported or clinical measures as well as the inclusion of various outcome indicators in the latent analyses), no meta-analysis was conducted, and study findings were summarized and presented in a narrative fashion. To help reduce the role of publication bias on the findings, I searched the grey literature, thesis databases, bibliographies of relevant published works, and recent conference proceedings for potentially eligible studies.

2.2.5 Quality assessment

I used a modified version of Newcastle-Ottawa Quality Assessment Scale (98) to independently assess the risk of bias in the included studies. The tool uses several components to evaluate selection bias, comparability, and outcome assessment. Given the review's focus on latent analyses, I also used a modified version of the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS) checklist (99) to assess the specific methodological quality of the included studies. The modified GRoLTS checklist (100) contains 15 yes/no items. Using this checklist is important in critical appraisal of LCA, LPA, or LTA studies and ensuring transparency and interpretability of their results.

2.3 Results

Out of the 3372 initial unique records identified, 30 met the inclusion criteria and were included in the systematic review (Figure 2.1).

2.3.1 Study settings and participants

An overview of the included studies is presented in Table 2.2. Although all studies met the criteria for having a population of people with OUD, the inclusion criteria of the individual studies varied considerably and included a wide range of participants such as people admitted to emergency departments (101, 102), people receiving opioid agonist treatment (OAT) (103-105), people involved with the justice system (106), people accessing harm reduction services (107, 108), social-economically disadvantaged PWID (108-111), and other people with OUD recruited through various large-scale surveys (112, 113).

Overall, three studies were longitudinal, and 27 were of cross-sectional nature. Mean/median age of the participants was between 30 to 45 years old in the majority of studies. One study had recruited younger people with a mean age of 21 (114), and one had included primarily >50-year-old participants (109). Two studies did not report any information on the sex or gender of the participants, and none reported sex- or gender-stratified analyses for latent classes. The sex ratio for the studies ranged from 43.7% males (112) to 85.8% males (115). Only 16 studies reported ethnicity ratios among their participants. The participants in most studies were White; however, race/ethnicity ratios varied greatly from 6% White (116) to 93.2% White (103). Most studies were conducted in the U.S. (n = 16), three in Australia (104, 117, 118), three in Mexico (110, 119, 120), two in England (113, 121), two in Canada (122, 123), and one in each of Russia and Estonia (124), Puerto Rico (115), Norway (108), and China (105), each. Two studies in Mexico were on the same population but were both included given

their different methodology (i.e., cross-sectional vs. longitudinal) and dissimilar nature of classes identified (110, 119).

2.3.2 PSU operationalization

PSU operationalization varied substantially among the studies and was measured based on clinical diagnosis of dependence or SUD using a standard tool (e.g., DSM-III, DSM-IV, DSM-5, Addiction Severity Index), lifetime, last six-month, last-month, simultaneous use, combined lifetime and last month, combined lifetime and last six months, combined last-year and weekly, combined last six months and daily/weekly, and upon discharge from a treatment facility (101, 102). One study that conducted an LPA, also included the mean number of days used in the past month (107). The majority of studies measured substance use via self-reports.

Overall, most studies included various indicators of heroin, amphetamines, cocaine, and crack. A measure of alcohol use was included as an outcome indicator in 14 studies (101-103, 105, 106, 108, 112, 115, 116, 121, 122, 125-127). Only four studies included validated measures of alcohol use (101, 103, 118, 127), and the rest mainly included subjective alcohol use measures in the last month or last six months. Nonetheless, eight studies labeled at least one class to indicate a considerable level of alcohol use (101, 103, 105-107, 112, 121, 123), and others did not find such a class. Moreover, measures of illicit PO use (e.g., OxyContin, fentanyl) or non-opioid prescription medication use (e.g., benzodiazepines) were included as outcome indicators of PSU in 12 (104, 106, 108, 109, 112, 117, 118, 122, 123, 128-130) and 17 studies (102, 103, 105, 106, 108, 109, 111, 112, 114, 118, 122, 123, 125, 127-130), respectively. However, only 11 studies labeled at least one class that indicated a considerable level of PO or non-opioid prescription medications (102, 104, 106, 108, 109, 112, 118, 122, 123, 125, 128). Lastly, a measure of cannabis use was included as an indicator in 17 studies

(102, 103, 106-108, 111-113, 115, 116, 119, 121-123, 125, 127, 130). However, only five labeled at least one class to indicate a considerable level of cannabis use (103, 107, 113, 121, 125). Additionally, only four studies included an outcome indicator for tobacco use.

Fifteen studies included several indicators of a single type of substance (i.e., frequency of use, length of substance use career) in their latent analysis (108-111, 115-117, 119, 120, 122, 124, 126, 128-130). Moreover, 15 studies included an indicator for the route of substance administration (i.e. IDU vs. non-IDU) in their assessment of classes of substance use patterns (108-111, 115-117, 119, 120, 122-124, 126, 129, 130). Including these characteristics as outcome indicators was reflected in the final class solutions.

2.3.3 Latent classes of PSU

Median number of classes was four, ranging from two to 15 classes. In detail, two studies identified two classes (111, 127), eight studies identified three classes (105, 109, 117, 120, 122, 126, 128, 130), seven studies identified four classes (101, 103, 110, 113, 118, 125, 129), five studies identified five classes (102, 107, 116, 119, 124), three studies identified six classes (106, 108, 114), and five studies identified seven or more classes (104, 112, 115, 121, 123). The study with 15 classes, reported heroin use conditional on membership in various trajectories of other substance types (121). Only four studies grouped their analyses by another unique characteristic of the participants: being on OAT (104, 108), urbanicity (115); and race (114). Although the classes identified across the studies varied considerably, the classes presented in Table 2.3 (i.e., infrequent/low PSU, primarily heroin use, primarily heroin and stimulant use, primarily stimulant use, and frequent PSU) were found in most studies.

While most identified classes fit into the overarching classes presented above, some classes were difficult to fit into a particular class due to variations in measurements and

indicators used to build classes. For example, a handful of studies focused on specific brands, such as OxyContin (118, 123) and Tylenol (122, 123), and two studies included a measure of fentanyl use as a unique indicator in their LCA (128, 129). Some studies also included indicators other than substance use practices (e.g., post-traumatic stress disorder [PTSD], hospital utilization, physical health) (101, 103, 112, 117) as well as demographic indicators (e.g., age group, sex, housing) in their analysis (102, 117); indicators that were reflected in the identified PSU classes.

2.3.4 Predictors of latent class membership

Comparisons about latent class memberships need to be interpreted with caution due to the heterogeneity of PSU operationalization across different studies. Of the 30 included studies, 18 reported detailed measures of effect size for predictors of latent class membership. The majority of studies compared their polysubstance substance class with lower frequency classes, the details of which are presented in Table 2.4.

2.3.4.1 Predictors related to risk profiles

Among studies that reported predictors of latent class membership, in comparison with lower frequency groups, belonging to higher frequency or severity PSU classes were associated with increased odds of various behaviours, such as frequent IDU (106, 124), sharing needles and paraphernalia (104, 109, 110, 119, 120, 124, 126), high-risk sexual behaviours (110, 119, 120, 127), as well as experiences of adversities such as, homelessness (106, 113, 118, 119, 123, 124, 130), incarceration (106, 110, 113), poor mental health and psychiatric profiles (106, 112, 114, 124, 127), chronic pain (114, 125), previous non-fatal ODs (104, 109-111, 117, 120), and HCV sero-positivity (111, 123). Mortality risk was only assessed in one cohort study of street- and low-threshold service-recruited people who engaged in PSU in

Norway, where membership in the polysubstance injectors and low-frequency injector classes not receiving OAT was associated with an increased hazard of mortality in comparison to frequent buprenorphine users (108).

2.3.4.2 Sociodemographic predictors

Most studies compared the classes based on their sociodemographic characteristics; however, comparisons based on age, sex/gender, and race/ethnicity were the most commonly examined. The findings of the studies regarding the association of age and substance use class membership were relatively consistent and increasing age was often associated with belonging to higher frequency or severity classes; however, a subset of studies reported no significant association between class membership and age.

Among 28 studies that reported on participants' sex, no study reported any details about participants' gender, and some confused sex with gender. Overall, the association of sex and latent classes of PSU were inconsistent. For example, compared to males, females were more likely to belong to adverse mental health, opioid, tobacco, cannabis use disorder classes (103), amphetamine-type stimulant polydrug use class (105), low-frequency PO use and depressed class (112), non-opioid prescription drug use class (125), non-opioids and benzodiazepine classes (102), polydrug and polyroute users class (110), and methamphetamine and heroin class (120). Conversely, compared to females, males were more likely to belong to the following classes: primarily alcohol, buprenorphine, and benzodiazepine use (106), very high-frequency PO, polysubstance, and elevated psychopathology (112), cannabis and/or cocaine use (125), PSU and heroin OD (102), heroin and methamphetamine injectors (110), infrequent PO and heroin (118), and polyroute stimulant use (129). Several studies reported no significant association between class membership and sex (111, 122, 124, 127, 130).

Among 16 studies that reported on the race/ethnicity of the participants, 11 reported detailed associations between this variable and class memberships. Overall, the findings regarding the association of race/ethnicity and PSU classes were inconsistent, and studies had used various racial/ethnic classifications in their assessments. For example, compared to non-Whites, White people were more likely to belong to buprenorphine use class (106), less likely to belong to the polydrug use class (125), and more likely to be classified as high severity users (127). Conversely, compared to White people, Hispanic and Black people were more likely to belong to heroin IDU class (111), Black people were more likely to be classified as crack/nasal heroin users (126), and American Indigenous people were more likely to belong to elevated PO, alcohol-tobacco-cocaine, bipolar, and polysubstance/very high psychopathology classes (112). Lastly, non-Russian PWID were more likely to belong to polydrug/polyroute injection class in a study conducted in Russia and Estonia (124). Some studies reported no significant association between class membership and race/ethnicity (109, 129, 130).

2.3.5 Quality of the evidence

As presented in Appendix C, most studies were of satisfactory quality in terms of risk of bias as evaluated by a modified version of Newcastle-Ottawa Quality Assessment Scale. While most studies had a sample size sufficient for LCA (131), had comparable participants, and were statistically sound, most suffered from measurement biases in their outcome and exposure ascertainment. The quality of LCA studies, which was assessed by a modified GRoLTS checklist, are presented in Appendix D and identified several limitations across the included studies.

2.4 Discussion

I systematically reviewed 30 studies that applied a latent analytical approach to identifying PSU patterns among people with OUD and identified five distinct PSU patterns: infrequent/low PSU in 16 studies, primarily heroin use in 22 studies, primarily heroin and stimulant use in 15 studies, primarily stimulant use in 13 studies, and frequent PSU in almost all included studies.

The findings of PSU patterns among people with OUD are comparable but not compatible with a previous review of PSU patterns in the general population, which classified PSU into clusters, including no or limited use (alcohol, tobacco, and cannabis), moderate use ("limited range" and amphetamines), and extended use ("moderate range", illicit prescription medications, and other illicit substances) (26). The findings also diverge from several previous reviews on PSU clusters/classes among adolescents, which mainly identified different subgroups of adolescents using varying frequencies and amounts of tobacco, alcohol, and cannabis (60, 132). These differences could be attributed to the dissimilar approaches in PSU measurement as well as distinct behavioural characteristics and substance use patterns of people with OUD in comparison with people in the general population or adolescents who may be primarily experimenting with PSU.

Although the results suggested certain distinct classes of PSU among people with OUD, PSU seems to be often the norm rather than an occasional practice or an exception among a minority group of people with OUD. Indeed, the findings are in line with a growing body of evidence that suggests concurrent and/or sequential use of multiple substances, including but not limited to stimulants, opioid/non-opioid prescription medications, and alcohol, is a common practice among people with OUD (27, 28, 43, 133). This established

body of evidence points to a range of recreational or therapeutic reasons for PSU among people with OUD. First, combining substances that have dissimilar impacts on CNS (e.g., opioids and benzodiazepines or stimulants and opioids, such as goofballs and speedballs) could magnify their euphoric effects (28, 43, 88, 133-135). Second, stimulants may be used concurrently or consecutively with heroin to reduce the undesirable experiences of opioid cravings or withdrawal (136), or balance out the effects of the heroin high (137-139). Lastly, PSU among people with OUD could also be driven by substance availability in the illicit drug supply. For example, the reduced availability of heroin in 2000 in Australia was associated with a decrease in the number of people who injected heroin and an increase in amphetamine injecting among them (45). Regardless of the motivations behind engaging in PSU, the findings are in line with the existing evidence suggesting PSU among people with OUD to be associated with several adverse mental and physical health outcomes (e.g., major depressive disorders, PTSD, risky sexual practices) in comparison with those who use few or no substances other than opioids (26, 28, 43, 88, 93, 133).

The findings are of particular importance in the context of the ongoing opioid epidemic in the US and Canada, where research studies are often "opioid-centric" and may "miss the forest for the trees" by viewing OUD in a silo and excluding people who use multiple substances (27). Policies aimed at tackling the opioid epidemic are also often disproportionately focused on the effectiveness of and access to OUD treatment (e.g., various OAT and antagonist therapies), opioid-OD prevention (e.g., take-home naloxone kits, fentanyl drug checking services), and preventing access to non-medical PO (e.g., prescription drug monitoring) (1, 27, 141-143). This exclusive focus on OUD and a single drug class may be justified by the fact that the drugs of choice among most people with OUD are arguably natural

(e.g., heroin and its derivatives) or synthetic opioids (e.g., fentanyl and its analogues) (48, 144-146). While continued support of these life-saving interventions is essential, the findings suggest that the extent of interventions' effectiveness for certain subpopulations of people with OUD (e.g., those who primarily use stimulants, have concurrent alcohol use disorder, or benzodiazepine use disorder as well as people using other substances while on OAT) might be limited (147, 148). Recognizing these complexities and considering them in developing care and treatment packages for OUD are essential in addressing the unique needs of these particular subpopulations.

Predictors of membership in different PSU classes varied significantly across different studies. Among studies that did assess these predictors, membership in higher intensity or frequency of PSU was positively associated with a range of individual- (e.g., sharing needles, frequent IDU, high-risk sexual behaviours), and socio-structural-level exposures (e.g., history of incarceration, homelessness, hospitalization). Study findings regarding the sociodemographic predictors of class membership, however, were relatively inconsistent. While these assessments are informative in characterizing the negative or positive predictors of PSU classes, these findings need to be interpreted with caution for a number of reasons. First and foremost, PSU operationalization and the proportion of classes identified significantly varied across the studies. For example, studies used several approaches to measuring patterns of substance use and included an array of different substances from tobacco to fentanyl. Assessments were rarely based on validated metrics and mainly according to arbitrary self-reported measures in the past few days, weeks, months, lifetime, or a combination of several different timelines. Moreover, several studies included multiple indicators of a single type of substance (e.g., frequency, length, and route of use for a certain

substance). Additionally, some studies' identification of various classes of PSU was informed by the inclusion of sociodemographic or mental-health-related outcome indicators. These heterogeneities were often reflected in the final class solutions and led to challenges in summarizing the evidence or comparing classes across individual studies. Second, most studies assessed cross-sectional associations between particular behavioural characteristics of the participants with PSU classes, which could raise concerns about temporality bias and the establishment of causality. Lastly, several studies did not assess these associations and reported their final class solutions in a merely descriptive fashion and, therefore, provided a limited picture of potential predictors of class membership in their analysis.

2.4.1 Limitations

While the systematic review was methodologically rigorous and comprehensive, it is subject to certain limitations, primarily due to the methodological shortcomings of the individual studies included. First, while all studies included people with OUD, the sampling framework, sociodemographic, and behavioural characteristics of the participants were heterogeneous. Second, the operationalization of PSU patterns varied across the studies and made it challenging to make direct comparisons and estimate pooled effect measures. Moreover, I only focused on latent analytical approaches and did not include studies that used traditional clustering approaches (e.g., k-means, hierarchical cluster analysis) in the review. Third, the majority of the participants in the studies were male, White, and from North America, which limits the generalizability of the findings to other contexts where OUD is a significant public health concern (e.g., West and Southeast Asia). Furthermore, the findings of these studies should be interpreted with an eye to the rapidly changing risk environment of illicit opioid use across the world, North America in particular. Future studies on measuring

PSU among people with OUD would benefit from looking at how PSU classes may have evolved in the context of a toxic drug supply where people with OUD may be knowingly or accidentally exposed to synthetic opioids. Despite these methodological limitations, most studies were robust, had a large sample size, and were of reasonable quality. Overall, this systematic review provides an overview of various classes and predictors of PSU patterns among people with OUD and helps inform the clinical and public health interventions aimed at addressing the opioid epidemic.

2.4.2 Methodological issues

This review shows that using latent class and person-centred approaches to identifying distinct PSU patterns among various subgroups of people with OUD is useful and informative. However, the quality assessment of the studies identified several areas for improvement for future studies that aim to apply this method to subpopulations of PWUD. Most studies used unvalidated or unstandardized measurement approaches for substance use indicators. Several studies also did not report how missing data were handled in their study. Moreover, further clarity and consistency about all possible models' fit indices and final model selection procedures are essential in creating reproducible, reliable, and comparable results. These shortcomings have been repeatedly highlighted in previous reviews aimed at identifying clusters or classes of substance use (60, 99, 100, 132) and could be improved by following the existing reporting guidelines for these types of analyses (99, 100).

2.5 Conclusions

This systematic review summarized the evidence that applied person-centred approaches to the classification of PSU among people with OUD. While heroin and its

derivatives were the most common class, I found that PSU was the norm, not the exception. However, the heterogeneities among PSU classes of people with OUD were considerable. The findings call for further investments and research in developing treatments and interventions that go beyond focusing on the use of opioids among this population and apply a holistic and comprehensive approach to providing care for people with OUD. Applying methodologically rigorous and transparent techniques, as well as using standardized metrics for evaluating the frequency and severity of substance use patterns, are required to allow direct comparisons across the studies' findings and improve their generalizability.

Figure 2.1. PRISMA flow diagram

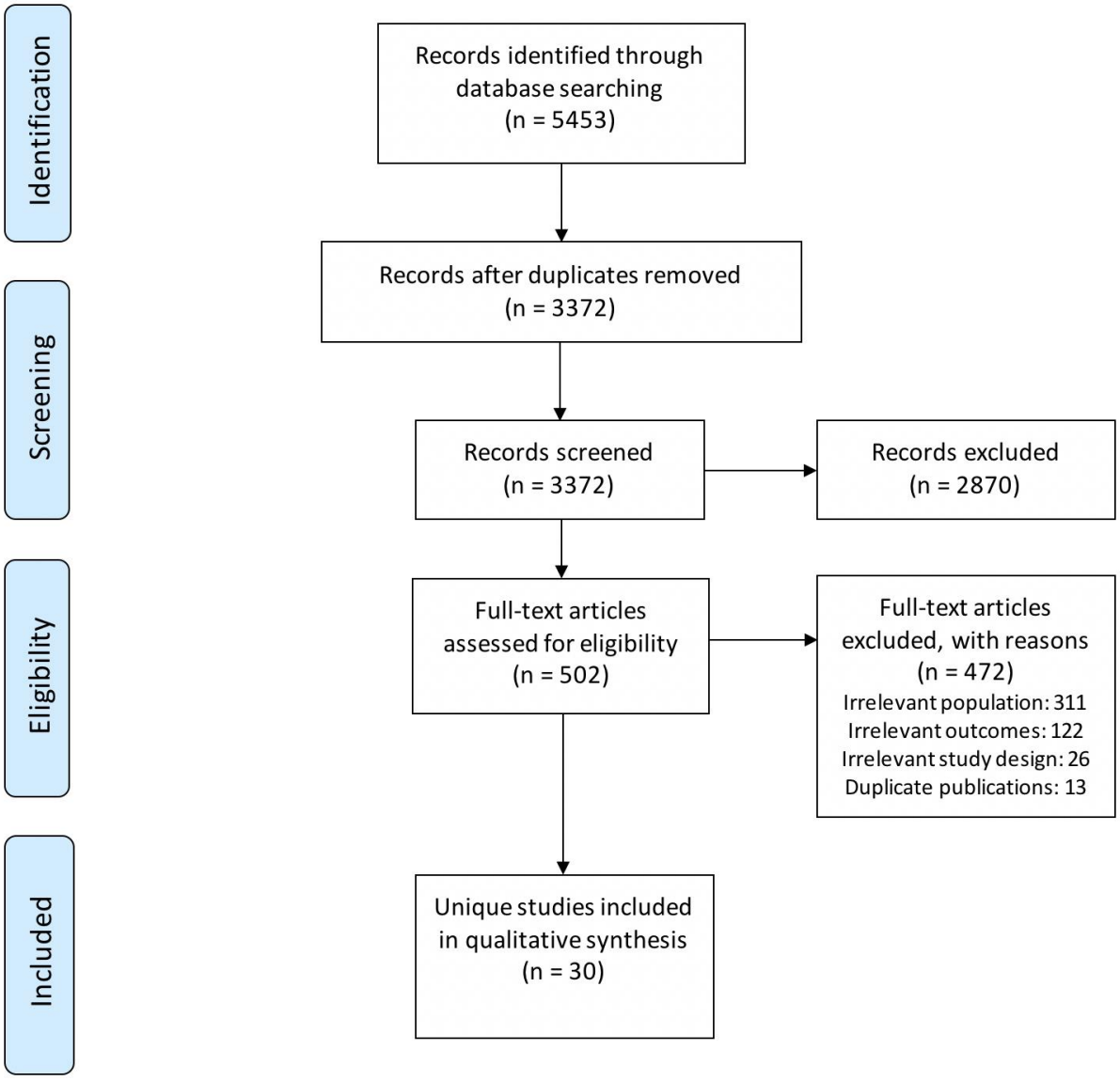


Table 2.1. An overview of the search strategy

Search concepts *Note: Search terms were combined using appropriate Boolean operators, and included keywords and subject heading terms relevant to three main concepts. Studies were limited to humans and no language restriction was applied.*	Polysubstance use (e.g., polydrug use OR polysubstance use OR concurrent drug use OR multiple drug use) AND opioid use disorder (e.g., opioid dependence OR heroin OR fentanyl OR morphine OR methadone OR oxycodone OR opioid agonist treatment) AND latent class approaches (e.g., latent class analysis OR LCA OR latent transition analysis OR LTA OR latent profile analysis OR LPA).
Databases *Note: Search terms were tailored to fit each database requirement.*	MEDLINE, Embase, CINAHL, PsycINFO, Web of Science, and Google Scholar (first 300 records) were systematically searched. I also hand-searched bibliographies of relevant published works and previous reviews, and relevant recent conference proceedings (i.e., Harm Reduction International Conference, American Psychiatric Association), and grey literature databases (i.e., OpenGrey, CADTH, European Monitoring Centre for Drugs and Drug Addiction) and theses.
Protocol registration	Open Science Framework (https://osf.io/6vjdf/).

Note: The review protocol was conceptualized and drafted in February 2020 and formally registered on the Open Science Framework in November 2020.

Table 2.2. Overview of included studies in the systematic review of latent polysubstance use among people with opioid use disorder

First author (Year)	Method (Study design)	Location	Participants	Age	Substance use characteristics	Inclusion/Exclusion Criteria	Quality Assessment
Afshar (2019)	LCA (Cross-sectional)	Chicago, U.S.	N = 6,224; 61.3% Men 48.8% White	≤25: 6.6% 26-25: 17.1% 36-45: 19.4% 46-55: 28.8% ≥55: 28.1%	***ED and inpatient encounters*** AUD (38.9%) Drug use (67.6%) Opioids (88.8%) UDS results: Non-prescribed opioids (14.5%) Cocaine (14.3%) Phencyclidine (1.8%) Benzodiazepines (10.1%) Amphetamines (1.7%)	***Inclusion criteria:*** Positive UDS for illicit or non-prescribed opiates, with or without PSU; and ≥18 years old. ***Exclusion criteria:*** UDS that were preceded by opioid or benzodiazepine prescription through the hospital pharmacy.	Very good
Anderson (2018)	LCA (Cross-sectional)	Northeast Ohio, U.S.	N = 375; 61.3 % Male; 93.2% White	M (SD): 35.6 (11.4)	***SUD (DSM-III)*** Opioids (76.0%) Alcohol (56.0%) Sedatives (24.0%) Amphetamines (12.6%) Cocaine (26.1%) Tobacco (81.6%) Cannabis (52.5%)	***Inclusion criteria:*** Adults seeking medically assisted detoxification in an inpatient crisis centre in Northeast Ohio. ***Exclusion criteria:*** NR.	Good
Betts (2016)	LCA (Cross-sectional)	Australia	N= 2,673; 65.8% Male; Ethnicity: NR	17-35: 35.9% 36-45: 38.4% 46-71: 25.7%	***L6M Substance Use*** Opioid substitution treatment (37.8%)	***Inclusion criteria:*** 16 years of age or older; report injecting an illicit drug at least monthly during L6M.	Good

First author (Year)	Method (Study design)	Location	Participants	Age	Substance use characteristics	Inclusion/Exclusion Criteria	Quality Assessment
					L6M (daily) Heroin (15.2%) Methadone (24.4%) Methamphetamine (2.3%) ***L6M (weekly)*** Heroin (29.8%) Methadone (10.2%) Methamphetamine (17.1%)	***Exclusion criteria:*** NR.	
Bobashev (2018)	LPA (cross-sectional)	Ohio, U.S.	N = 200; 68% Male; 74% White 20% Latin 3% Black 2% Native American 1.5% Other	M (SD): 38.0 (10.2)	***LM Substance Use*** Heroin (98%) Alcohol (46%) Cannabis (43%) Crack cocaine (38%) Cocaine (20%) Crystal methamphetamine (7%) ***Mean (SD) Days Used in Past Month*** Heroin: 25.6 (8.6) Cocaine: 2.1 (6.5) Crack cocaine: 4.7 (9.4) Crystal methamphetamine: 0.6 (3.4) Prescription pills: 2.9 (6.8)	***Inclusion criteria:*** Accessing services at a syringe exchange program. ***Exclusion criteria:*** NR.	Satisfactory

First author (Year)	Method (Study design)	Location	Participants	Age	Substance use characteristics	Inclusion/Exclusion Criteria	Quality Assessment
					Cannabis: 5.5 (9.8) Alcohol: 5.3 (9.7)		
Bunting (2020)	LCA (Cross-sectional)	Kentucky, U.S.	N = 6,569 81.9% Male 60.7% White	M (SD): 32.7 (8.1)	***LM*** Use alcohol to cope: 27.5% Use prescription drugs to cope: 50.7% Use illegal drugs to cope: 71.7% Lifetime IDU: 65.7%	***Inclusion criteria:*** Individuals entering Kentucky Department of Correction jails or prisons in need of substance abuse treatment between 2015-2017; used opioids in the 12-months before incarceration; and used more than one substance on a given day in the month before incarceration ***Exclusion criteria:*** NR.	Good
Carlson (2014)	LCA (Cross-sectional)	Ohio, U.S.	N = 390; 54.6% Male; 49.2% White 44.8% African American 1.5% Hispanic 1.5% Pacific Islander 3% Other	M (SD): 21 (1.7)	***L6M Substance Use*** Immediate-release Oxycodone (92.3%) Hydrocodone (83.6%) Oxycodone (29.0%) Codeine (25.9%) Morphine (7.7%) Other pain medications (7.7%) Hydromorphone (6.7%) Methadone (6.4%)	***Inclusion criteria:*** 18-23 years; self-reported non-medical use of pharmaceutical opioids on five or more occasions in L3M; expressed intention to use pharmaceutical opioids again; residence in Columbus, Ohio metropolitan area; identified which drugs they have used based on provided images.	Very good

First author (Year)	Method (Study design)	Location	Participants	Age	Substance use characteristics	Inclusion/Exclusion Criteria	Quality Assessment
					Buprenorphine/naloxone (4.4%) Fentanyl (1.3%) Oxymorphone (0.3%)	***Exclusion criteria:*** Reported any heroin use or illicit IDU; has pending criminal charges; has previously accessed substance use disorder treatment.	
Chen (2018)	LCA (Longitudinal)	Shanghai, China	N= 564, N=503 follow-up 47.3% Male; Ethnicity: NR	M (SD): 33.6 (7.92)	***LM Substance Use*** Heroin (35.0%) Alcohol (41.0%) Other opioids (9.7%) Cocaine (1.2%) Tranquilizers (15.5%) ATS (33.0%) Cannabis (14.3%) Hallucinogens (7.4%) Inhalant (0.6%)	***Inclusion criteria:*** Patients enrolled into the compulsory treatment facilities in Shanghai; ≥18 years; met DSM-IV criteria for heroin dependence; used heroin in the LM ***Exclusion criteria:*** NR.	Good
Daniulaityte (2019)	LCA (Cross-sectional)	Ohio, U.S.	N = 356 50.3% Male; 88.8% White	M (SD): 39.2 (9.6)	***L6M Substance Use*** Heroin/fentanyl use (67.3%) NPB (37.6%) Alcohol (9.0%) Cannabis (25.0%) Cocaine (powder or crack) (25.3%)	***Inclusion criteria:*** ≥18 years; current moderate to severe OUD(DSM-5); residence in the Dayton, Ohio, or surrounding counties; and non-prescribed buprenorphine use during L6M ***Exclusion criteria:*** NR.	Very good

First author (Year)	Method (Study design)	Location	Participants	Age	Substance use characteristics	Inclusion/Exclusion Criteria	Quality Assessment
					Non-prescribed benzodiazepines (13.2%) Non-prescribed gabapentin (13.8%) Methamphetamine (16.0%)		
De Nadai (2019)	LCA (Cross-sectional)	U.S. (national)	N = 36,309 43.7% Male; 52.9% White 21.4% Black 19.4% Hispanic/other	M (SD): 45.6 (17.5)	Prevalence of P-OUD for the sample was 2.1%. Further info NR.	***Inclusion criteria:*** Civilians; non-institutionalized U.S. residents; and ≥18 years ***Exclusion criteria:*** Homeless or incarcerated people	Good
Eastwood (2017)	LCA (Cross-sectional)	England (national)	N=54,357; 75.% Male, 86.5% White	M (SD): 32.9 (7.8)	***IDU*** Never (33.6%) Lifetime (34.2%) Current (32.2%) ***Length of Heroin Use Career*** (Mean years, SD): 11.4 (7.5)	***Inclusion criteria:*** ≥18 years; diagnosed with OUD; and presented for treatment in England between 1 April 2008 and 31 March 2009 ***Exclusion criteria:*** NR.	Good
Eastwood (2019)	Multi-level, Latent Class Growth	England (national)	N = 7,719 Sex/Gender: NR Ethnicity: NR	Med (IQR): 41 (23-71)	***LM*** Heroin (85.8%) Alcohol (41.7%) Crack (40.3%)	***Inclusion criteria:*** Patients who initiated OAT between 1 April 2008 and 31 March 2009 and were enrolled for five years, ending 31	Good

First author (Year)	Method (Study design)	Location	Participants	Age	Substance use characteristics	Inclusion/Exclusion Criteria	Quality Assessment
	Analysis (longitudinal)				Cannabis (27.2%) Unspecified drug (19.7%) Cocaine powder (4.7%) Amphetamines (4.1%)	March 2014 and followed-up to 30 September 2016; and either continuously enrolled in OAT or there was no more than 21 days between the end of one prescribing episode and the initiation of another. ***Exclusion criteria:*** NR.	
Fong (2015)	LCA (Cross-sectional)	33 States, U.S.	N = 19,101 54% Male; 82% White	M (SD): 34 (10)	***LM Substance Use*** Heroin (56%) Only heroin (26%) PO (74%) Only PO (44%) Heroin and PO (29%)	***Inclusion criteria:*** Admitted to one of 85 OUD treatment programs across 33 states between February 2011 and December 2013. ***Exclusion criteria:*** NR.	Good
Gicquelais (2019)	LCA (Cross-sectional)	Baltimore, U.S.	N = 671; 76% Male; 74% African American 24% White	Med (IQR): 52.7 (45.5-58.0)	***L6M Substance Use*** Injected cocaine (26.2%) Injected heroin (42.5%) Speedball (34.4%) Injected PO (6.0%) Snorted heroin (51.3%) Snorted cocaine (17.1%) Smoked crack (60.7%)	***Inclusion criteria:*** ≥18 years old; reported a history of IDU; used cocaine, crack, heroin during L6M; used PO, sedatives, or tranquilizers obtained outside of the medical setting during L6M.	Good

First author (Year)	Method (Study design)	Location	Participants	Age	Substance use characteristics	Inclusion/Exclusion Criteria	Quality Assessment
					Oral nonmedical PO use (19.7%) Oral nonmedical prescription sedative and/or tranquilizer use (26.5%) Alcohol use (62.6%) Cannabis use (27.3%) Lifetime use of street fentanyl (39.5%)	***Exclusion criteria:*** Missing data (e.g., HIV viral load, homelessness, OD).	
Gjersing (2018)	LCA (Longitudinal)	7 cities (Oslo, Bergen, Trondheim, Stavanger, Sandnes, Tromso, and Kristiansand) in Norway	N = 884 75% Male; Ethnicity: NR	M (SD): 41.54 (10.2)	***LM Substance Use*** methamphetamine daily; IDU (21%) Amphetamine; non-IDU (23%) Heroin daily; IDU (24%) Heroin; non-IDU (19%) Prescription drugs daily; IDU (3%) Prescription drugs daily; non-IDU (32%) Alcohol daily (9%) Cannabis daily (34%)	***Inclusion criteria:*** Street- or low-threshold individuals who reported illegal opioid and/or stimulant use during LM. ***Exclusion criteria:*** NR.	Good
Harrell (2012)	LCA (Cross-sectional)	Baltimore, U.S.	N = 552 58% Men;	Med (IQR): 33 (147)	***LM Substance Use*** 20+ Cigarettes (48.8%)	***Inclusion criteria:*** Participants who reported using cocaine or	Good

First author (Year)	Method (Study design)	Location	Participants	Age	Substance use characteristics	Inclusion/Exclusion Criteria	Quality Assessment
			50% Black 50% White		Alcohol (59.6%) Heroin – IDU (52.9%) Crack cocaine – smoking (43%) Marijuana – smoking (36.7%) Heroin – nasal (36.9%) Cocaine – IDU (30.5) Speedball –IDU (28.4%)	heroin in the L6M and were 18-50 years old ***Exclusion criteria:*** NR	
Hautala (2017)	LCA (Cross-sectional)	San Juan, Puerto Rico	Rural N = 315 90.8% Male; Ethnicity: NR Urban N = 455 82.5% Male; Ethnicity: NR	Rural M (SD): 41.8 (147) Urban M (SD): 40.7 (147)	***Rural [Non-IDU (weekly)]*** Binge Drinking (21.6%) Marijuana (32.2%) Benzodiazepine (23.2%) Crack Cocaine (11.5%) ***Rural [IDU (weekly)]*** Cocaine (29.3%) Heroin (35.6%) Speedball (85%) ***Urban [Non-IDU (weekly)]*** Binge Drinking (24.6%) Marijuana (19.8%) Benzodiazepine (16.5%) Crack Cocaine (16.3%) ***Urban [IDU (weekly)]*** Cocaine (26.4%)	***Inclusion criteria:*** People who injected drugs in the L12M; ≥18 years; able to complete the survey in either English or Spanish; and able to provide informed consent. ***Exclusion criteria:*** NR.	Satisfactory

First author (Year)	Method (Study design)	Location	Participants	Age	Substance use characteristics	Inclusion/Exclusion Criteria	Quality Assessment
					Heroin (39.1%) Speedball (90.3%)		
Kuramoto (2011)	LCA (Cross-sectional)	Baltimore, U.S.	N= 1061 63% Male Ethnicity: 94% African-American	M (SD): 39 (7)	***L6M (Weekly)*** Alcohol use (53%) Marijuana use (20%) Heroin IDU (59%) Heroin snorting (38%) Speedball IDU (47%) Cocaine IDU (12%) Cocaine snorting (45%) Crack smoking (36%)	***Inclusion criteria:*** at least weekly contact with drug users; ≥18 year; willing to become peer educators; willing to bring in a risk network member for assessment; and were not recently enrolled in other HIV behavioural interventions. ***Exclusion criteria:*** NR.	Good
Liu (2020)	LCA (Cross-sectional)	18 states, U.S.	N= 120,706 61.4% Male; Ethnicity: NR	25-44: 50.3%	***Substances at Discharge*** Heroin (45.8%) Non-heroin, opioid (39.7%) Tobacco (20%) Benzodiazepines (9.4%) Psychoactive/psychotropic (7.3%) Cocaine (6.4%) Alcohol (6.2%) Marijuana (5.8%)	***Inclusion criteria:*** ED visitors 11 years or older; ED encounter from unintentional or undetermined poisonings from known "drugs of abuse". ***Exclusion criteria:*** ED visits with only ICD-10-CM diagnosis codes that did not provide information on the type of drug and/or drugs not usually abused to get a euphoric or analgesic sensation.	Satisfactory

First author (Year)	Method (Study design)	Location	Participants	Age	Substance use characteristics	Inclusion/Exclusion Criteria	Quality Assessment
Meacham (2018a)	LTA	Tijuana, Mexico	N = 735; N=572 (148) 62% Male; Ethnicity: NR	M (SD): 37.4 (8.9)	***L6M Substance Use (Baseline, FU)*** Heroin IDU (95%, 82%), Heroin and methamphetamine co-injection (56%, 51%), methamphetamine smoking (41%, 38%), methamphetamine IDU (28%, 31%)	***Inclusion criteria:*** Injecting illicit drugs within the LM confirmed by track marks; ≥18 years; speaking Spanish or English; and current residence in Tijuana with no plans to move for three years. ***Exclusion criteria:*** NR.	Good
Meacham (2018b)	LCA (Cross-sectional)	Tijuana, Mexico	N = 735 62% Male Ethnicity: NR	M (SD): 37.4 (8.9)	***L6M Substance Use (Baseline)*** Heroin IDU (95%), Heroin and methamphetamine co-injection (56%), Methamphetamine smoking (41%), Methamphetamine IDU (28%) Marijuana smoking (31%) PO (<5%)	***Inclusion criteria:*** Injecting illicit drugs within the LM confirmed by track marks; ≥18 years; speaking Spanish or English; and current residence in Tijuana with no plans to move for three years. ***Exclusion criteria:*** NR.	Good
Meacham (2015)	LCA (Cross-sectional)	Tijuana, Mexico	N = 1025 85.5% Male Ethnicity: NR	M (SD): 36.6 (8.39)	***L6M Substance Use*** Cocaine IDU (9.1%)	***Inclusion criteria:*** Injecting illicit drugs within the LM confirmed by track marks; ≥18 years; speaking	Good

First author (Year)	Method (Study design)	Location	Participants	Age	Substance use characteristics	Inclusion/Exclusion Criteria	Quality Assessment
					Cocaine non-IDU (7.4%) Methamphetamine IDU (33.7%) Methamphetamine non-IDU (38.8%) Speedball (heroin/cocaine) (11.7%)	Spanish or English; and current residence in Tijuana with no plans to move for 18 months. ***Exclusion criteria:*** NR.	
Monga (2007)	LCA (Cross-sectional)	Several cities, Canada	N= 679 66.5% Male Ethnicity: NR	M (SD): 34.7 (9.4)	***LM Substance Use*** Alcohol (64.7%) Cannabis (63%) Cocaine; IDU (43.1%) Cocaine; non-IDU (14.1%) Crack; IDU (6.6%) Crack; non-IDU (52.4%) Dilaudid (33.2%) Heroin; IDU (56.6%) Heroin; non-IDU (16.2%) Illicit Methadone (21.1%) Tylenol (32.6%) Valium (35.9%)	***Inclusion criteria:*** Used illegal opioids for a minimum of 1 year on the majority of days in the week; and not been in a drug treatment program in the previous L6M. ***Exclusion criteria:*** NR.	Good
Nielsen (2011)	LCA (Cross-sectional)	Four jurisdictions, Australia	N = 192; 63% Male; Ethnicity: NR	M (SD): 32.1 (8.3)	***LM Substance Use*** Problematic alcohol use (17.1%) Methamphetamine (50%)	***Inclusion criteria:*** ≥16 years; entered treatment for drug or alcohol use in L6M; reported	Unsatisfactory

First author (Year)	Method (Study design)	Location	Participants	Age	Substance use characteristics	Inclusion/Exclusion Criteria	Quality Assessment
					MDMA (14%) Benzodiazepine (illicit) (76.5%) Cannabis (59.9%) Pharmaceutical opioid (illicit) (67.7%) Days used heroin (Mean: 14.2) Days used PO (Mean: 17.8)	misuse of any pharmaceutical at least once a month in the L6M; and ability to communicate in English to enable informed consent and comprehension of study questions. ***Exclusion criteria:*** NR.	
Patra (2009)	LCA (Cross-sectional)	Several cities, Canada	N = 582 Sex/Gender: NR Ethnicity: NR	M (SD): 35.2 (9.7)	***LM*** Alcohol (60.1%) Cannabis (61.7%) Heroin (30.1%) Illicit Methadone (8.4%) Morphine (22.5%) Oxycontin (22.5%) Tylenol (29.7%) Cocaine (39.2%) Benzodiazepines (35.6%)	***Inclusion criteria:*** Regular illicit opioid users; and people not enrolled in any drug treatment program at original assessment. ***Exclusion criteria:*** NR.	Good
Peacock (2015)	LCA (Cross-sectional)	Several cities, Australia	Wave 1: N = 606 Wave 2: N = 547	Med (IQR): 31 (41-47)	***Dependence*** 51% pharmaceutical opioid dependence; 40% Heroin dependence;	***Inclusion criteria:*** ≥18 years; English language proficiency; self-reported extra-medical pharmaceutical opioid use on a monthly or more frequent basis in	Very good

First author (Year)	Method (Study design)	Location	Participants	Age	Substance use characteristics	Inclusion/Exclusion Criteria	Quality Assessment
			69% Male; Ethnicity: NR		26% Methamphetamine dependence; 19% Benzodiazepine dependence; 38% Risky alcohol consumption (based on AUDIT)	L6M; and self-reported injecting, snorting, chewing, smoking or dissolving/drinking a pharmaceutical opioid in LM and at least monthly in L6M. ***Exclusion criteria:*** Had not been a resident of the city/state for L6M; had been in prison for LM; and had only tampered with an OAT medication, or reported only using their opioid medication as per a doctor's instructions.	
Roth (2015)	LCA (Cross-sectional)	San Diego, U.S.	N = 511 73.8% Male; 51.5% White	M (SD): 43.5 (11.7)	Mean length of IDU career: 21.1 Ever used synthetic drugs: 31.8% Lifetime drug treatment: 78.7% Ever OD: 42.1% Shared injection (L6M): 72.4% Median # of IDU partners (L6M): 2	***Inclusion criteria:*** ≥18 years; injected drugs within the LM; intended to reside in San Diego County for years; willing to provide contact information to maintain contact with study staff; and provided blood for HIV and HCV test. ***Exclusion criteria:*** NR.	Good

First author (Year)	Method (Study design)	Location	Participants	Age	Substance use characteristics	Inclusion/Exclusion Criteria	Quality Assessment
Schneider (2019)	LCA (Cross-sectional)	Baltimore City, U.S.	N = 298 68.8% Male; 57.7% Black 37.3% White 5% Other	18-44: 45.4% ≥45: 54.7%	***LM Substance Use*** Marijuana (42.6%) Crack; smoked (47.3%) Heroin; smoked/snorted (30.5%) Heroin; IDU (89.9%) Cocaine; smoked/snorted (13.4%) Cocaine; IDU (47.0%) Speedball; IDU (54.4%) Pain Relievers (ingested) (24.2%) Pain Relievers (injected) (9.1%) Tranquilizers (ingested) (25.5%) Buprenorphine (ingested) (12.8%)	***Inclusion criteria:*** ≥18 years; able to provide consent orally in English; and had ever injected drugs. ***Exclusion criteria:*** NR.	Satisfactory
Schneider (2020)	LCA (Cross-sectional)	West Virginia, U.S.	N = 420 61.2% Male; 83.6% White	M (SD): 35.8 (8.5)	***Last 6M IDU*** Stimulants (76.9%) Opioids (85.7%) Speedball (38.3%) Fentanyl (54.8%) Buprenorphine/Suboxone (30.2%) ***Last 6M Non-IDU***	***Inclusion criteria:*** ≥18 years; and ever used drugs of any form and by any route of administration. ***Exclusion criteria:*** Excluded one survey from a transgender participant to preserve their anonymity.	Satisfactory

First author (Year)	Method (Study design)	Location	Participants	Age	Substance use characteristics	Inclusion/Exclusion Criteria	Quality Assessment
					Stimulants (78.1%) Opioids (47.6%) Sedatives/Tranquilizers (41.7%) Buprenorphine/Suboxone (29.1%) ***Last 6M*** OD (42.6%) Take-Home Naloxone (46.5%)		
Tavitian-Exley (2018)	LCA (Cross-sectional)	Kohtla-Järve (Estonia) and St Petersburg (Russia)	N = 1402 76% Male; 58% Russian	<30: 38%	***Last 6M Substance Use*** Primarily injected opiates (82%) Primarily injected ATS (16%) No primary drug (2%)	***Inclusion criteria:*** ≥18 years; injected drugs in LM; lived in St Petersburg or Kohtla-Järve; and provided informed consent. ***Exclusion criteria:*** NR.	Good
Wu (2011)	LCA (Cross-sectional)	Several cities, U.S.	N = 343 68% Male; 45% White 31% African-American 20% Hispanic	M (SD): 37.5 (10.1)	***Abuse/Dependence*** Nicotine (41%); Cocaine (28%); Alcohol (24%); Cannabis (17%); Sedative (6%); Amphetamine (5%); Hallucinogen (1.5%); Inhalant (0.3%)	***Inclusion criteria:*** ≥18 years; met DSM-IV criteria for opioid dependence; and in need of medical management for opioid withdrawal. ***Exclusion criteria:*** Serious psychiatric/medical conditions; known allergy or sensitivity to buprenorphine, naloxone, or	Very good

First author (Year)	Method (Study design)	Location	Participants	Age	Substance use characteristics	Inclusion/Exclusion Criteria	Quality Assessment
						clonidine; were receiving medications contraindicated with clonidine or had a systolic blood pressure <100 mm Hg or pulse <56 beats per minute; had been enrolled in a methadone treatment program or had participated in another investigational drug study in LM; could not remain in the area for the duration of active treatment; and pregnant or lactating women.	

Notes: AUD: Alcohol Use Disorder; ED: Emergency Department; UDS: Urine Drug Screen; ATS: Amphetamine-Type Stimulant; PO: Prescription Opioids; OUD: Opioid Use Disorder; LCA: Latent Class Analysis; LPA: Latent Profile Analysis; LTA: Latent Transition Analysis; M (SD): Mean (Standard Deviation); Med (IQR): Median (Interquartile Range); NR: Not Reported; LM: Last Month; L6M: Last 6 months

Table 2.3. Polysubstance use classes identified across the studies included in the review

PSU classes	Characteristics
Infrequent/low PSU	This class was identified in 16 studies and was characterized by low indicator probabilities for PSU. Primary subpopulations identified in this class included people with low use of PO or non-PO and those with no or infrequent substance use. The proportion of this class varied considerably, ranging from 7.7% to 90%.
Primarily heroin use	This class was identified in 22 studies and was characterized by PSU with injection or non-injection use of heroin as a substance of choice. Primary subpopulations identified in this class included people who primarily use heroin and opioid agonist treatment medications, heroin and alcohol use or heroin and PO. The proportion of this class ranged from 7% to 80.2%.
Primarily heroin and stimulant use	This class was identified in 15 studies and was characterized by PSU with injection or non-injection use of heroin and stimulants as substances of choice, either concurrently or separately over a defined period of time. Primary subpopulations identified in this class included people who primarily used heroin and cocaine (speedball or co-use separately), heroin and crack or heroin and methamphetamine (goofball or co-use separately). The proportion of this class ranged from 6.1% to 67%.
Primarily stimulant use	This class was identified in 13 studies and was characterized by PSU with injection or non-injection use of stimulants as substance of choice. Primary subpopulations identified in this class included people who primarily use amphetamine-type substances or Crack and cocaine. The proportion of this class ranged greatly from 8.5% to 67%.
Frequent PSU	This class was identified in nearly all included studies and was characterized by PSU with high-frequency injection or non-injection use of multiple drugs simultaneously or separately over a specified period. Primary subpopulations identified in this class included people with PSU of different substances via various routes of administration, PSU including alcohol, or PSU including prescription drugs. The proportion of this class ranged from 1.5% to 53%.

Notes: PSU: Polysubstance use; PO: Prescription Opioids

Table 2.4. Summary of findings of the studies included in the review of latent polysubstance use among people with opioid use disorder

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
Afshar (2019)	Identify subgroups of patients with opioid misuse and assess association with health outcomes	Age, Sex, Race, Insurance coverage, Elixhauser mortality score, Comorbidities, Health service use, Health service encounters, Urine drug screen results, Prior health care encounters, Poverty level, Education, Housing status	Hospital utilization, socioeconomic status, mental illness, substance use type, and opioid use type	***Class 1:*** High hospital utilization with known opioid-related conditions (36.5%) ***Class 2:*** Illicit use, low SES, and psychoses (12.8%) ***Class 3:*** AUD with complications (38.2%) ***Class 4:*** Low hospital utilization and incidental opioid misuse (11.5%)	*Class 1 had greatest proportion with 30-day unplanned hospital readmission at 13.9%. *Class 2 had greatest proportion of being discharged to inpatient psychiatry services and leaving against medical advice. *Class 4 had the greatest proportion with naloxone administration in the hospital and in-hospital death but the lowest proportion with readmission. *Detailed predictors of latent class membership not reported.
Anderson (2018)	Examine how PTSD, multiple SUD, and MDD may co-occur in a sample of adults seeking medically-supervised detoxification and to examine differences between identified subgroups on key	Trauma history, PTSD diagnostic status, Depression, Problematic substance use, Negative consequences of alcohol or drug use	At admission: PTSD, MDD, opioid, alcohol, sedative, amphetamine, cocaine, tobacco, and cannabis use	***Class 1:*** Probable PTSD; MDD; opioid, tobacco, cannabis use disorder (23.7%) ***Class 2:*** Probable MDD; alcohol, opioid, tobacco, and cannabis use disorder (25.1%)	*Class 1 reported more severe opioid, cannabis, sedative, and cocaine use disorder than other classes; greater PTSD and MDD symptoms; and more likely to be female. *Greater psychiatric comorbidity is associated with more severe addiction problems. *Detailed predictors of latent class membership not reported.

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
	clinical characteristics relevant to PTSD.			***Class 3:*** Alcohol & tobacco use disorder (22.7%) ***Class 4:*** Opioid & tobacco use disorder (28.5%)	
Betts (2016)	To identify PSU profiles between two groups of PWID, those receiving and not receiving OAT and compare associations among the resulting classes on a range of factors	OAT treatment, Sex, Age, Relationship status, Employment, Housing status, Education	OAT type, PSU pattern	**OAT** ***Class 1:*** Methadone/heroin, low PSU (38.5%) ***Class 2:*** Methadone/heroin, high PSU (16.7%) ***Class 3:*** Buprenorphine, low PSU (23.3%) ***Class 4:*** Methadone, moderate PSU (21.5%) **No OAT** ***Class 5:*** PSU (28.4%) ***Class 6:*** Heroin use (29.5%) ***Class 7:*** Morphine use (17.1%)	*PSU profiles were generally at increased odds of negative drug-related outcomes for both people on or off OAT. *PSU was associated with thrombosis among OAT receivers (OR=2.13), injecting with used needles among OAT receivers (OR=2.78) and non-receivers (OR=2.78), and violent criminal offences among OAT receivers (OR=2.30) and non- receivers, (OR=1.87). *Non-fatal OD was related specifically to a class of PWID who were not receiving OAT and used morphine frequently (OR=1.83).

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
				Class 8: Methamphetamine use (25.5%)	
Bobashev (2018)	To investigate patterns of polydrug use among participants of a syringe service in order to identify subpopulations who demonstrate distinct patterns of polydrug use and examined demographic and attitudinal correlates	Age, Sex, Ethnicity, Employment, Lifetime and LM frequency of drug use, Locations of use, Treatment history, HIV/HCV risk, Ways that drugs are obtained, Drug use types, Drug combinations in lifetime and L6M, Distress when not being able to use drugs, Cost of drugs, Availability of drugs, Risk of arrest, Overall health risks, Daily desire to use drugs	Lifetime simultaneous use, binary past-month use, patterns of substance use, and frequency of substance use	***Class 1:*** Heroin and alcohol use (10.5%) ***Class 2:*** Heroin and stimulant use (9%) ***Class 3:*** Mostly heroin use (56%) ***Class 4:*** Heroin and cannabis (13%) ***Class 5:*** Part-time or occasional drug use (11%)	*Drug use frequency was correlated with anxiety when drugs were unavailable. * Polydrug use was facilitated by perceived availability of heroin and cocaine. * Class 1 reported prescription medication use before heroin use, and initiated heroin chronologically earlier. *Class 3 represented that largest group and were generally younger than other classes and reported recent chronological heroin initiation * Class 2 were more likely to be Latino/a and more educated than other classes. * Class 4 consisted of younger participants. *Detailed predictors of latent class membership not reported.
Bunting (2020)	Identify PSU patterns among a justice-involved population	Age, Education, Sex, Ethnicity, Rurality, Employment,	*LM* Alcohol, cocaine, cannabis, heroin,	***Class 1:*** Primarily Alcohol (9.4%)	*Compared to Class 3* *Class 1: Older (OR=1.02); male (OR=1.76); alcohol (OR=27.68); # of convictions

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
		Homelessness, Economic hardship, HCV, Chronic pain, Physical health, Anxiety, Depression, Mental health, Alcohol, Illegal drugs, Incarceration, Arrest history	buprenorphine, non-medical PO, amphetamines, and tranquilizers	***Class 2:*** Primarily Heroin (32.2%) ***Class 3:*** Less PSU (34.3%) ***Class 4:*** Tranquilizer PSU (16.3%) ***Class 5:*** Primarily Buprenorphine (7.8%) ***Class 6:*** Stimulant Opioid (13.1%)	(OR=1.01); unemployed pre-prison (OR=0.77); prescription drugs (OR=0.68); illegal drugs (OR=0.38); history of arrests for drug crimes (OR=0.74). *Class 2: Younger (OR=0.98); urban living pre-prison (OR=0.24); economic hardship (OR=1.07); lifetime IDU (OR=5.12); alcohol (OR=0.76); prescription drugs (OR=0.73); illegal drugs (OR=2.54); arrests for violent crimes (OR=0.62); arrests for drug crimes (OR=0.79). *Class 4: Lower education (OR=0.94); rural living pre-prison (OR=1.27); lifetime IDU (OR=1.46); anxiety (OR=1.04); alcohol (OR=1.69); prescription drugs (OR=2.90); # of convictions (OR=1.01). *Class 5: Younger (OR=0.98); lower education (OR=0.93); male (OR=1.56); White (OR=1.46); rural living pre-prison (OR=2.71); economic hardship (OR=1.05); lifetime IDU (OR=2.06); anxiety (OR=1.04); prescription drugs (OR=1.79); chronic pain (OR=0.77), depression (OR=0.96); arrests for drug crimes (OR=0.56).

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
					*Class 6: Male (OR=1.41); homeless pre-prison (OR=1.42); lifetime IDU (OR=1.53); HCV+ (OR=1.31); lower education (OR=0.94); urban living pre-prison (OR=0.61); depression (OR=1.05); chronic pain (OR=0.78); alcohol (OR=2.92); illegal drugs (OR=1.42); # of convictions (OR=1.01); arrests for property crimes (OR=1.45).
Carlson (2014)	Describe the heterogeneity in the pattern of non-medical pharmaceutical opioid use among a 18-23-year-old people who use non-medical pharmaceutical opioids but are not opioid-dependent	Age, Years since opioid use, Number of days drunk, Sex, Education, Employment, Income, Relationship status, Housing, Source of opioids, Legitimate opioid prescription, Sold opioids, Given opioids away, Health status, has pain, pain disorder, ASPD, Depression, GAD, Mania, PTSD, Alcohol, Tranquilizers, Cigarettes, Cannabis,	Frequency of non-medical opioid use, OUD, oral opioid administration, different kinds of opioids used, used CNS depressants with opioids, used opioids to get high only, used opioids to self-medication only, and used opioids to get high and self-medicate	***Class 1:*** Non-white, high-frequency opioid use, high PSU (53%) ***Class 2:*** Non-white, weekly opioid use, low PSU (29%) ***Class 3:*** Non-white, less frequent opioid use, low OUD criteria, little PSU, oral opioid use (18%) ***Class 4:*** White, high-frequency opioid use, PSU (35%) ***Class 5:*** White, mixed frequency opioid use, low	*Class 1 membership associated with a larger mean number of days drunk in LM, mental health disorders, using other drugs such as cannabis and MDMA, higher alcohol dependence, and higher cannabis use dependence. *Class 4 had the highest proportion of participants reporting having pain and self-medicating. *Class 1 membership was associated with older age when compared to Class 2 (OR=1.27) and Class 3 (OR=1.32). *Class 4 membership associated with older age in comparison to Class 5 (OR=1.31), and higher education level when compared to Class 6 (OR=2.55).

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
		Cocaine, Stimulants, MDMA, LSD, Alcohol with opioids, Tranquilizers with opioids, Cannabis with opioids, Cocaine with opioids, Stimulants with opioids, Hallucinogens with opioids, Alcohol abuse, Alcohol dependence, Cannabis abuse, Cannabis dependence, Amphetamine abuse or dependence, Tranquilizer abuse or dependence, Cocaine abuse or dependence		oral opioid use, mixed moderate PSU (26%) ***Class 6:*** White, low-frequency opioid use, low opioid disorder criteria, oral opioid use (39%)	
Chen (2018)	Identify the latent classes of individuals who share homogenous patterns of using heroin, alcohol,	Sex, Age, Education, Employment, Homelessness, Marital status, Legal status, Physical health, Times of compulsory	*LM* Heroin use (by dosage), alcohol, other opiate/opioids, cocaine, tranquilizers/anti-	***Class 1:*** Alcohol & drug co-use (13.7%) ***Class 2:*** Low polydrug use (76.5%)	*Compared to Class 1* *Class 3 associated with an increased hazard of heroin relapse (HR=2.10). *Class 3 members were younger at recruitment, had a higher proportion of female participants, and had better social supports.

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
	amphetamine-type stimulants, cannabis, and other illicit drugs; to identify predictors of latent class membership; and assess the relationship between diverse latent classes and heroin relapse over a 5-year follow-up	treatment, Age at the onset of heroin use, IDU, Temperament, Social support	anxiolytic, amphetamine-type stimulants, cannabis, hallucinogens, inhalants	***Class 3:*** Amphetamine-type stimulant polydrug use (9.7%)	*Detailed predictors of latent class membership not reported.
Daniulaityte (2019)	Characterize heterogeneity in patterns of NBP and other opioid use among people living with OUD; and examine correlates of class membership	Age, Sex, Race, Education, Marital status, Employment status, Chronic pain, MDD, Generalized anxiety disorder, PTSD, History of NPB and other opioid use and mode of administration, SUD treatment, history of buprenorphine-based treatment, Source of NPB, Frequent use of	*L6M* Days of NPB use, Days of heroin/fentanyl use, Ever using NPB to get high, Ever using non-prescribed pain pills, Ever using prescribed pain pill, and SUD treatment, Years since first NPB use, Years since the	***Class 1:*** Heavy heroin/fentanyl use and sporadic NPB use (61%) ***Class 2:*** More use of formal treatment, low NPB use (29%) ***Class 3:*** Intense NPB, less formal treatment (10%)	*Class 1 had a higher proportion of participants reporting IDU, a higher prevalence of frequent cocaine use, and the highest prevalence of unintentional OD and homelessness in the past 6-months. *Class 3 had the lowest prevalence of reported unintentional OD, hospitalization, incarceration, and homelessness. *There were no statistically significant differences in chronic pain and psychiatric comorbidity between classes. *Predictors of latent class membership not reported.

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
		other drugs in L6M, Adverse consequences in L6M	first use of any other illicit opioids		
De Nadai (2019)	Characterize common symptom patterns and highlight how they related to POUD to inform planning for clinic design and public policy	Age, Ethnicity, Sex	PO, Alcohol, tobacco, cannabis, cocaine, heroin, stimulant, sedative use disorder, antisocial personality disorder, bipolar disorder, MDD, generalized anxiety disorder, social phobia, panic disorder, agoraphobia, specific phobia, PTSD, and previous treatment	***Class 1:*** Low average POUD, mentally healthy (60.8%) ***Class 2:*** Low average POUD, depressed (15.2%) ***Class 3:*** Low average POUD, alcohol tobacco (15.0%) ***Class 4:*** Elevated POUD, alcohol-tobacco-cocaine (3.8%) ***Class 5:*** Elevated POUD, internalizing (2.3%) ***Class 6:*** Elevated POUD, bipolar (1.3%) ***Class 7:*** Very high POUD, Polysubstance/elevated psychopathology (1.1%)	*Compared to Class 1* *Increasing age was associated with lower odds of being assigned to classes 2-8. *Males were less likely to be in Class 2 (OR=0.27), Class 5 (OR=0.36), but more likely to be in Class 3 (OR=3.44) and Class 7 (OR=1.65). *American Indian/Alaska Native group were more likely to be in Class 4 (OR=4.87), Class 6 (OR=3.59), and Class 8 (OR=6.12). *Class 7 had higher rates of substance-related treatment-seeking behaviour and a higher prevalence of heroin use disorder. *Class 8 had a higher prevalence of every examined form of psychopathology, except MDD. *Class 7 and 8 had a higher proportion of participants who reported lifetime P-OUD.

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
				Class 8: Very high POUD, Polysubstance/very high psychopathology (0.4%)	
Eastwood (2017)	Estimate the effectiveness of OUD treatment in England and contrast the effectiveness of local treatment systems	Sex, Age, Ethnicity, Employment, Homelessness, Deprivation, IDU status, Length of opioid use career, Treatment history	*L6M* In remission from OUD, Abstinent from all opioids and crack cocaine, completed all opioid pharmacotherapy and psychosocial interventions, met all care plan goals, and no representation	***Class 1:*** Heroin and low likelihood of problem substance use (56%) ***Class 2:*** Heroin, problem crack cocaine and alcohol use (5%) ***Class 3:*** Heroin and crack cocaine use (33%) ***Class 4:*** Heroin, crack and cannabis use (6%)	*Compared to Class 1* *Class 2, 3, and 4 had a higher proportion reporting less employment and more homelessness. *Class 2 and 4 were less likely to receive opioid pharmacotherapy. *Class 4 was more likely to receive psychosocial interventions. *Class 2 was more likely to receive more in-patient services, less incarceration, but more drop-out. *Class 3 reported more incarceration, unsuccessful transfers and drop-outs, but fewer deaths; less likely to report treatment completion and no re-presentation in L6M. *Predictors of latent class membership not reported.

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
Eastwood (2019)	Identify trajectory of patients characterized by increasing use of alcohol, crack cocaine, cocaine powder, amphetamines, and unspecified drug use; and assess whether a positive and negative change in heroin use is associated with an increase in using alcohol and other drugs	Sex, Age, Ethnicity, Employment, Homelessness, Social deprivation score, Treatment admission latent drug use class, IDU status, Length of heroin use career, Treatment referral route, Other interventions (psychosocial, detoxification, or residential rehabilitation), Previous treatment for OUD	*LM* Heroin, alcohol, crack, cannabis, unspecified drug, cocaine powder, and amphetamine use	Group membership conditional on heroin use trajectory group: **Crack cocaine** ***Class 1:*** Gradual decreasing (9.5%) ***Class 2:*** Increasing (12.0%) ***Class 3:*** Continued low-level (59.3%) ***Class 4:*** Continued high-level (5.3%) ***Class 5:*** Rapid decreasing (13.9%) **Alcohol** ***Class 1:*** Continued high-level (17.1%) ***Class 2:*** Continued low-level (49.4%) ***Class 3:*** Increasing (15.9%) ***Class 4:*** Decreasing (17.6%) **Cannabis**	*Members of the 'continued high-level' heroin use class* *More likely to be members of the 'continued high-level' alcohol class (RRR=1.24), and less likely to be members of the 'decreasing' alcohol use class (RRR=0.57). *More likely to be members of the crack cocaine 'continued high-level' (RRR=58.7), 'increasing' (RRR=6.45), and 'gradual decreasing' (RRR=5.65) classes, but less likely to be in 'rapid decreasing' class (RRR=0.66). *Less likely to be members of the 'high and increasing' cannabis class (RRR=0.49). *More likely to be members of the 'increasing' unspecified drug class (RRR=1.70).

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
				Class 1: Continued low-level (59.2%) ***Class 2:*** Low and decreasing (23.8%) ***Class 3:*** High and increasing (17.1%) **Unspecific drug** ***Class 1:*** Increasing (13.6%) ***Class 2:*** Continued low-level (71.1%) ***Class 3:*** Decreasing (15.3%)	
Fong (2015)	Identify patterns of non-opioid substance misuse among cohort at the early stage of opioid treatment to inform the development of targeted treatment program initiatives	Age, Sex, Ethnicity, Tobacco use, Treatment history, Employment, Chronic pain, Bodily pain as a reason to enroll, Opioid injection, Urbanicity, Heroin use only, PO use only, Any non-opioid drug use	Heavy alcohol use, cannabis, MDMA/ecstasy, cocaine/crack cocaine, methamphetamine, hallucinogens, anti-anxiety medications, prescription sleep medications, muscle	Among those accessing OUD treatment: ***Class 1:*** No or comparatively low non-opioid substance use (73%) ***Class 2:*** Non-opioid prescription drug use (16%) ***Class 3:*** Cannabis and/or cocaine use (8.5%)	*Compared to Class 1* *Class 2: Male (OR=0.58); tobacco (1.25); employed (OR=0.68); chronic pain (OR=1.56); bodily pain as a reason for enrolment (OR=1.26); urban dweller (OR=0.82); PO use only (OR=0.80); heroin use only (OR=0.28). *Class 3: Older age (OR=0.77); male (OR=1.05); employed (OR=0.80); opioid injection (OR=1.56); urban dweller (0.86); PO use only (OR=0.60); heroin use only (OR=0.42).

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
			relaxants, and anti-depressants	***Class 4:*** Any polydrug use	*Class 4: Older age (OR=0.64); White (OR=0.47); tobacco use (OR=1.41), chronic pain (OR=1.53), bodily pain as a reason for treatment (OR=1.37), opioid injection (OR=1.86); PO use only (OR=0.41); heroin use only (OR=0.30).
Gicquelais (2019)	Identify predominant substance use typologies among a group of current and former PWID; and to examine the relationship of these typologies with sharing syringes and OD during L6M	OD, Syringe sharing, Obtaining syringes from a syringe program or pharmacy, Sex, Race, Age, Homelessness, Incarceration history, Income, Depressive symptoms, Frequency of alcohol consumption	*L6M* Cocaine (IDU), heroin (IDU), speedball, PO (IDU), crack (smoking), cocaine (snorting), heroin (snorting), illicit prescription sedatives or tranquilizers (ingestion), and illicit PO (ingestion)	***Class 1:*** Infrequent use (76%) ***Class 2:*** Prescription drug use (12%) ***Class 3:*** Heroin and/or cocaine injection (12%)	*Compared to Class 1* *Class 2 was positively associated with OD (OR = 4.3) and syringe sharing (OR = 1.9). *Class 3 were positively associated with OD (OR = 2.8), syringe sharing (OR = 2.4), and obtaining syringes from a syringe program or pharmacy (OR = 3.1).
Gjersing (2018)	Assess risk of mortality in a cohort of street- and low-threshold service-	Age, Sex, Homelessness, Informal income generation, Incarceration history,	*LM* IDU (daily & <daily): Amphetamine, heroin, prescription drugs	**On OAT** ***Class 1:*** Frequent methadone users (44%)	*On OAT:* *Class 1: high probability (98%) of frequent methadone use. * Class 2: high probability (93%) of frequent buprenorphine use.

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
	recruited people who engage in PSU	Years of injecting, OD history, Current OAT status, Use during the LM, Geographic location, Deceased	Non-IDU (daily & <daily): Alcohol, cannabis, amphetamine, heroin, prescription drugs, methadone, buprenorphine	***Class 2:*** Frequent buprenorphine users (39%) ***Class 3:*** OAT heroin injectors (17%) **No OAT** ***Class 4:*** Polysubstance injectors (21%) ***Class 5:*** Frequent heroin injectors (21%) ***Class 6:*** Low frequent injectors (58%)	*Class 3: high probability (62%) probability of frequent heroin injecting, non-IDU prescription drug use (82%), and amphetamine IDU (57%). Class 3 had a higher probability of homelessness and OD experience (91). *No OAT:* *Class 4: 42% probability of heroin IDU and frequent use of amphetamine, 63% probability of prescription drugs IDU. *Class 5: 100% probability for frequent heroin IDU. Class 6: Lower probability of homelessness or shelter use and dealing as an income source, lower probability of OD experience (91) *Detailed predictors of latent class membership not reported. *Mortality hazard:* *Class 4 (HR=3.65) and 6 (HR=3.48) membership was associated with an increased hazard of mortality in comparison to those in Class 2.
Harrell (2012)	Examine patterns of drug use among a sample of heroin and	Age, Sex, Race, Lifetime polydrug use, Smokes 20+ cigs per	*LM* Cigarettes, alcohol, heroin (IDU), crack	***Class 1:*** Crack/Nasal-Heroin users (43.5%) ***Class 2:*** PSU (34.8%)	*Compared to Class 2*

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
	cocaine users; and assess latent classes for relationships with risky behaviours and infectious diseases	day, Positive for opioids, Positive for cocaine, Psychiatric disorder, Jail, Shared needle in lifetime, Casual sex, Sold sex, Paid for sex, Drugs for sex, HCV, HIV	cocaine (smoking), marijuana (smoking), heroin (nasal), cocaine (IDU), and speedball (IDU).	***Class 3:*** Heroin Injectors (21.8%)	*Class 1 were more likely to identify as Black (OR=6.97) and exchange drugs for sex (OR=2.50). *Compared to Class 3* *Sharing needles was more likely among Class 2 (OR=2.66) and having HCV (OR = 0.10) among Class 1. *No significant differences were found for HIV.
Hautala (2017)	Identify separate urban and rural profiles of weekly injection and non-injection substance use and examine possible correlates of latent class membership.	Obtained sterile needles, Shared syringes, Shared cooking equipment, Backloading	*Last Year* Non-IDU: Binge drinking, marijuana, benzo, crack, and cocaine IDU: Cocaine, heroin, and speedball.	**Rural PWID** ***Class 1:*** Primary heroin injectors (7%) ***Class 2:*** Primary cocaine, heroin, and speedball injectors (26%) ***Class 3:*** Primary speedball injectors (67%) **Urban PWID** ***Class 1:*** Primary heroin injectors (21%) ***Class 2:*** Primary speedball injectors and marijuana (10%)	*PSU profiles vary across rural and urban communities in Puerto Rico. * Some form of injection heroin was used by nearly all participants in both samples. * Similar PSU profiles also share similar injection behaviour correlates. *Detailed predictors of latent class membership not reported.

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
				Class 3: Primary speedball injectors (42%) ***Class 4:*** Cocaine, heroin, and speedball injectors (21%) ***Class 5:*** High polysubstance (6%)	
Kuramoto (2011)	Identify subtypes of inner-city heroin and cocaine users based on type of drug used and route of administration; and assess whether classes differ in depressive symptoms, injection risk, and drug network compositions	Sex, race, age, education, unemployment in the past 6 months, homeless in the past 6 months, HIV self-report status and lifetime drug treatment, depressive symptoms, injection risk, drug network composition	L6M (Weekly) Alcohol use, Marijuana use, Heroin injecting, Heroin snorting, Speedball injecting, Cocaine injecting, Cocaine snorting, Crack smoking	***Class 1:*** Heroin injecting (13%) ***Class 2:*** Polydrug and polyroute (8%) ***Class 3:*** Heroin and cocaine injecting (38%) ***Class 4:*** Heroin snorting (26%) ***Class 5:*** Crack smoking (14%)	*Class 2 had the highest depressive symptoms risk. *Injection risk was lowest in Class 1 and significantly differed from Class 3. *The IDU subtypes also varied in the drug network compositions. *Class 4 and 5 had similar depressive symptoms risk but vastly differed in the drug network compositions. *Detailed predictors of latent class membership not reported.
Liu (2020)	Describe typologies of emergency department visits involving suspected nonfatal drug ODs;	NR.	*Substance at Discharge* Heroin, non-heroin opioids, marijuana, benzodiazepines,	***Class 1:*** Mostly heroin OD (42.5%) ***Class 2:*** Mostly non-heroin opioid OD/use (27.3%)	*Class 1: Largest probabilities of males (68.1%) and 25–34-year-olds (39.2%); 100% probability of heroin OD.

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
	and characterize the classes of patients affected by nonfatal drug ODs.		other depressants/sedatives, anti-depressants, cocaine, other stimulants, hallucinogens, alcohol, tobacco, inhalants, and psychoactive/psychotropic drugs, sex, age group	***Class 3:*** Opioid, polysubstance (11%) ***Class 4:*** Female, younger (< 25), other non-opioid drugs (10.5%) ***Class 5:*** Female, older (> 55 years), mostly benzodiazepine (8%)	*Class 2: Lower probabilities of males (59.8%) and higher % of >55 years (28.5%); 0% probability for heroin OD. Class 3: higher probabilities for males (67.7%); substantial PSU (62.8%). *Class 4: higher representation of females (55.5%), those ages younger than 25 years (34.2%); highest probabilities for OD/use anti-depressants (41.6%) and other depressants/sedatives (22.8%). *Class 5: highest percentage for females (58.1%), and age groups >55 (29.0%); benzodiazepines at discharge (100%). *Detailed predictors of latent class membership not reported.
Meacham (2018a)	Characterize longitudinal polydrug and polyroute use patterns from baseline to 6M FU within a prospective cohort PWID in Tijuana; and determine probabilities of	Sex, Age, Income, Whole life in Tijuana, Ever received professional help, Ever on methadone, Ever in rehabilitation centre, Ever attended a 12-step program, Ever went to jail, Receptive syringe	*L6M* Heroin injection, methamphetamine injection, heroin and methamphetamine co-injection, and methamphetamine smoking	***Class 1:*** Heroin-only injectors (38% at both baseline and 6M FU). ***Class 2:*** Co-injectors (3% baseline, 15% FU) ***Class 3:*** Heroin and methamphetamine injectors (37% baseline, 32% FU)	*Compared to Class 1* *Class 2 at baseline: Sex exchange (OR=2.99) *Class 3 at baseline: Female (OR=0.59); ever in rehabilitation (OR=1.62); ever jailed (OR=1.62); sharing syringe (OR=1.64); sharing paraphernalia (OR=1.67); urgent need for help (OR=1.77). *Class 4 at baseline: female (OR=1.58); young (OR=0.97); higher income (OR=1.65); lived in

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
	transitioning between polydrug and polyroute use statuses	sharing, Cooker, Cotton, Water sharing, Unprotected Sex, Sex exchange, Drug use before sex, OD, Great or urgent need for help		***Class 4:*** Polydrug and polyroute users (22% baseline, 14% FU).	Tijuana (OR=0.58); ever received help (OR=1.56); ever on methadone (OR=1.75); ever in rehabilitation (OR=1.72); ever 12-step program (OR=2.76); ever jailed (OR=1.62); sharing syringe (OR=3.61); sharing paraphernalia (OR=3.81); unprotected sex (OR=2.19); sex exchange (OR=2.63); drug use before sex (OR=2.23); OD (OR=2.03). *Of all participants, 61% remained in the same status while 39% transitioned to a different status. *Class 4 were most likely to "move" or transition "down" to other groups. *Class 1 had the highest probability of remaining in the same latent status at FU. *ORs are significant at p<0.05 and unadjusted.
Meacham (2018b)	Identify discrete classes of polydrug use in a cohort of PWID; and determine the association of class membership with HIV risk behaviours and recent	HIV injection risk behaviours, HIV sex risk behaviours, OD, HIV-sero-positivity, Age, Sex, Education, Deported to Tijuana, Whole life in Tijuana, Ever experienced	*Daily* Heroin injecting, Heroin and meth co-injecting; Methamphetamine smoking; Methamphetamine injecting	***Class 1:*** Polydrug, polyroute and cocaine (5%) ***Class 2:*** Polydrug and polyroute (29%) ***Class 3:*** Stimulant and heroin injectors (4%)	*Compared to Class 5* *Membership in Classes 1 and 2 was associated with sharing cookers, cotton or rinse water (Class 1, OR=7.22; Class 2, OR=4.35), using drugs before or during sex (Class 1, OR=7.31; Class 2, OR=3.55), and ever experiencing forced sex (Class 1, OR=3.70; Class 2, OR=3.10).

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
	OD, individual-level demographic and risk environment covariates.	forced sex, Age of first drug use/injection, Risk environment	*<Daily* Heroin and meth co-injecting, Methamphetamine smoking, Methamphetamine injecting Marijuana smoking, Tranquilizer ingesting, Heroin smoking or snorting, Methamphetamine snorting; Cocaine smoking or snorting; Cocaine injecting	***Class 4:*** Methamphetamine and heroin injectors (10%) ***Class 5:*** Predominantly heroin injection (52%)	*Higher education (OR=1.09), higher income (OR=3.35), and higher age at IDU debute (OR=1.05), were also associated with being in Class 2. *Injecting heroin at first injection (OR=0.26), and more hours on the street (OR=1.09) were independently associated with membership Class 3. *No predictor was significant for membership in class 4. *ORs are significant at p<0.05 and adjusted.
Meacham (2015)	Describe classes of cocaine and methamphetamine injecting and non-	Age, Sex, Income ≥3,500 pesos/month, Sex exchange, 2+ casual sex partners, Drug use before sex,	*L6M* Cocaine (IDU), cocaine (non-IDU), methamphetamine (IDU), and	***Class 1:*** No polydrug use (predominately heroin) (50.2%)	*Compared to Class 1* *Class 2: Younger (OR=0.97); female (OR=1.89); higher income (OR=0.62); drug use before sex (OR=2.25); receptive syringe sharing (OR=2.67).

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
	injecting polydrug use in a sample of PWID.	Daily+ heroin injection, Years injecting, OD, Receptive sharing.	methamphetamine (non-IDU).	***Class 2:*** Methamphetamine and heroin (43.7%) ***Class 3:*** Methamphetamine, cocaine, and heroin (6.1%)	*Class 3: Sex exchange (OR=2.64); multiple sex partners (OR=12.96); >daily heroin injection (OR=0.39); receptive syringe sharing (OR=2.36); previous OD (OR=3.33).
Monga (2007)	Categorize illegal opioid users in Canada in order to describe and analyze their drug use patterns.	Depression, HCV, HIV, Pain, OD in L6M, Living on the street	*LM* Alcohol, cannabis, cocaine (IDU and non-IDU), crack, Dilaudid, heroin, illicit methadone, Tylenol, and benzodiazepines.	***Class 1:*** Tylenol and benzodiazepines (38.3%) ***Class 2:*** Non-IDU heroin and crack (10.2%) ***Class 3:*** IDU heroin and cocaine (51.5%)	*Compared to Class 1* *Class 2: Age (OR=0.95); OD in L6M (OR=0.25); Depression (OR=0.40); Pain (OR=0.35); HCV (OR=0.49). *Class 3: Age (OR=0.97); Depression (OR=0.53). *Sex, living on the street and HIV did not significantly predict class membership.
Nielsen (2011)	Compare the characteristics of an Australian drug treatment sample presenting with POA and a sample presenting with heroin as their	NR	Age, sex, lifetime number of ODs, physical health, mental health, previous drug treatment, lifetime heroin use, lifetime opioid injection,	***Class 1:*** Traditional opioid injectors in treatment (80.2%) ***Class 2:*** High-risk, disadvantaged, injectors (7.8%)	*PO group were less likely to report an OD history (OR = 0.90) and more likely to initiate opioid use for pain (OR=2.52) than those with primary heroin problems. *While most PO people were similar to heroin users in demographics, health and injecting drug use, there was a small, distinct group of PO that did not typically inject and who

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
	primary drug of concern.		stable housing, opioid injection, and accessing opioids illicitly.	***Class 3:*** Non-injectors and iatrogenic graduates (12%)	commonly initiated opioid use for pain and also experienced elevated physical and mental health disability.
Patra (2009)	Identify different classes of users characterized by distinct drug combinations; and explore the potentially differential association of the diverse emerging drug type classes with specific social and health indicators.	Age, Sex, Study site, Personal health status, Unstable housing status, HCV, Illegal income, Shared needles or injection equipment	*LM* Alcohol, cannabis, PO, cocaine, crack, benzodiazepines, and IDU.	***Class 1:*** IDU PO and cocaine use (12.7%) ***Class 2:*** Non-IDU PO use (8.1%) ***Class 3:*** IDU cocaine and crack use (18.4%) ***Class 4:*** Non-IDU PO and crack use (17.4%) ***Class 5:*** Non-use (7.7%) ***Class 6:*** IDU heroin and crack use (18.7%) ***Class 7:*** IDU intensive PSU (5%) ***Class 8:*** Alcohol use (12%)	*Compared to Class 5* *Class 6 had significantly greater odds to live on the street (OR=10.96). *Class 3 had significantly greater odds of being HCV-positive (OR=3.18). *Class 2 were less likely to be HCV-positive (OR=0.35). *Members of classes 2 (OR=3.05), 3 (OR=2.73), 4 (OR=2.72), and 7 (OR=4.61) had higher odds of poor personal health status. *All classes had higher odds of illegal income with ORs ranging from 6.06 to 36.05.
Peacock (2015)	Identify distinct groups of people who tamper with pharmaceutical	Age, Sex, State, Employment, Education, Income, Relationship status,	*LM* Non-prescribed use of OxyContin, MS	***Class 1:*** Frequent OAT group (39%) ***Class 2:*** Mixed OAT/heroin group (7%)	*Compared to Class 1* *Class 3 had lower odds of a prison history (OR=0.63), benzodiazepine dependence (OR=0.37) and heroin dependence (OR=0.60),

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
	opioids; determine groups' demographic and clinical profiles; assess any change in the rate and frequency of non-prescribed pharmaceutical opioids, benzodiazepine, illicit drugs, and prescribed OAT use following introduction of the reformulation; and assess any change in drug- related harms following introduction of the reformulation.	Homelessness, Incarceration history, Pain, Pharmaceutical opioid dependence, Heroin dependence, Methamphetamine dependence, Benzodiazepine dependence, Risky alcohol consumption.	Contin, and benzodiazepines. *L6M* Heroin and methamphetamine, methadone, and buprenorphine.	***Class 3:*** Infrequent pharmaceutical opioid and heroin group (44%) ***Class 4:*** Frequent oxycodone group (25%)	and greater odds of being male (OR=1.48), reporting non-everyday pain (OR=1.50) and risky alcohol use (OR=1.47). *Class 2 was similar, except for lower odds of reporting income <$400 per week (OR=0.51), and greater odds of heroin dependence (OR=2.17). *Class 4 had higher odds of poor educational attainment (OR=2.13) and homelessness (OR=2.86).
Roth (2015)	Examine habitual drug use among PWID and identify distinct patterns of heroin and meth mixing in San Diego	Ethnicity, HCV, OD history, Age, STI history Homeless, past 6 months Tested HIV Seropositive	Heroin injecting, Meth smoking, Meth snorting, Meth injecting, Prescription drug swallowing,	***Class 1:*** Meth by multiple routes (51%) ***Class 2:*** Heroin by injection (49%)	*Compared to Class 1* Class 2: age (OR=0.79); Hispanics (OR=1.84); Blacks (OR=3.23); homeless (OR=0.42), HIV+ (OR=0.17), STI (OR=0.59); HCV+ (OR=2.25); ever ODd on opioids (OR=1.89).

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
			Binge drinking, Marijuana smoking		
Schneider (2019)	Examine how combinations of substances and routes of administration are associated with non-fatal OD and with receiving OD training; and understand if individuals who are most at risk for OD are also the ones receiving OD response trainings most frequently and are carrying naloxone.	Sex, Race, Age, Education, Housing	Marijuana, crack (smoked), heroin (smoked/snorted), heroin (injected), cocaine (smoked/snorted), cocaine (injected), speedball (injected), pain relievers (ingested), pain relievers (injected), tranquilizers (ingested), and Buprenorphine (ingested)	***Class 1:*** Cocaine/heroin injection (40.2%) ***Class 2:*** Heroin-only injection (32.2%) ***Class 3:*** Multi-drug/multi-route use (27.6%)	*No significant differences in age, sex, race, or education between classes. *Class 3 had the highest and Class 2 had the lowest prevalence of homelessness. *Class 3 had the highest OD rates and class 2 had the lowest OD rates. *Class 3 had the lowest and class 2 had the highest OD training rates. *No significant differences between classes in terms of current naloxone possession. *Detailed predictors of latent class membership not reported.
Schneider (2020)	Identify classes of polysubstance drug use in a rural sample of PWID; identify sociodemographic	Age, Sex, Race, Education, Homelessness	*L6M* Stimulants (IDU), opioids (IDU), speedball (IDU), fentanyl (IDU),	***Class 1:*** Polydrug/polyroute use (35.0%)	*Class 3 was younger than Class 1 and 4. Class 3 had a greater proportion of males than Class 1, 2, and 4. There were also no significant differences between classes for race/ethnicity or education.

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
	correlates of drug use classes; and test for associations between drug use classes and OD history and receipt of take-home naloxone.		Buprenorphine/Suboxone (IDU), stimulants (non-IDU), opioids (non-IDU), sedatives/tranquilizers (non-IDU), and Buprenorphine/Suboxone (non-IDU)	***Class 2:*** Polyroute stimulant/injection opioid use (33.3%) ***Class 3:*** Polyroute stimulant use (20.3%) ***Class 4:*** Injection opioid use (11.3%)	*Class 3 had less homelessness than class 2 and 1. Class 1 had more homelessness than Class 4. *The classes differed in terms of OD and having received THN; Class 1 had the highest probability of OD Class 3 the lowest. Class 2 and 1 had the highest levels of THN receipt while class 3 had the least. *Detailed predictors of latent class membership not reported.
Tavitian-Exley (2018)	Identify classes of polydrug use; and investigate factors associated with different categories of polydrug use among PWID.	Age, Sex, Ethnicity, Education, Regular income, Drug treatment, Injecting risk behaviours, Sexual risk behaviours, HIV, HCV, HSV sero-positivity.	*L6M Substance Use* Main drug class injected (ATS or opioids); injection of additional opioids; injection of additional stimulants; use of additional opioids; use of additional stimulants; number of drugs injected; and number of non-injection drugs used	***Class 1:*** Polydrug polyroute injection (9%) ***Class 2:*** Opiate-stimulant poly-injection (7%) ***Class 3:*** Non-injection stimulant co-use (12%) ***Class 4:*** Opiate-opioid poly-injection (16%) ***Class 5:*** Single drug injection (56%)	*Compared to Class 5* *Class 1: Non-Russian (OR=1.8); Kohtla-Jaïrve city (OR=3.4); daily injection (OR=2.5); Injected >2 a day (OR=2.7); Shared needles/syringes (OR=2.5); Shared paraphernalia (OR=2.7); Filled from working syringe (OR=3.6). *Class 2: Daily injection (OR=3.0); Injected >2 a day (OR=4.0); Shared needles/syringes (OR=2.3); Lent needles/syringes (OR=2.4); Shared paraphernalia (OR=1.8); Filled from working syringe (OR=1.8); Any sex in L6M (OR=1.9); >2 sex partners (OR=1.7). *Class 3: Completed secondary school (OR=0.7); Non-regular income (OR=0.6);

First author (Year)	Objectives	Covariates/Predictors	Outcome indicators	Results-latent classes	Results-significant predictions
					Kohtla-Ja¨rve city (OR=14.9); Filled from working syringe (OR=3.2); Any sex in L6M (OR=1.5). *Class 4: Age <30 (OR=1.6); Non-Russian (OR=1.6); Kohtla-Ja¨rve city (OR=0.1); Injected >2 a day (OR=1.6); Shared needles/syringes (OR=1.6); >2 sex partners (OR=1.6); Regular sex partner injects (OR=3.2); Casual sex partner injects (OR=2.1).
Wu (2011)	Determine whether various SUD relate to a latent poly-SUD trait or latent groups; identify demographic characteristics of opioid-dependent adults with increased odds of poly-SUD; and, explore the association of latent poly-SUD with subscales from ASI, HRBS, and SF-36.	Sex, Age, Race/Ethnicity, Education, Employment, Treatment setting, Addiction severity index subscales, Total HIV risk score, HIV Risk Behaviour Scale subscales, SF-36 subscales.	*Abuse/Dependence* Nicotine; cocaine; alcohol; cannabis; sedative; and amphetamine.	***Class 1:*** Low severity (90%) ***Class 2:*** High severity (10%)	*Compared to Class 1* *Class 2: More likely to be younger, inpatients, and white, higher total HIV and sexual risk scores, and greater psychiatric problems. *ORs not reported.

Notes: POUD: Prescription opioid use disorder; NBP: Non-prescription buprenorphine; MDD: Major depressive disorder; OR: Odds ratio; HR: Hazard ratio; HSV: Herpes simplex virus; IDU: Injection drug use; STI: Sexually transmitted infections; OAT: Opioid agonist therapy; CNS: Central Nervous System; PO: Prescription opioids; RRR: Relative risk ratio; LM: Last month; L6M: Last six months; OUD: Opioid use disorder; SUD: Substance use disorders; THN: Take-home Naloxone.

Chapter 3: Shifts in substance use patterns among a cohort of people with opioid use disorder after reformulation of OxyContin in BC, Canada: An interrupted time series study

3.1 Introduction

In Canada, deaths due to drug OD have surpassed motor vehicle incidents and homicide deaths combined, and opioid-related fatal ODs continue to account for most of drug OD deaths (9). Several factors have been cited as potential contributors to Canada's opioid epidemic throughout the past few decades. These include prescription-related practices (e.g., increased rates of opioid prescription and prescription of higher doses of opioids), patient-related behaviours (e.g., diversion, doctor shopping, and PSU involving PO), as well as environmental- and structural-level determinants (e.g., aggressive marketing campaigns by pharmaceutical companies to promote the use of controlled-release opioids for addressing non-cancer pain, changes in pain management guidelines validating liberal use of opioids, endorsing substance use-related stigma and criminalization, and the increasingly toxic supply of drugs) (22).

One of the widely-cited narratives about the rapid increase in opioid toxicity deaths and hospitalizations in Canada revolves around the introduction of long-acting oxycodone (OxyContin, Purdue Pharma) into the provincial drug formularies in 2000 (149-151). OxyContin was marketed as a safe, potent alternative to previously available weaker opioids (e.g., codeine and meperidine) that could serve as a long-acting opioid. However, its controlled-release characteristic was easily defeated when people learned to crush the pills and swallow, snort, or inject them to experience a morphine-like high (151). Several studies

have provided evidence pointing to the contribution of OxyContin to increased opioid consumption and opioid toxicity deaths in Canada (151-154). For example, a study of people enrolled in Ontario's public drug plan 2003-2008 reported that although the prescription of other opioids had remained relatively constant, OxyContin's prescription had increased by over 100% and contributed to the excess opioid toxicity deaths (155). Ten years after the introduction of OxyContin into the Canadian drug formulary, PO use had quadrupled despite the number of patients living with chronic pain remaining relatively constant (152).

The Canadian government tried to rectify the situation by implementing policies, such as prescription monitoring programs (14), and developing opioid prescription guidelines (156). More notably, in February 2012, Purdue Pharma replaced OxyContin with a tamper-resistant and 'abuse-proof' formulation called OxyNeo, which was neither crushable nor water-soluble (152). Shortly after, in March 2012, seven Canadian provinces announced that OxyContin would be delisted from the provincial drug formularies to address the soaring opioid toxicity deaths by restricting access to OxyContin (150, 152). This supply-level intervention meant that with a few exceptions (e.g., for people on social assistance), OxyContin would no longer be covered by the provincial drug benefits programs. The landscape of oxycodone prescription in Canada changed again in November 2012 when Health Canada approved a generic form of sustained-release non-tamper-resistant oxycodone, which was subject to specific prescription monitoring regulations and covered by public drug plans in a few provinces (157, 158). Unsurprisingly, the implementation of this nation-wide supply reduction policy has been associated with reduced opioid medication dispensing across Canada. Between February 2012 and April 2016, the quantity of dispensed opioids across Canada dropped by 14.9%, with ON (22.8% drop) and BC (30% drop) having

the largest declines. Moreover, post-introduction of OxyNeo, the national oxycodone dispensing rate dropped by 46.4% (152). The rates of OD-related deaths in BC, however, continued to increase and led to the declaration of a public health emergency due to drug-related fatal and non-fatal ODs in April 2016 (12).

While estimates on aggregate-level ecological dispensing patterns of OxyContin help shed light on how opioid prescription patterns changed in Canada after the above-mentioned intervention, the understanding of potential modifications in individual-level substance use patterns of people with OUD after the policy was implemented remains limited. Indeed, a considerable body of international evidence suggests that supply-level reduction of opioids often have 'unintended consequences' and could lead to shifts in people's substance use patterns and increases in PSU practices due to the supply shock in the illicit drug market (159-172). For example, during Australia's 'heroin drought' in the early 2000s, the price of street heroin doubled, and its purity dropped by half, and the number of heroin injection initiators declined. On the other hand, sharing of injecting equipment, and the number of people initiating injecting methamphetamine or benzodiazepine increased drastically (45, 163-165). More recently, during the heroin shortage in Europe from 2010-2011, which was attributed to fungal diseases affecting Afghanistan's poppy crops, flooding of trafficking routes in Pakistan, and increased enforcement interventions that disrupted trafficking flows, PSU increased among people with OUD (159, 166). Some suppliers even made heroin purchases conditional on buying cocaine (159).

In this study, I use self-reports of substance use among people with OUD in a long-running cohort of PWUD in Vancouver and assess if reducing access to OxyContin in Canada in March 2012 has had any meaningful effect in reducing the use of illicit opioids among

people with OUD. I also aim to provide a quantitative assessment of how participants' substance use patterns changed after this large-scale prescription supply reduction intervention.

3.2 Methods

3.2.1 Data sources

Data for this analysis was derived from VIDUS and ACCESS cohort studies (74, 75), the details of which are presented in Section 1.5. In brief, VIDUS includes HIV-seronegative PWID, and ACCESS includes people PWUD who are living with HIV.

3.2.2 Study period and population

For this analysis, I included data from participants from the first study visit where they met the criteria for OUD (i.e., using illicit opioids on a regular basis or having received OAT in the previous six months). This approach has been previously used in substance use research (173, 174). Additionally, only those participants who had at least one follow-up visit before (January 01, 2006 to February 30, 2012) and after (April 01, 2012 to November 30, 2018) the policy change were included. Overall, data were included from 154 months; 74 before and 80 after the policy change was implemented in March 2012 (150).

3.2.3 Outcomes of interest

I assessed six self-reported dichotomous outcomes measuring regular use of different substances during the previous six months, including heroin, PO, methamphetamine, crack, cocaine, and fentanyl. Given that most participants had not reported using fentanyl during the study, I have only reported descriptive statistics for at least monthly use of fentanyl semi-annually during the study period.

3.2.4 Statistical analysis

Data was initially inspected visually by plotting the outcome variables over time to help evaluate the underlying trend and identify potential outliers. Seasonality, which is a potential time-varying confounder, was assessed for all outcomes using the fma package in R (175, 176), although no seasonality was detected. I conducted separate quasi-experimental interrupted time series (ITS) on all outcomes except for fentanyl due to the low prevalence of fentanyl use among the participants. ITS is a robust quasi-experimental design that utilizes data obtained at several intervals to examine potential causal associations between a particular intervention and specific outcomes (177). The outcomes were summarized as monthly proportions based on the date of the interview. I used these aggregated figures to fit segmented linear regression models (51) that included terms for baseline intercept, existing (or baseline) trend before reformulation of OxyContin, as well as immediate level change and trend change after the policy change. This allowed an assessment of participants' immediate and long-term substance use practices after the policy change while controlling for baseline levels and trends. As monthly observations might have been correlated over time, I also tested for autocorrelation (using the Durbin-Watson test and autocorrelation function [ACF] and partial-ACF plots) and made the necessary adjustments as appropriate (177-179). I also considered a one-month phase-in period (i.e., March 2012) to allow enough time for the policy change to be incorporated into prescription practices and removed it from the analysis.

Using the ITS models, I also estimated the absolute change of the prevalence of each outcome in the following dates, had the policy change not occurred: April 2016 (i.e., date of declaration of public health emergency in response to the surge in drug-related fatal and non-fatal ODs in BC (12)), and November 2018 (at the end of the study period). All analyses were

conducted in R software (version 3.6.3). P-values were two-sided and considered significant at a level <0.05.

3.3 Results

3.3.1 Participants' characteristics

A total of 1014 participants who contributed to 17472 visits during the study were included in the analysis. Characteristics of the participants at first observation during the study period are presented in Table 3.1. At baseline, most participants were from the VIDUS cohort (642; 63.3%) and self-identified as men (642; 63.9%). The median (IQR) age of the participants was 41.9 (35.6, 47.5), and they predominantly self-identified as White (461; 45.7%) or Indigenous (325; 32.2%).

3.3.2 Participants' substance use patterns after reformulation of OxyContin

Figure 3.1 presents the monthly proportion of regular heroin use among participants. At the beginning of the study period (i.e., January 2006), the model estimated a 49.83% prevalence of regular heroin use. As shown in Figure 3.1, the trend of regular heroin use was already significantly declining before the reformulation of OxyContin (-0.36% per month [95% CI: -0.45% to -0.28%]; p<0.00001). Following the policy change, the model estimated a significantly increasing trend (0.47% per month [95% CI: 0.35% to 0.58%]; p<0.00001) and level (5.17% [95% CI: 0.68% to 9.67%]; p=0.0253) change in the prevalence of regular heroin use among the participants. The predicted absolute change of the prevalence of regular heroin use in the month before the declaration of the public health emergency and at the end of the study period was an increase of 27.90% and 42.50%, respectively.

Figure 3.2 presents the monthly proportion of regular non-prescribed PO use among the participants. At the beginning of the study period, the model estimated a 22.18% prevalence of regular PO use. As indicated in Figure 3.2, the trend of regular PO use was already declining significantly before the reformulation of OxyContin (-0.17% per month [95% CI: -0.20% to -0.14%]; p<0.00001). Following the policy change, the model estimated a significantly increasing trend (0.11% per month [95% CI: 0.07% to 0.15%]; p<0.00001) and level (2.21% [95% CI: 0.46% to 3.96%]; p=0.0141) change in the prevalence of regular PO use among the participants. The predicted absolute change in the prevalence of regular PO use in March 2016 and November 2018 included an increase of 7.64% and 11.20%, respectively.

Figure 3.3 presents the monthly proportion of regular methamphetamine use among the participants. At the beginning of the study period, the model estimated a 5.91% prevalence of regular methamphetamine use. As shown in this Figure, regular methamphetamine use was relatively stable with a non-significant positive trend before reformulation of OxyContin (0.02% per month [95% CI: -0.02% to 0.08%]; p=0.3368). Following the policy change, the model estimated a significantly increasing trend (0.10% per month [95% CI: 0.02% to 0.16%]; p=0.0285) and a non-significantly increasing level (2.28% [95% CI: -0.54% to 5.11%]; p=0.1150) change in the prevalence of regular methamphetamine use among the participants. The predicted absolute change of the prevalence of regular methamphetamine use in March 2016 and November 2018 included an increase of 7.24% and 10.36%, respectively.

Figure 3.4 presents the monthly proportion of regular crack use among the participants. At the beginning of the study period, the model estimated a 73.40% prevalence of regular crack use. As indicated in Figure 3.4, the trend of regular crack use was already significantly declining before the reformulation of OxyContin (-0.35% per month [95% CI: -0.44% to -

0.25%]; p<0.00001). Following the policy change, the model estimated a non-significantly increasing trend (0.04% per month [95% CI: -0.10% to 0.18%]; p=0.5609) and a significantly decreasing level (-6.31% [95% CI: -10.94% to -1.69%]; p=0.0082) change in the prevalence of regular crack use among the participants. The predicted absolute change of the prevalence of regular crack use in March 2016 and November 2018 included a decrease of 4.58% and 3.26%, respectively.

Figure 3.5 presents the monthly proportion of regular cocaine use among the participants. At the beginning of the study period, the model estimated a 25.29% prevalence of regular cocaine use. As indicated in this figure, the trend of regular cocaine use was already significantly declining before the reformulation of OxyContin (-0.12% per month [95% CI: -0.175 to -0.07%]; p<0.00001). Following the policy change, the model estimated a non-significantly increasing trend (0.01% per month [95% CI: -0.05% to 0.08%]; p=0.6290) and level (1.78% [95% CI: -1.11% to 4.69%]; p=0.2301) change in the prevalence of regular cocaine use among the participants. The predicted absolute change in the prevalence of regular cocaine use in March 2016 and November 2018 included an increase of 2.50% and 3.03%, respectively.

Lastly, Figure 3.6 shows the semi-annual prevalence of monthly fentanyl use among participants. As indicated in the figure, the overall semi-annual prevalence of monthly fentanyl was negligible (i.e., close to zero) before 2014 and started to rise drastically as of mid-2014, reaching 4.7% in the second half of 2018.

3.4 Discussion

In this study, I assessed how longitudinal substance use patterns among a cohort of

people with OUD in Vancouver shifted after the supply reduction intervention involving the reformulation of OxyContin in BC. The findings suggest that although this intervention may have influenced the provincial-level prescription or consumption of OxyContin (151, 152, 158), it was not associated with a decline in illicit opioid use among the participants. The ITS models estimated that contrary to one of the policy's primary goals, the policy change was significantly associated with an increase in the prevalence and trend of regular heroin and illicit PO use. In addition, although the policy change was not associated with significant increases in crack or cocaine use, it was significantly associated with an upward trend in the regular use of methamphetamine among participants.

As polysubstance use is common among the cohort participants, it is important to note that only some and not all people with OUD may have transitioned to other types of drugs or initiated a new class of drugs after reformulation of OxyContin. Indeed, it is plausible that those who faced shortages in their opioid supplies might have resorted to other illicit drugs, including heroin and other similar or more potent PO (e.g., hydrocodone, morphine, and methadone) that are either cheaper or covered by most insurance providers. These findings are in line with previous natural experiences elsewhere. As the shortage of heroin continued across Europe, heroin supplies were adulterated with other substances (e.g., benzodiazepines, paracetamol, amphetamines, desomorphine) and non-opioid-related ODs increased among people with OUD (159). European consumers' responses to these supply-level shortages varied greatly across the community of people with OUD; while some sought substance use treatment, others resorted to injecting drugs, shifted their primary drug of choice to other drugs, or engaged in PSU by supplementing their 'heroin' use with other illicit substances to compensate for the poor quality of heroin (159, 160, 166). Similar observations have been

reported outside the European context (e.g., U.S., Iran, Kenya) where shifts in substance use patterns and engagement in PSU practices have increased after reductions in the supply of opioids (161, 167-170).

Although such 'unintended consequences' of supply reduction policies that target a single group of opioids have been shown to lead to significant drops in their use of prescription in the short term, they typically do not stop people's use of opioids altogether (22, 140, 165, 180). Several studies in Canada, U.S., and Australia, have shown that people with OUD's substance use patterns were altered, and some engaged in PSU practices after the reformulation of OxyContin (180-184). For example, in a qualitative study conducted from March-December 2012 in Ontario, Canada, a group of marginalized people who were regular PO consumers reported shifting to other opioid or non-opioid illicit drugs or supplementing their opioids with other drugs post-implementation of the policy (151). Moreover, in a quasi-experimental assessment of 2566 people with OUD initiating OAT in the U.S., 36% declared their primary drug of choice before the policy change to be oxycodone. However, their preference shifted towards hydromorphone (32%) and fentanyl (20%), and their use of heroin increased by 100% after the policy change (182). Another recent interrupted time series analysis of state-wide mortality data even argues that the reformulation of OxyContin has been the 'primary' factor that ignited U.S.'s heroin epidemic. Evans et al. looked at data from 2004 to 2014 and concluded that the combined rate of PO- and heroin-related mortality was not reduced after the reformulation of OxyContin and concluded that the reduction in deaths caused by reductions in PO-related mortality was compensated by increases in heroin-related deaths (161). Similarly, at Sydney's supervised injection facility, client visits for injection of OxyContin declined drastically post-policy change; however, this positive impact was partly

offset with increasing visits for injecting heroin, morphine, and fentanyl (181). In the current study, the observed absolute difference for the prevalence of regular PO and heroin use before the declaration of the public health emergency in April 2016, suggests that reducing access to the oxycodone family of drugs might have had little impact on reducing illicit opioid use among people with OUD, which had been presented as an important driver for implementing the policy in the first place.

Although the participants' longitudinal regular use of crack and cocaine was not significantly impacted and continued on a downward trend, there was a considerable shift towards increased regular use of methamphetamine among the participants. This observation is also comparable with previous natural experiments elsewhere (140, 159, 163-170). It is not surprising that similar behaviours were observed in the Canadian context following an 'oxycodone drought' (150). However, given the increasing rates of production, distribution, and access to methamphetamine in the past decade, it is unlikely that this supply-reduction intervention has been responsible for the upward trend of methamphetamine use among people with OUD which began in the early 2010s. For example, a recent assessment of methamphetamine use among 1984 PWUD in Vancouver estimated the self-reported use of methamphetamine in the previous six months among the participants to have increased from 19% in 2006 to 36% in 2017; an increase that was significantly associated with several individual-level substance use and sexual behaviours (185). In the U.S., self-reported monthly use of methamphetamines increased from 18.8% in 2011 to 34.2% in 2017 among participants of public and private OAT centres. Individual-level motivations for methamphetamine use included a desire for a synergic high, substituting opioids with methamphetamine, and balancing out opioids' numbing effects (185, 186). Regardless of

how much of the increase in regular methamphetamine use among people with OUD is attributed to the policy change, the findings highlight the urgent need to develop policies and interventions to address the increasing prevalence of methamphetamine among people with OUD in BC.

Data suggested that participants' increased self-reported use of illicit fentanyl was not associated with the policy change, a finding that should be interpreted with caution for several reasons. First, the prevalence of self-reported fentanyl use among the participants was considerably lower than what has been observed in BC's provincial surveys of harm reduction clients surveys in 2015 (13% past-three-day self-reported fentanyl use) and 2018 (43% past-week self-reported fentanyl use), respectively (46, 187, 188). This observation could be partly rooted in the VIDUS and ACCESS participants' continuous semi-annual engagement with substance use surveys that could increase their self-perceived risk for fentanyl use. Second, although illicit fentanyl started to increasingly appear in Vancouver's illicit drug market in early 2012 and the first fentanyl-involved OD was recorded in April 2012 (24), most people's exposure to fentanyl was initially unknown and might have been through heroin contaminated with fentanyl, fentanyl sold as heroin, or counterfeit oxycodone pills containing fentanyl (189-193). For example, 73% of the people who tested positive in the BC's harm reduction clients survey in 2015 were unaware of their exposure (46). Therefore, it is possible that some of the participants who self-reported shifts to regular heroin or PO use might have indeed been exposed to fentanyl unknowingly. Altogether, these observations highlight the importance of continued investments in public awareness and novel interventions (e.g., access to safer supplies of opioids and expansion of low-threshold harm-reduction-oriented addiction care) tailored towards tackling the toxic drug supply in

BC.

3.4.1 Limitations

I acknowledge the limitations of the study. First, I was not able to limit the participants to people who were primarily using OxyContin before and after the policy change. Data on OxyContin use alone was not available before or after the policy change, and limiting the sample to this subgroup was not feasible. Therefore, I studied participants' use of all non-prescribed PO (including OxyContin) before and after the policy change. Second, using ITS to assess the impact of the regulatory changes about OxyContin and leveraging data from a cohort of people with OUD in Vancouver allowed for reducing selection-attrition biases as well as controlling for the pre-existing levels and trends of regular substance use patterns among the study participants. However, I was unable to include data from an external control group, and unmeasured residual confounding cannot be ruled out. Third, although reaching a representable sample of marginalized PWUD is quite challenging, and the non-random nature of participant recruitment in the cohorts may limit the generalizability of the findings to all marginalized people with OUD in Vancouver or other international settings. Fourth, the main outcomes of interests were based on self-reports and are subject to potential reporting biases. However, previous studies have shown PWUD's self-reports of substance use to be sufficiently trustworthy (194). Moreover, if there is any potential self-reported bias, it would be consistent across the study and, therefore, not significantly impact the findings due to the ITS design of the study. Fifth, given that cohort data is collected semi-annually, the interview dates were used to create the date variable.

3.5 Conclusions

In summary, this ITS analysis suggests that the reformulation of OxyContin in BC does not seem to have been played an important role in reducing overall illicit opioid use among people with OUD. The model estimates point to a shift in substance use patterns of people with OUD following the shrinkage in the OxyContin supply in Vancouver. It is of utmost importance to recognize that supply-reduction efforts are only a single part of the comprehensive response to the opioid epidemic in Canada. While such 'well-intended' policies might lead to short-term drops in the use or prescription of certain opioids, they are not a 'silver bullet', may lead to unintended harms, and often fail to result in meaningful positive, long-term, population-level outcomes.

Figure 3.1. Regular heroin use among people with opioid use disorder before and after delisting OxyContin in Vancouver, BC, Canada

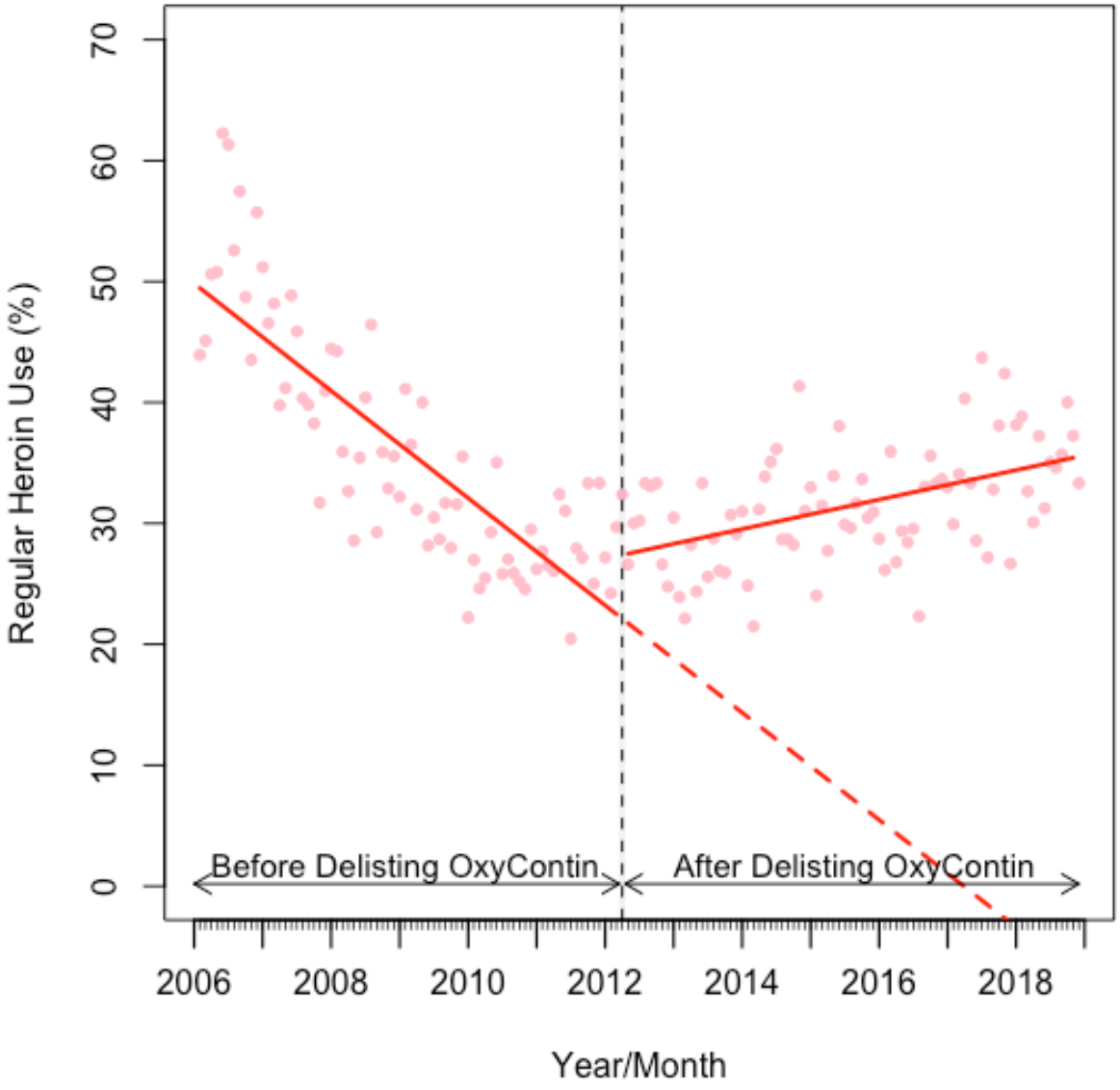


Figure 3.2. Regular prescription opioids use among people with opioid use disorder before and after delisting OxyContin in Vancouver, BC, Canada

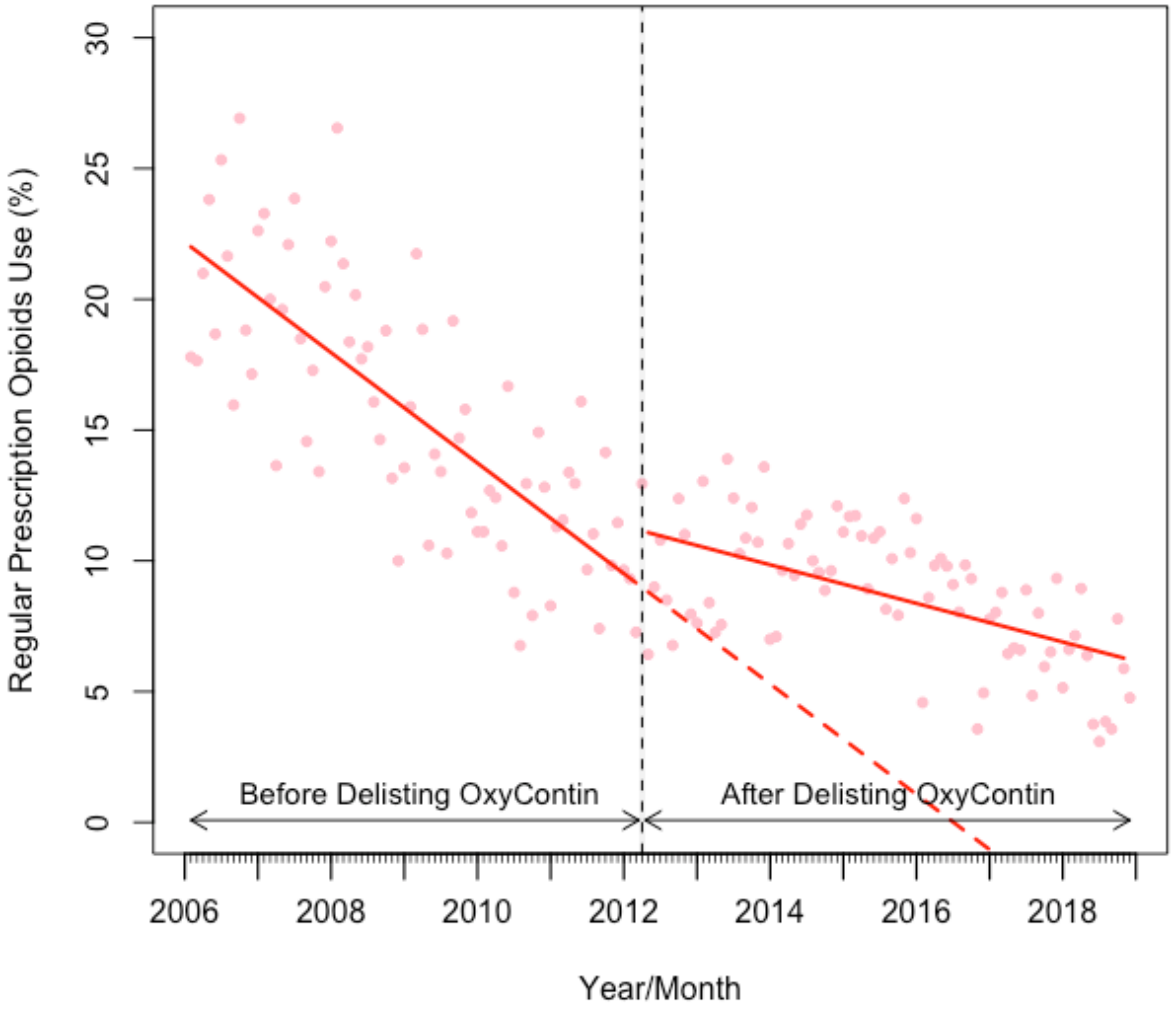


Figure 3.3. Regular methamphetamine use among people with opioid use disorder before and after delisting OxyContin in Vancouver, BC, Canada

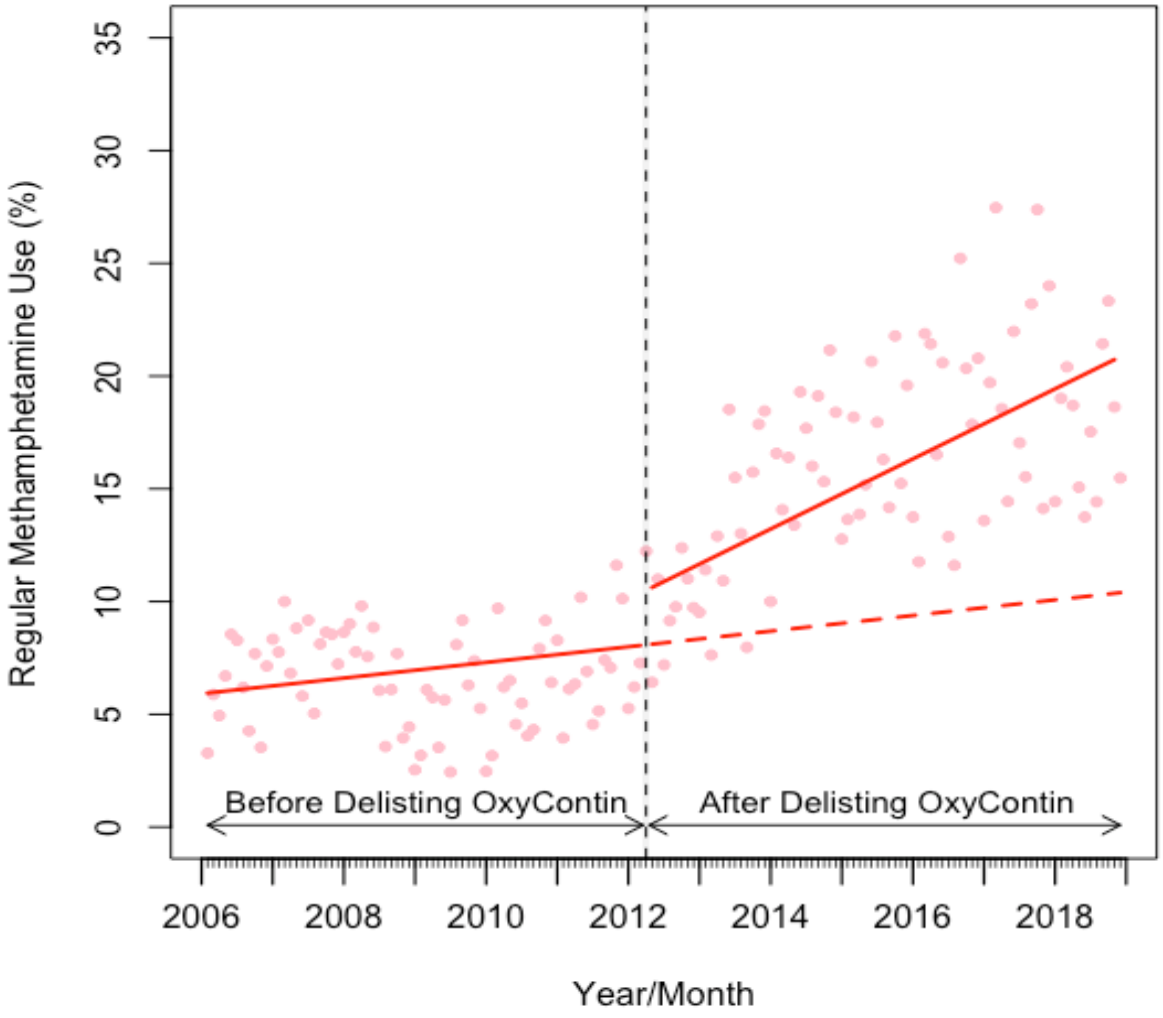


Figure 3.4. Regular crack use among people with opioid use disorder before and after delisting OxyContin in Vancouver, BC, Canada

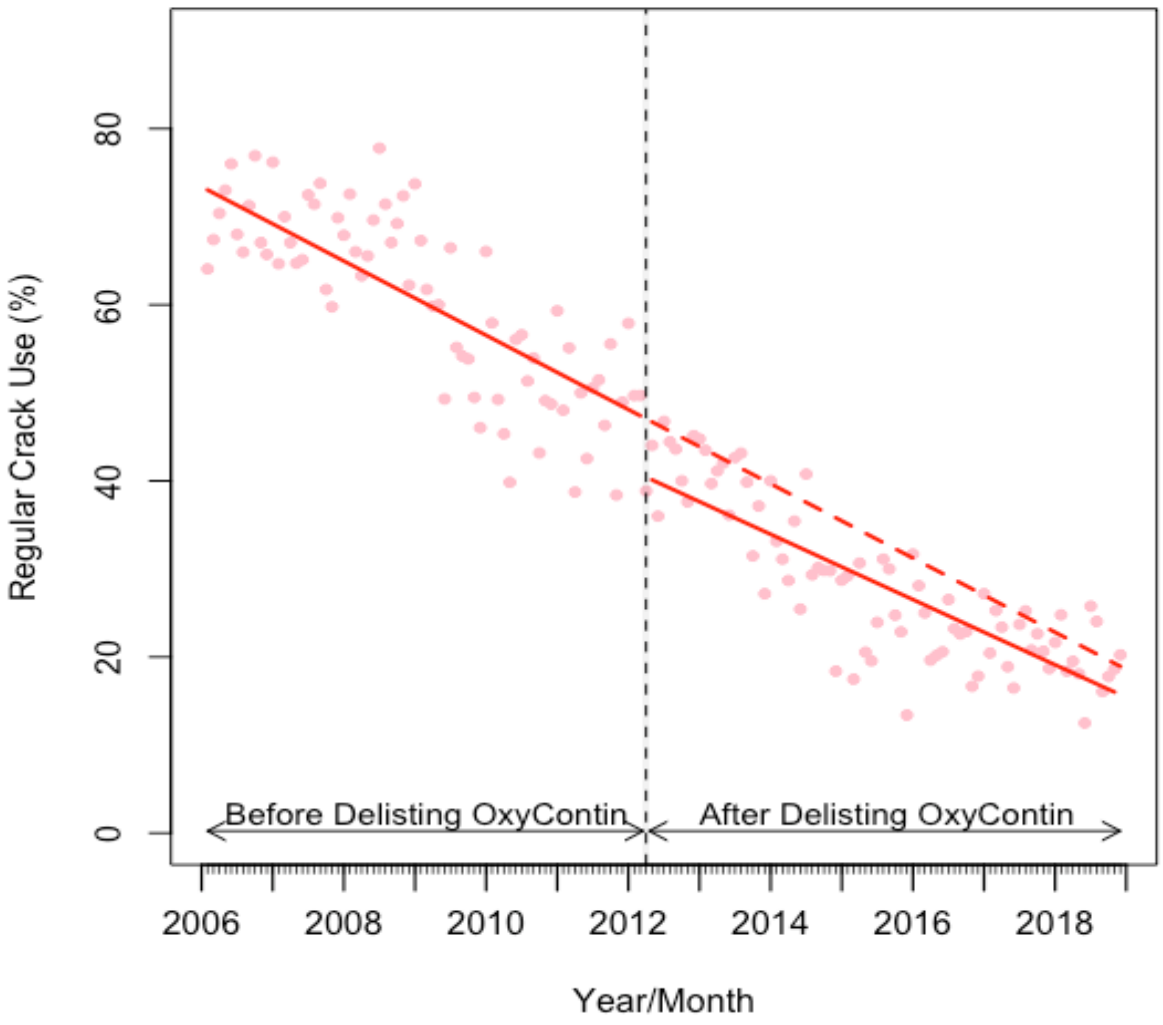


Figure 3.5. Regular cocaine use among people with opioid use disorder before and after delisting OxyContin in Vancouver, BC, Canada

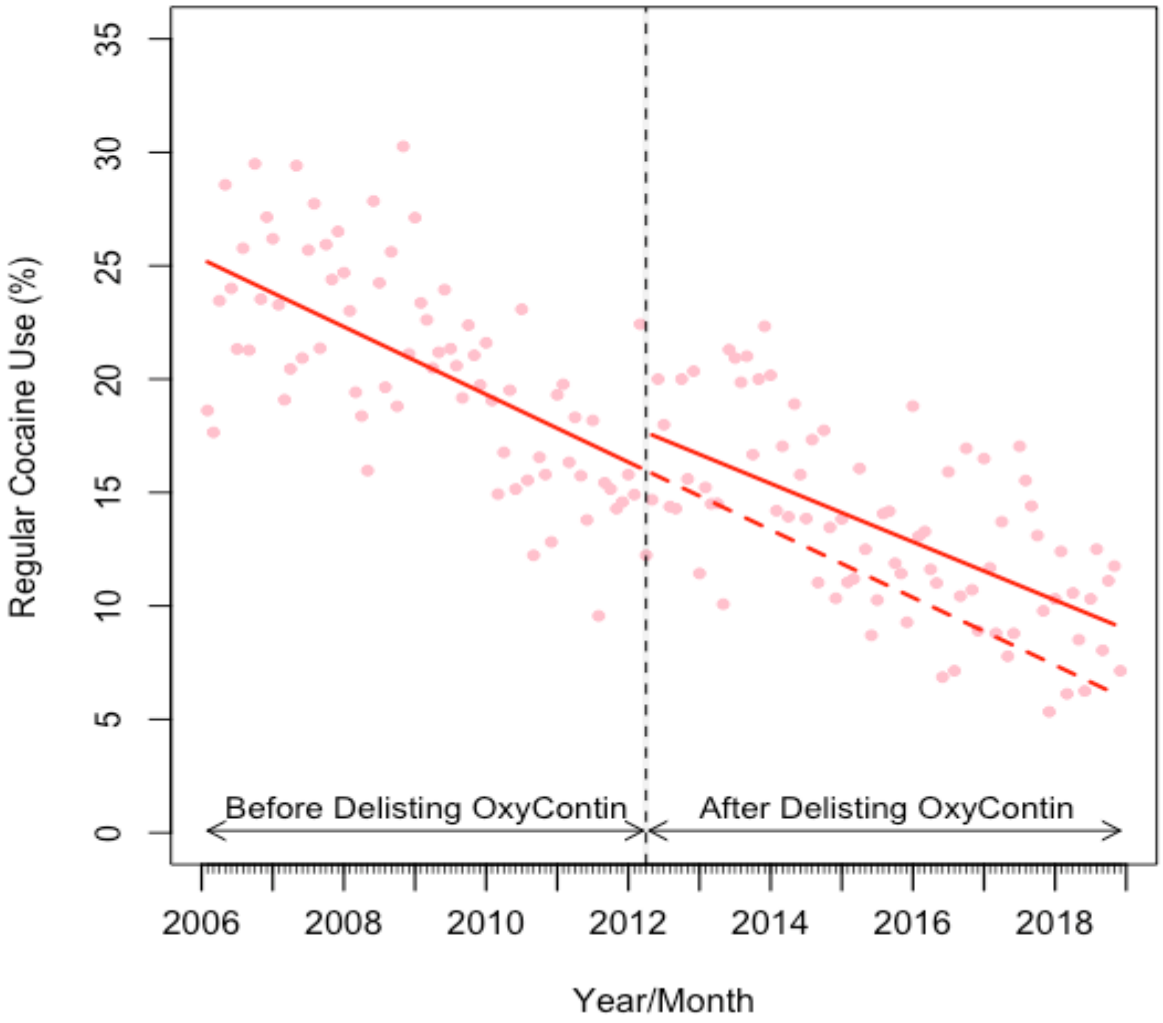


Figure 3.6. Monthly fentanyl use among people with opioid use disorder before and after delisting OxyContin in Vancouver, BC, Canada

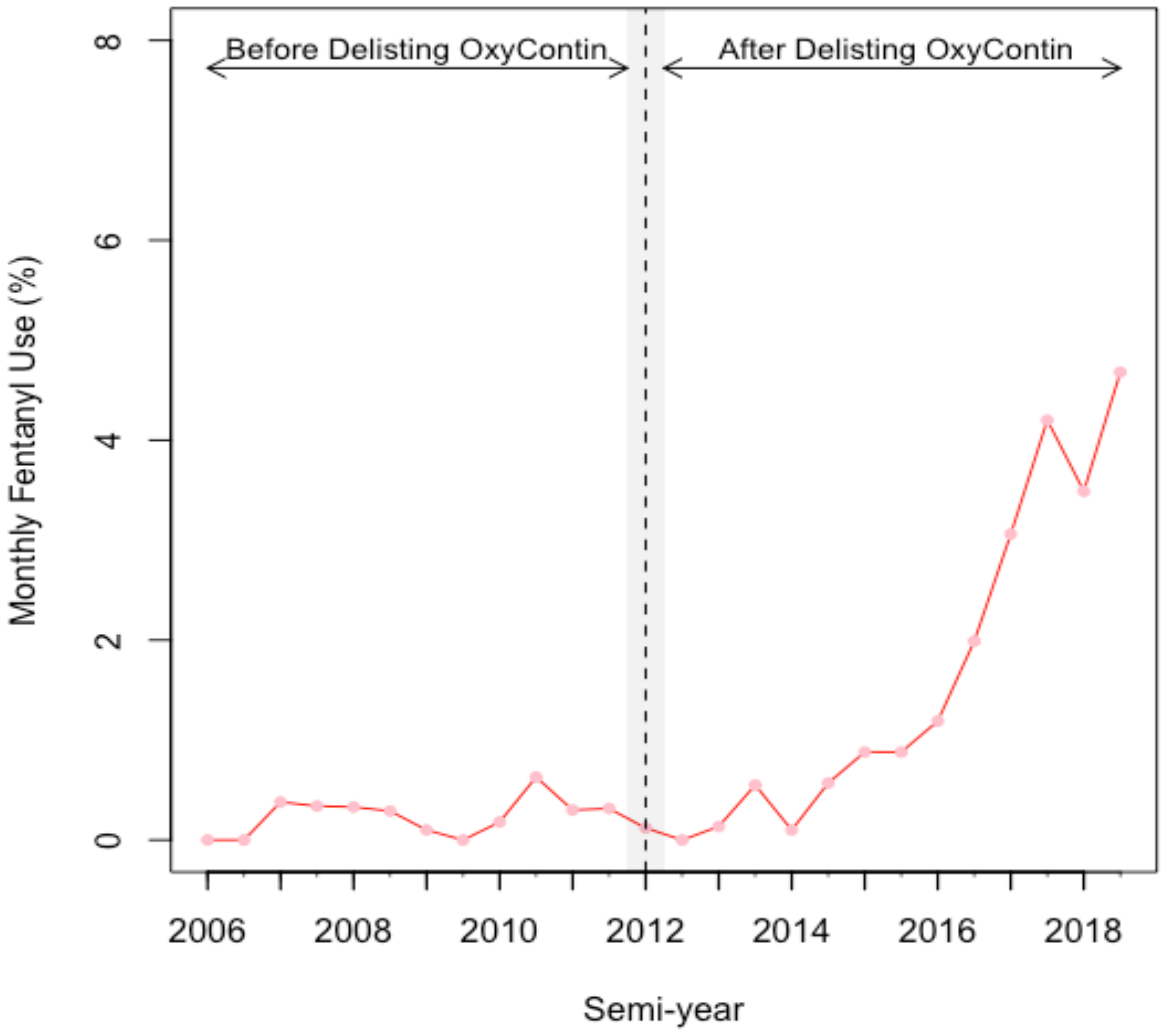


Table 3.1. Socio-demographic characteristics of 1014 people with opioid use disorder in Vancouver, Canada (January 2006-November 2018)

Characteristics	First observation in the study period; n (%)
Cohort	
VIDUS	642 (63.3)
ACCESS	372 (36.7)
Age (Median, IQR)	41.9 (35.6, 47.5)
Self-reported gender	
Man	642 (63.9%)
Woman	352 (35.1%)
Transgender	11 (1.0%)
Ethnicity	
White	461 (45.7)
Indigenous	325 (32.2)
Asian or Black	29 (2.8)
Other	194 (19.3)
Homelessness (L6M)	346 (34.1)
Incarceration (L6M)	186 (18.5)
Residence in DTES (L6M)	744 (73.4)

Notes: IQR: Interquartile ranged; L6M: Last six months; DTES: Downtown Eastside

Chapter 4: Polysubstance use trajectories among a cohort of people with opioid use disorder in Vancouver, BC, Canada

4.1 Introduction

SUD remains an important public health and sociopolitical concern in North America and beyond (195, 196). While most research studies focus on single types of substances or drugs of choice, a growing body of clinical and epidemiological studies indicate that an increasing number of people are engaging in PSU (26, 28). PSU is difficult to measure, and people's substance use practices often change over time (26, 197, 198). However, it is generally defined as using two or more substances or classes of substances either concurrently or individually over a defined period of time (26, 44). Regardless of its definition and compared to mono-substance use, PSU has been associated with reduced retention in substance use treatment as well as multiple unfavourable health outcomes, such as depression, anxiety, manic excitement, exposure to violence, OD, and risky sexual practices (27, 28, 199-201).

Several studies indicate that PSU is particularly common among individuals with OUD (27, 28, 43, 44, 133, 200). Combining opioids with other substances could boost their euphoric properties or help lessen the unpleasant experiences of opioid-related withdrawal (26, 28). PSU among people with OUD could also be driven by issues related to substance availability locally. For example, in the North American context, the shortages in heroin and PO supplies may have contributed to shifts in substance use patterns among people with OUD and co-use of opioids with other drugs (195, 202).

Despite the continuously increasing number of opioid-related deaths in North America, PSU among people with OUD is not fully understood. The existing evidence is limited to

small-scale cross-sectional studies that often opt for a variable-centred approach and suffer from methodological shortcomings. Using person-centred methods in contrast with variable-centred approaches would help detect unobserved/hidden subgroups with distinct PSU patterns and allow for the identification of the individual-level differences in substance use patterns based on a set of characteristics rather than the variability of a particular variable (203, 204). Therefore, this study aims to characterize longitudinal latent classes of PSU and their correlates to help shed light on the heterogeneities within different subgroups of people with OUD and improve the effectiveness and acceptability of interventions tailored towards them.

4.2 Methods

4.2.1 Data source and participants

Data for this study were based on VIDUS, ACCESS, and ARYS cohort studies, the details of which are presented in Section 1.5. The cohort participants for this analysis were restricted to PWUD who completed at least one interview during the study follow-up (2005-2018) and met the criteria for OUD at baseline. People with OUD were defined as those who reported using illicit opioids on a regular basis (i.e., at least weekly use/injection) or those receiving OAT in the previous six months. This approach has been used in previous substance use research (173, 174) and is supported by the DSM-5 criteria for OUD (7).

4.2.2 Data analysis

RMLCA was used to identify various latent classes emerging over the course of the study period. RMLCA is an extension of the LCA method that could be used for analyzing longitudinal studies without forcing a functional form of time (e.g., quadratic, cubic, quartic) to the data (58). This approach allows for greater flexibility in modeling discontinuous patterns

of substance use across different time points, and has helped identify longitudinal classes of substance use in a variety of populations (204-209). To determine the longitudinal classes of PSU and covariates of class membership, I followed a standard three-step approach (131, 210). First, I determined the latent classes based on item response patterns over time. Following an established approach that considers a combination of selection criteria (210-212), the final class solution was chosen based on relative model fit indices (e.g., Akaike Information Criterion [AIC], Bayesian Information Criterion [BIC]), entropy), classes' stability across different random starting values, and interpretability and utility of the final model in light of the existing literature. Second, I assigned people to appropriate latent classes according to their posterior class membership probabilities. Third, I used the assigned classes to build multivariable logistic regression models using generalized estimating equations (GEE)(213) to identify covariates associated with membership in each latent class. GEE is an approach that helps fitting models for longitudinal data by adjusting for the correlated nature of the observations by opting an exchangeable working correlation structure and handles missing values by using the all available pairs method (213, 214). Separate bivariable GEE models were built to compare covariates of class membership between different classes compared to the lowest frequency of use group. Within each logistic regression analysis, variables with p-values <0.1 in the bivariable analysis were retained for multivariable analyses. Final models were selected via a backward variable selection approach and lowest quasi-likelihood under the independence model criterion statistic (Quasi-information criterion [QIC])(215, 216). Adjusted odds ratios (AOR) along with their 95% confidence intervals (CI) were reported. Classes of PSU identified via RMLCA were graphed over time to show different trajectories over time and illustrate class membership trends over calendar time. All tests were considered

statistically significant at $p<0.05$. Analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC).

4.2.3 Outcome indicators

Outcome indicators included in the RMLCA analysis are presented in Table 4.1. They consisted of binary variables on at least weekly illicit opioid use, cocaine use, methamphetamine use, crack use, cannabis use, illicit PO use, and heavy alcohol use (defined as 14+ drinks weekly or 5+ drinks daily [for men] and 7+ drinks weekly or 4+ drinks daily [for women] during the previous six months) (7). All variables were measured during the last six months. The selection of the indicators was informed by a comprehensive literature review of latent classes of substance use among people with OUD. Weekly use of benzodiazepine, ecstasy/MDMA, speedball, and goofball were also considered as outcome indicators but were excluded from the RMLCA due to their low prevalence (i.e., <5%). Participants with missing values for any of the key outcome indicators were excluded (i.e., 277 observations); and 24952 visits were included for the analysis.

4.2.4 Covariates

The selection of covariates for predicting latent class membership was informed by Rhodes' Risk Environment framework (78) and previous research on substance use patterns among marginalized PWUD. Socio-demographic covariates included as potential predictors of class membership included cohort (ACCESS, VIDUS, or ARYS), age, sex (male or female), ethnicity (White or Indigenous or BPOC [Black person and person of color]), regular job (yes or no), HIV sero-positivity (yes or no), and major or persistent pain (yes or no). Participants' behavioural covariates included history of unprotected sex (yes or no) and at least weekly IDU (yes or no). Additionally, socio-structural covariates, including participants' history of

hospitalization (yes or no), incarceration (yes or no), drug dealing (yes or no), homelessness (yes or no), Downtown Eastside (DTES) residence (218), a neighbourhood with a widespread open drug scene characterized with a high concentration of substance use, poverty, and social services (yes or no), and accessing OAT (yes or no) were included. All activities, experiences, and behaviours referred to the previous six months.

4.3 Results

In total, 2627 participants with OUD provided 24952 observations over the course of the study. The median number of visits was 7 (Q1-Q3: 3-16), median follow-up time was 5.4 years (Q1-Q3: 2.3-10.6), and the median age of the participants at baseline was 36 (Q1-Q3: 25-45). Most participants at baseline were male (63.3%), and of White ethnicity (52.3%). Overall, 26.3% were living with HIV at baseline. During the previous six months at baseline, 69.8% had injected drugs on an at least weekly basis, 64% resided in DTES, 41.3% reported unprotected sex, 50.5% had major pain, 49.5% had accessed OAT, 46.5% had episodes of homelessness, 41.3% had dealt drugs, 27.1% had a regular job, 22.0% were hospitalized, and 19.3% had a history of incarceration.

4.3.1 PSU classes

Two to seven models were assessed to identify the final class solution. Although the six-class model had slightly lower fit indices than the five-class model, it was an expanded version of the five-class model, and all classes except one (without any defining characteristics) were replicated in the six-class model. Moreover, the five-class model had a higher entropy (i.e., class separation). Therefore, the five-class model was selected as the best-estimated solution due to its higher interpretability, utility, and parsimony of the classes. Figure

4.1. provides model fit indices for all models. Baseline characteristics of the participants stratified by class type are presented in Table 4.2. The five-class RMLCA model and its respective item response probabilities are presented in Figure 4.2.

4.3.1.1 Class 1: Low/infrequent use

Class one (30% of the sample) was characterized by unlikely use of different drug types during the previous six months. In particular, this class included those who were unlikely to use methamphetamine (0%) on at least a weekly basis in the previous six months.

4.3.1.2 Class 2: Primarily opioid and methamphetamine use

Class two (22% of the sample) was characterized by an elevated likelihood of at least weekly use of illicit opioids (63%) and methamphetamine (64%). This class also consisted of people who were unlikely to use cocaine (3%) and crack (2%) on at least a weekly basis.

4.3.1.3 Class 3: Primarily cannabis use

Class three (15% of the sample) was characterized by a high likelihood of cannabis use (97%) and low likelihood of using illicit opioids (3%) and methamphetamines (3%).

4.3.1.4 Class 4: Primarily opioid and crack use

Class four (29% of the sample) was characterized with a high likelihood of at least weekly use of illicit opioids (70%), crack (73%) and low likelihood of using methamphetamines (8%).

4.3.1.5 Class 5: Persistent PSU

Class five (4% of the sample) was characterized with a considerable likelihood of high-intensity weekly use of different drug types during the previous six months. In particular, this class consisted of people who had a high likelihood of cannabis (75%), illicit opioids (73%), cocaine (54%), crack (59%), and heavy alcohol use (45%).

4.3.2 Predictors of class membership

The findings of the bivariable and multivariable GEE analyses of factors associated with RMLCA class membership are presented in Tables 4.3 and 4.4, respectively. The trend of different classes over calendar time is presented in Figure 4.3. Notably, membership in Class 1 was increasing from 2005 to 2011 and started decreasing from there. Membership in Class 2 started increasing in 2008 with a more rapid surge from 2012 onwards, and membership in Class 4 has been consistently decreasing since 2006. Membership in class 5 was relatively consistent over time and remained below 10%.

In comparison to Class 1, membership in Class 2 was significantly and positively associated with being male (AOR: 1.40; 95% CI: 1.25, 1.57), at least weekly IDU (AOR: 4.37; 95% CI: 4.07, 4.69), unprotected sex (AOR: 1.16; 95% CI: 1.11, 1.22), hospitalization (AOR: 1.06; 95% CI: 1.01, 1.11), drug dealing (AOR: 1.23; 95% CI: 1.17, 1.29), residence in DTES (AOR: 1.10; 95% CI: 1.04, 1.16), and homelessness (AOR: 1.18; 95% CI: 1.12, 1.24) in the previous six months. Conversely, membership in Class 2 was significantly and negatively associated with age (AOR: 0.94; 95% CI: 0.93, 0.94), BPOC ethnicity (AOR [vs. White]: 0.83; 95% CI: 0.72, 0.95), and having accessed OAT (AOR: 0.87; 95% CI: 0.82, 0.92) in the previous six months.

In comparison to Class 1, membership in Class 3 was significantly and positively associated with being male (AOR: 1.68; 95% CI: 1.46, 1.94), BPOC ethnicity (AOR [vs. White]: 1.30; 95% CI: 1.11, 1.52), unprotected sex (AOR: 1.10; 95% CI: 1.03, 1.17), and drug dealing (AOR: 1.26; 95% CI: 1.18, 1.34) in the previous six months. Conversely, membership in Class 3 was significantly and negatively associated with age (AOR: 0.98; 95% CI: 0.98, 0.99).

In comparison to Class 1, membership in Class 4 was significantly and positively associated with at least weekly IDU (AOR: 4.76; 95% CI: 4.49, 5.04), unprotected sex (AOR: 1.08; 95% CI: 1.04, 1.13), HIV sero-positivity (AOR: 1.11; 95% CI: 1.00, 1.24), hospitalization (AOR: 1.06; 95% CI: 1.02, 1.10), incarceration (AOR: 1.10; 95% CI: 1.04, 1.16), drug dealing (AOR: 1.31; 95% CI: 1.26, 1.37), residence in DTES (AOR: 1.13; 95% CI: 1.07, 1.19), and homelessness (AOR: 1.21; 95% CI: 1.15, 1.26) in the previous six months. Conversely, membership in Class 4 was significantly and negatively associated with age (AOR: 0.96; 95% CI: 0.96, 0.97), BPOC ethnicity (AOR [vs. White]: 0.83; 95% CI: 0.73, 0.95) and having accessing OAT (AOR: 0.84; 95% CI: 0.80, 0.88) in the previous six months.

In comparison to Class 1, membership in Class 5 was significantly and positively associated with being male (AOR: 1.41; 95% CI: 1.16, 1.70), being Indigenous (AOR [vs. White]: 1.33; 95% CI: 1.10, 1.61), having a regular job (AOR: 1.11; 95% CI: 1.02, 1.22), at least weekly IDU (AOR: 6.13; 95% CI: 5.55, 6.78), unprotected sex (AOR: 1.47; 95% CI: 1.34, 1.61), hospitalization (AOR: 1.24; 95% CI: 1.13, 1.35), incarceration (AOR: 1.31; 95% CI: 1.17, 1.46), drug dealing (AOR: 1.92; 95% CI: 1.74, 2.11), residence in DTES (AOR: 1.19; 95% CI: 1.07, 1.31), and homelessness (AOR: 1.32; 95% CI: 1.20, 1.45) in the previous six months. Conversely, membership in Class 5 was significantly and negatively associated with age (AOR: 0.95; 95% CI: 0.94, 0.95), and having accessed OAT (AOR: 0.67; 95% CI: 0.61, 0.74) in the previous six months.

4.4 Discussion

In this study, I assessed the longitudinal patterns of different PSU classes among people with OUD in a large and long-running cohort of PWUD in Vancouver, BC, Canada. I found

five distinct classes of PSU over the course of the study (2005-2018), which were distinguished by people's low/infrequent use of any substances, primarily opioid and methamphetamine use, primarily cannabis use, primarily opioid and crack use, and persistent PSU. The findings are in line with a growing body of evidence that indicates concurrent and/or sequential use of multiple substances is quite common among people with OUD (26, 27, 28, 43, 133, 200, 217).

The results further highlight that people with OUD are a heterogeneous population that include distinct subgroups who vary across numerous characteristics (26, 28) and, therefore, have differing needs. Although all the participants in this longitudinal study met the criteria for OUD at baseline, their substance use patterns over time varied greatly. For example, participants in the study ranged greatly from a sizeable subgroup of people unlikely to report frequent use of any particular type of drugs (i.e., Class 1) to a small subgroup of people who engaged in persistent PSU of multiple drugs (i.e., Class 5). Overall, consistent with an existing body of evidence about people with OUD, membership in higher frequency PSU groups was positively associated with younger age, male sex, and several behavioural (e.g., frequent IDU (108, 109), unprotected sex (119, 127)) and socio-structural adversities (e.g., residence in DTES (218), history of incarceration (108, 109, 128), homelessness (105, 106, 108, 109, 113, 116, 118, 128-130), hospitalization (101, 102, 104, 108, 109, 111, 119, 128, 130), as well as drug dealing (219-222)).

Participants in Class 1 represented a subgroup of people with OUD who did not engage in high-intensity substance use. While this could be viewed as a behavioural characteristic of this subgroup of the population, it could also be partly due to the fact that at baseline, 78% of the people in this class had accessed OAT during the previous six months. In addition, in comparison with all other PSU classes, having accessed OAT at any point during the follow-

up was significantly and positively associated with membership in Class 1. These findings are not surprising given the well-established role of OAT in helping reduce the frequency of current and future use of different types of substances among people with OUD (121, 148, 223, 224). What is particularly interesting is that having accessed OAT at baseline was not necessarily predictive of reduced prospective substance use for a considerable proportion of the participants (e.g., 29.3% of Class 5, 43.5% of Class 4, 64.3% of Class 3, and 43.4% of Class 2 had also accessed OAT in the six months prior to baseline). These results are in line with the findings of several clinical studies highlighting that while OAT helps some people with OUD, it is not an ideal option for everyone (225, 226), and several individual and contextual complexities could impact substance use patterns post-OAT as well as retention in OAT (223-229). Recognizing these dissimilarities and diversities is essential in developing effective and acceptable interventions aimed at providing sustained care and treatment for all subgroups of people with OUD with varying substance use patterns and practices.

All classes, including the low PSU class, reported co-use of opioids and stimulants. This observation is consistent with an increasing body of evidence that highlights the emergence of "twin epidemics" in the North American context (137, 230). In the U.S., fatal ODs including opioids and stimulants have more than doubled since 2000 (30, 231), and in the Canadian province of BC, which includes the setting where the study participants were recruited from, illicit drug-related deaths that involved cocaine and methamphetamines have increased significantly since 2015 (232). People with OUD may opt to co-use stimulants and opioids for several reasons (28, 107, 200, 233). For example, a recent study on a group of Australian PWUD who were receiving OAT reported reduced negative side effects of stimulants, prolonged opioid intoxication, delayed opioid withdrawal, and enhanced euphoria

as their main motivations for co-using opioids and stimulants (234). Another qualitative study in Canada reported additional reasons for concurrent use of stimulants among people receiving methadone maintenance treatment, such as facilitating engagement in survival activities and desire for experiencing stimulant intoxication (139). Given the high probability of co-use of stimulants and opioids across multiple classes over the course of the study and the elevated risk of fatal OD and cardiac arrest among this sub-population of people with OUD (28, 138, 233-236), supporting low-threshold addiction care, putting harm-reduction services at the core of treatment services, and further investments in developing therapeutic options for stimulant use disorder are essential in addressing the special needs of this subgroup of people with OUD.

Across all latent classes except Class 1, the probability of reporting co-use of at least weekly cannabis during the previous six months was over 30%. In Class 3, cannabis appeared to be the dominant drug of use, and people in this class reported using at least weekly cannabis almost all the time. These findings are in line with a growing body of evidence that points to frequent co-use of opioids and cannabis among people with OUD (122, 127, 237, 238). Estimates of co-use of cannabis use among people with OUD vary greatly across the literature, ranging from 14% in China (105) to over 60% in Canada (122, 123); differences that could be associated with cost, criminality, availability, and cultural acceptability of cannabis across different settings (237, 238). Data on adverse effects of cannabis use on OAT are mixed (237-241). I noted that membership in Class 3 was not associated with reduced access to OAT. This observation is in line with findings of a considerable body of evidence (237, 242-247) as well as a recent systematic review of cannabis use among patients receiving OAT that suggests cannabis use to be unlikely to undermine favorable OAT treatment outcomes (237). While reasons for particular patterns of co-use of cannabis and opioids were not collected in this

study, previous studies suggest that cannabis use may help support retention in OAT and reducing opioid-related craving and withdrawal symptoms (106, 237, 238, 246-248).

Overall, the findings of this study indicate that paying close attention to the heterogeneities and diversities within the population of people with OUD is critical not only for improving how client-centred addiction care and treatment are provided, but also in optimizing resource allocation in the collective efforts aimed at tackling the opioid epidemic. The existing interventions and investments often tend to overemphasize the importance of investing in increased access to and effectiveness of pharmacological options for OUD, opioid OD prevention, fentanyl drug checking, access to safer supply of opioids, and limiting access to illicit opioids (1, 27, 141-143, 249). While these interventions should indeed remain an essential part of the response to the opioid OD epidemic, they are often not client-centred and overlook the needs of certain subgroups of people with OUD who do not fit in a single "box" of those who mainly use opioids (e.g., people who engage in PSU involving stimulants) and may not respond well to opioid-centric interventions. While effective pharmacological interventions for stimulant use disorder remain to be developed, it would be beneficial to offer behavioural and harm reduction interventions tailored towards addressing stimulant use disorder in OAT settings.

4.4.1 Limitations

I acknowledge the limitations of the study, most of which are common in studies of substance use among people who are marginalized. First, the findings of a non-random sample of PWUD in Vancouver may not be generalizable to all PWUD in BC or elsewhere. However, recruiting a large representative sample of PWUD that are followed over a long period of time is quite challenging, if not impossible, especially as no registries of PWUD exist in most

settings. Second, primary analyses were based on self-reported measures of substance use practices in the previous six months. The findings are therefore prone to recall and social desirability biases. Third, I could not measure simultaneous use of drugs or the order of using drugs (e.g., stimulants first and opioids seconds or vice versa) mainly due to the longitudinal nature of the study and how variables have been measured throughout the years since the establishment of the cohorts over two decades ago. The only measures available for simultaneous substance use were participants' reports of speedball and goofball use during the previous six months, which were excluded from the RMLCA due to their small sample size. Future studies could provide a complete picture of PSU among people with OUD if they make efforts to measure concurrent use of different substances. Moreover, due to the small sample size of people who reported frequent benzodiazepine use, I could not identify classes of people who co-use benzodiazepines and opioids despite the considerable body of evidence on the prevalence and consequences of co-using benzodiazepine and opioids among people with OUD in other settings (26, 42, 133). It is important to note that these subgroups do exist among people with OUD and need to be paid special attention in clinical care and intervention developments. Forth, given the observational nature of this study, causality cannot be inferred. Lastly, future studies on PSU need to assess the longitudinal impact of exposure to synthetic opioids on people with OUD's substance use practices.

4.5 Conclusions

The longitudinal assessment of PSU classes among people with OUD in Vancouver underscored the heterogeneous characteristics of people with OUD. The findings showed how and why interventions heavily focused on opioid use cessation, substance use abstinence, and

individual behaviour change among people with OUD may fail to recognize people's diverse needs and motivations for substance use and, therefore, have limited effectiveness and acceptability among a large proportion of people with OUD. The observed heterogeneities are of particular importance for clinicians and other care providers in addiction medicine as well as health policymakers who develop programs and interventions for addressing the opioid epidemic. Care for people with OUD needs to be client-centred. Providing a "one size fits all" approach that is exclusively focused on opioid medication-assisted therapy or restricting access to illicit opioids is likely to have a limited impact.

Figure 4.1. Model fit indices for RMLCA models

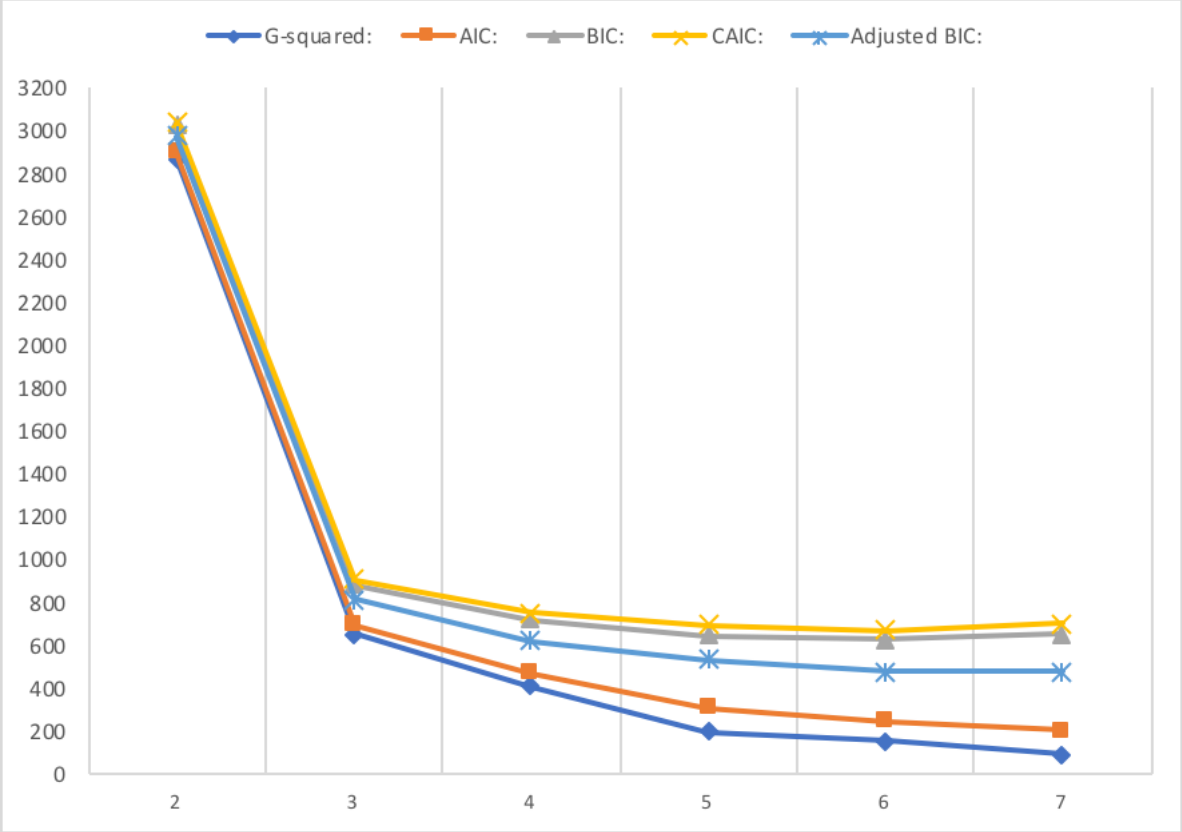
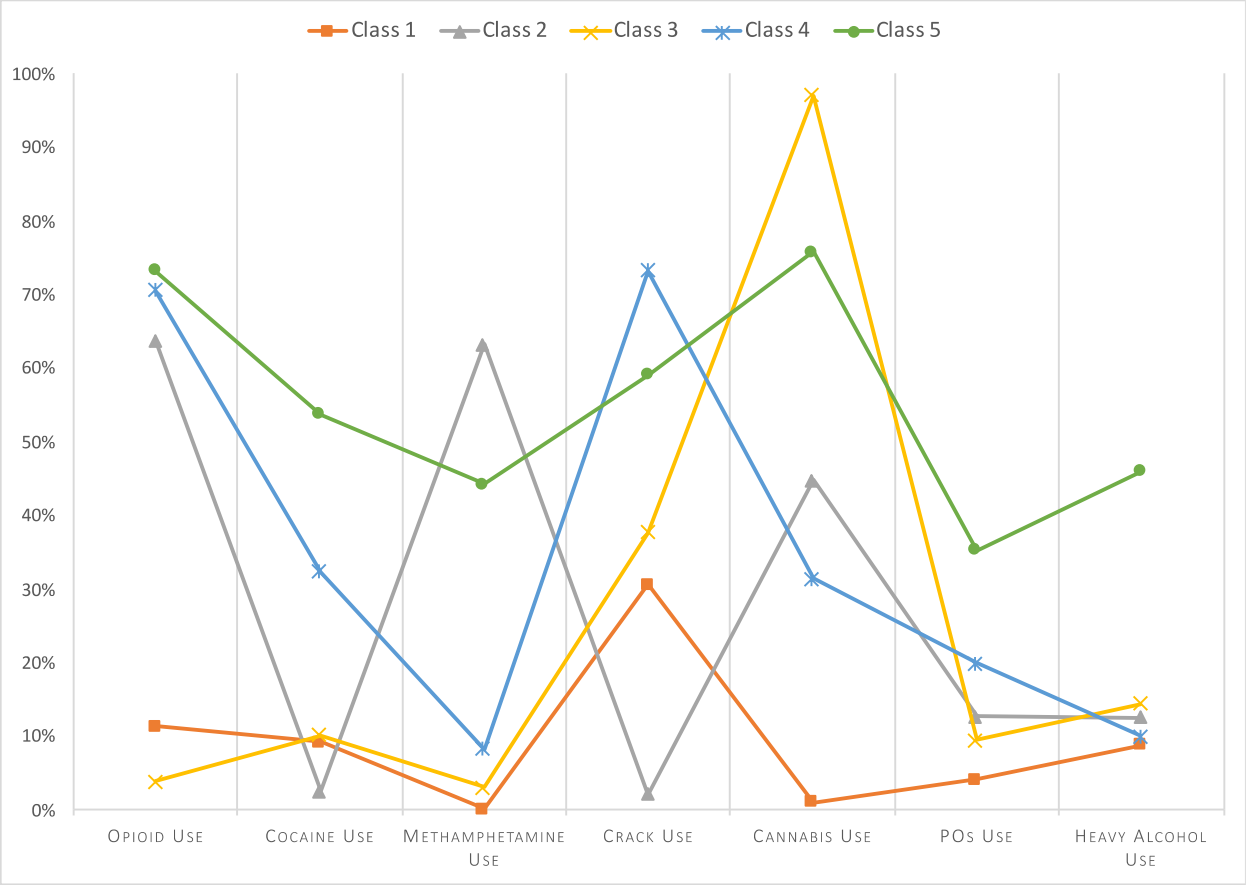
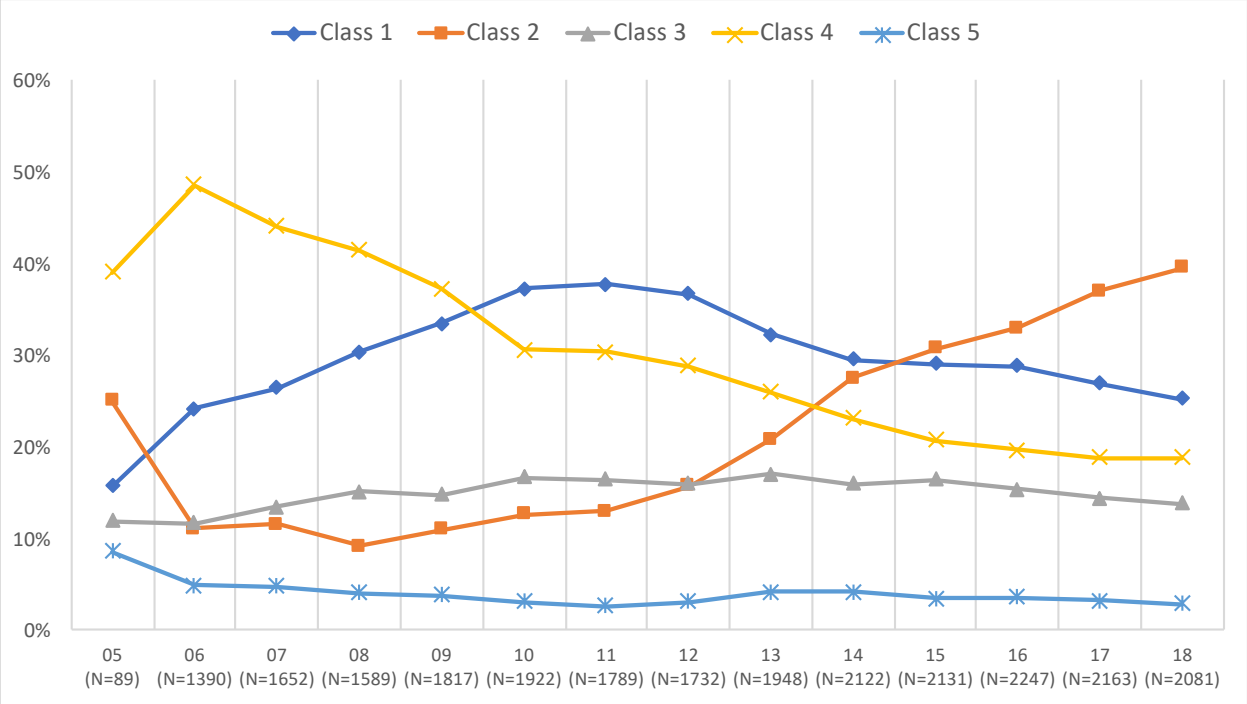


Figure 4.2. Item response probabilities across different latent classes during the study period (2005-2018)



Note: All drugs refer to at least weekly use except heavy alcohol use. All variables refer to the previous 6 months. Class 1 (30%: Low/Infrequent substance use); Class 2 (22%: Primarily opioids and methamphetamine use); Class 3 (15%: Primarily cannabis use); Class 4 (29%: Primarily opioids and crack use); Class 5 (4%: Persistent PSU).

Figure 4.3. Trend of RMLCA class membership over calendar year (2005-2018)



Note: Class 1 (Low/Infrequent substance use); Class 2 (Primarily opioids and methamphetamine use); Class 3 (Primarily cannabis use); Class 4 (Primarily opioids and crack use); Class 5 (Persistent PSU)

Table 4.1. Binary variables used for the RMLCA, at baseline (N = 2627)

Characteristics	N (%)
Weekly Illicit Opioid Use (L6M)	1775 (67.6)
Weekly Cocaine Use (L6M)	632 (24.2)
Weekly Methamphetamine Use (L6M)	706 (27.0)
Weekly Crack Use (L6M)	1347 (51.6)
Weekly Cannabis Use (L6M)	1181 (45.1)
Weekly Prescription Opioids Use (L6M)	665 (25.4)
Heavy Alcohol Use (L6M)	392 (14.9)

Note: L6M: Last six months; Weekly use refers to at least weekly use

Table 4.2. Baseline characteristics of participants with opioid use disorder (N = 2627)

Characteristics	Class 1	Class 2	Class 3	Class 4	Class 5	P-value
Cohort						
ACCESS	141 (35.1)	101 (15.2)	82 (32.5)	318 (29.1)	38 (18.5)	
VIDUS	44 (10.9)	303 (45.6)	65 (25.9)	209 (19.1)	89 (43.4)	<0.0001
ARYS	217 (54.0)	261 (39.2)	105 (42.6)	567 (51.8)	78 (38.1)	
Age (Median Q1, Q3)	42 (33, 49)	27 (23, 35)	39 (27, 46)	37 (27, 46)	29 (23, 40)	<0.0001
Sex (at birth)	228 (56.8)	435 (65.5)	183 (72.4)	676 (61.8)	135 (66.1)	0.001
Ethnicity						0.002
White	185 (46.8)	382 (57.7)	126 (50.3)	543 (49.8)	104 (51.0)	<0.0001
Indigenous	125 (31.5)	212 (32.1)	72 (28.7)	363 (33.3)	74 (36.1)	
BPOC	86 (21.7)	68 (10.2)	53 (21.0)	184 (16.9)	26 (12.9)	
Regular job (L6M)	92 (22.9)	209 (31.5)	85 (33.5)	255 (23.3)	66 (32.2)	<0.0001
Weekly IDU (L6M)	156 (38.7)	530 (79.6)	75 (29.5)	911 (83.2)	150 (73.6)	<0.0001
Pain (L6M)	32 (48.5)	220 (50.8)	29 (46.5)	116 (50.9)	45 (53.7)	0.928
Unprotected sex (L6M)	123 (30.8)	350 (53.6)	88 (34.9)	400 (36.9)	107 (52.5)	<0.0001
HIV sero-positivity	141 (35.2)	106 (16.0)	82 (32.9)	321 (29.4)	38 (18.7)	<0.0001
OAT (L6M)	312 (77.9)	288 (43.4)	162 (64.3)	471 (43.5)	59 (29.3)	<0.0001
Hospitalization (L6M)	75 (18.9)	163 (24.8)	49 (19.8)	235 (21.8)	48 (23.8)	0.180
Incarceration (L6M)	46 (11.6)	133 (20.1)	34 (13.5)	234 (21.7)	49 (24.3)	<0.0001
Drug dealing (L6M)	107 (26.6)	272 (40.9)	83 (32.8)	502 (45.9)	113 (55.3)	<0.0001
DTES residence (L6M)	238 (59.2)	409 (61.4)	139 (54.9)	766 (70.0)	125 (61.4)	<0.0001
Homelessness (L6M)	108 (27.1)	375 (56.9)	79 (31.2)	527 (48.4)	121 (59.4)	<0.0001

Notes: Class 1 (Low/Infrequent substance use), Class 2 (Primarily opioids and methamphetamine use), Class 3 (Primarily cannabis use), Class 4 (Primarily opioids and crack use), Class 5 (Persistent PSU); L6M: Last six months; BPOC: Black person and person of color; IDU: Injection drug use; Data are n (%) unless otherwise specified; P-values are based on chi-square tests.

Table 4.3. Bivariable GEE analysis of factors associated with each class membership

Characteristics	Class 2 vs. 1		Class 3 vs. 1		Class 4 vs. 1		Class 5 vs. 1	
Cohort	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
VIDUS vs. ACCESS	4.79 (4.02, 5.70)	<0.0001	1.69 (1.40, 2.04)	<0.0001	1.71 (1.44, 2.03)	<0.0001	4.48 (3.48, 5.78)	<0.0001
ARYS vs. ACCESS	1.23 (1.08, 1.40)	0.002	1.04 (0.91, 1.20)	0.549	1.10 (0.99, 1.22)	0.076	1.22 (0.98, 1.51)	0.072
Age (per year older)	0.94 (0.93, 0.94)	<0.0001	0.98 (0.98, 0.99)	<0.0001	0.95 (0.95, 0.96)	<0.0001	0.93 (0.93, 0.94)	<0.0001
Calendar year	1.02 (1.01, 1.03)	0.005	0.93 (0.92, 0.94)	<0.0001	0.83 (0.82, 0.84)	<0.0001	0.92 (0.90, 0.93)	<0.0001
Sex (male)	1.18 (1.05, 1.33)	0.007	1.58 (1.38, 1.81)	<0.0001	0.95 (0.86, 1.05)	0.323	1.15 (0.95, 1.39)	0.144
White ethnicity								
Indigenous vs. White	0.91 (0.80, 1.04)	0.154	1.01 (0.87, 1.16)	0.934	1.06 (0.94, 1.18)	0.341	1.30 (1.07, 1.58)	0.008
BPOC vs. White	0.55 (0.46, 0.64)	<0.0001	1.26 (1.09, 1.46)	0.002	0.80 (0.70, 0.92)	0.001	0.74 (0.58, 0.94)	0.014
Regular job (L6M)	1.03 (0.98, 1.08)	0.259	1.07 (1.01, 1.13)	0.015	0.91 (0.87, 0.96)	0.0001	1.03 (0.94, 1.13)	0.524
Weekly IDU (L6M)	4.50 (4.21, 4.81)	<0.0001	1.04 (0.98, 1.11)	0.232	5.80 (5.48, 6.14)	<0.0001	7.56 (6.80, 8.40)	<0.0001
Pain (L6M)	1.07 (1.03, 1.12)	0.001	1.02 (0.97, 1.08)	0.395	1.05 (1.00, 1.10)	0.034	1.15 (1.07, 1.24)	<0.0001
Unprotected Sex (L6M)	1.37 (1.30, 1.45)	<0.0001	1.14 (1.07, 1.21)	0.0001	1.17 (1.11, 1.24)	<0.0001	1.77 (1.61, 1.94)	<0.0001
HIV sero-positivity	0.58 (0.52, 0.66)	<0.0001	0.87 (0.77, 0.99)	0.042	0.84 (0.76, 0.94)	0.001	0.60 (0.49, 0.73)	<0.0001
OAT (L6M)	0.72 (0.68, 0.77)	<0.0001	0.92 (0.85, 0.99)	0.022	0.69 (0.65, 0.73)	<0.0001	0.50 (0.45, 0.56)	<0.0001
Hospitalization (L6M)	1.07 (1.02, 1.12)	0.003	0.95 (0.90, 0.99)	0.038	1.06 (1.01, 1.11)	0.012	1.16 (1.07, 1.26)	0.0001
Incarceration (L6M)	1.37 (1.27, 1.47)	<0.0001	1.15 (1.05, 1.26)	0.004	1.57 (1.47, 1.67)	<0.0001	2.17 (1.91, 2.45)	<0.0001
Drug dealing (L6M)	1.58 (1.50, 1.66)	<0.0001	1.34 (1.25, 1.42)	<0.0001	1.99 (1.89, 2.09)	<0.0001	3.12 (2.83, 3.45)	<0.0001
DTES (L6M)	1.18 (1.12, 1.25)	<0.0001	1.05 (0.98, 1.12)	0.173	1.50 (1.41, 1.59)	<0.0001	1.48 (1.34, 1.64)	<0.0001
Homelessness (L6M)	1.65 (1.57, 1.75)	<0.0001	1.10 (1.03, 1.17)	0.005	1.75 (1.66, 1.85)	<0.0001	2.51 (2.28, 2.76)	<0.0001

Notes: Class 1 (Low/Infrequent substance use), Class 2 (Primarily opioids and methamphetamine use), Class 3 (Primarily cannabis use), Class 4 (Primarily opioids and crack use), Class 5 (Persistent PSU); L6M: Last six months; BPOC: Black person and person of color; IDU: Injection drug use.

Table 4.4. Multivariable GEE analysis of factors associated with each class membership

Characteristics	Class 2 vs. 1		Class 3 vs. 1		Class 4 vs. 1		Class 5 vs. 1	
	AOR (95% CI)	**P-value**	**AOR (95% CI)**	**P-value**	**AOR (95% CI)**	**P-value**	**AOR (95% CI)**	**P-value**
Age (per year older)	0.94 (0.93, 0.94)	<0.0001	0.98 (0.98, 0.99)	<0.0001	0.96 (0.96, 0.97)	<0.0001	0.95 (0.94, 0.95)	<0.0001
Calendar year	1.04 (1.03, 1.05)	<0.0001	0.95 (0.94, 0.96)	<0.0001	0.85 (0.84, 0.85)	<0.0001	0.96 (0.94, 0.98)	<0.0001
Sex (male)	1.40 (1.25, 1.57)	<0.0001	1.68 (1.46, 1.94)	<0.0001	-	-	1.41 (1.16, 1.70)	0.001
Ethnicity								
Indigenous vs. White	0.91 (0.81, 1.03)	0.135	1.12 (0.97, 1.30)	0.119	0.94 (0.85, 1.05)	0.291	1.33 (1.10, 1.61)	0.003
BPOC vs. White	0.83 (0.72, 0.95)	0.010	1.30 (1.11, 1.52)	0.001	0.83 (0.73, 0.95)	0.005	1.04 (0.83, 1.32)	0.719
Regular Job (L6M)	-	-	-	-	-	-	1.11 (1.02, 1.22)	0.023
Weekly IDU (L6M)	4.37 (4.07, 4.69)	<0.0001	-	-	4.76 (4.49, 5.04)	<0.0001	6.13 (5.55, 6.78)	<0.0001
Unprotected Sex (L6M)	1.16 (1.11, 1.22)	<0.0001	1.10 (1.03, 1.17)	0.004	1.08 (1.04, 1.13)	0.001	1.47 (1.34, 1.61)	<0.0001
HIV sero-positivity	-	-	-	-	1.11 (1.00, 1.24)	0.048	-	-
OAT (L6M)	0.87 (0.82, 0.92)	<0.0001	-	-	084 (0.80, 0.88)	<0.0001	0.67 (0.61, 0.74)	<0.0001
Hospitalization (L6M)	1.06 (1.01, 1.11)	0.018	-	-	1.06 (1.02, 1.10)	0.005	1.24 (1.13, 1.35)	<0.0001
Incarceration (L6M)	-	-	-	-	1.10 (1.04, 1.16)	0.001	1.31 (1.17, 1.46)	<0.0001
Drug dealing (L6M)	1.23 (1.17, 1.29)	<0.0001	1.26 (1.18, 1.34)	<0.0001	1.31 (1.26, 1.37)	<0.0001	1.92 (1.74, 2.11)	<0.0001
DTES (L6M)	1.10 (1.04, 1.16)	0.001	-	-	1.13 (1.07, 1.19)	<0.0001	1.19 (1.07, 1.31)	0.001
Homelessness (L6M)	1.18 (1.12, 1.24)	<0.0001	-	-	1.21 (1.15, 1.26)	<0.0001	1.32 (1.20, 1.45)	<0.0001

Notes: Class 1 (Low/Infrequent substance use); Class 2 (Primarily opioids and methamphetamine use); Class 3 (Primarily cannabis use); Class 4 (Primarily opioids and crack use); Class 5 (Persistent PSU); Pain (L6M) was not considered due to data unavailability; Cohort is not included due to duplicated info with Age and HIV (Cohort ~ Age group X HIV group); Cells left blank indicate that the respective variables were not selected in the final model selection procedure. Comparisons are yes vs. no unless specified otherwise; L6M: Last six months; BPOC: Black person and person of color; IDU: Injection drug use.

Chapter 5: Polysubstance use trajectories and non-fatal overdose among a cohort of people with opioid use disorder in Vancouver, BC, Canada

5.1 Introduction

North America continues to contend with a surging number of illicit drug-related fatal and non-fatal ODs (195, 202). In the U.S., where drug-related ODs are the leading cause of injury-related deaths, an estimated 90,000 people lost their lives due to drug-related ODs in 2020 (250). OD-related hospitalizations have also been steadily rising. For example, 967,615 non-fatal drug-related ODs were treated in emergency departments across 29 states in the U.S. in 2017, corresponding to a 4.3% increase compared with 2016 (251). In Canada, between January 2016 and December 2020, an estimated 21,174 opioid toxicity deaths, as well as 11,176 stimulant-related and 24,671 opioid-related poisoning hospitalization, have been reported (11).

In most high-income settings that benefit from robust recording systems for fatal ODs, the understanding of drug-related OD deaths is considerably better than that of non-fatal ODs (25). Indeed, rates of non-fatal ODs are often underestimated and not adequately recorded in OD surveillance systems for a number of reasons. While some people experiencing non-fatal ODs may get revived by their peers (e.g., through naloxone administration), others may be reluctant to seek care and get connected to post-OD services due to the stigma associated with drug-related OD in healthcare settings (252). Studies also suggest that some PWUD fear encountering law enforcement at OD scenes and avoid calling for help (e.g., 9-1-1) when witnessing an OD event (253-255). These issues are all concerning given the well-established independent association of non-fatal ODs with future fatal ODs (256-259), and given that non-

fatal overdoses often lead to significant morbidity (e.g., hypoxic brain injury). Moreover, non-fatal ODs have been correlated with excess social (e.g., criminal justice system), economic (e.g., lost productivity), and healthcare (e.g., medical service utilizations) costs. For example, the White House's Council of Economic Advisors estimated the total annual cost of the non-fatal opioid-related ODs in the U.S. to have been as high as 504 billion USD in 2015 (260). In Canada, estimates on the economic burden of non-fatal ODs are unavailable, but the annual cost of major mental health conditions, including SUD has been estimated to be about 42.3 billion CAD in direct and 6.3 billion CAD in indirect costs (261).

The majority of the evidence on drug-related ODs assesses predictors and harms associated with specific types of substances. For example, cocaine, heroin, and PO have been reported to be the most frequently associated substances with unintentional drug ODs across the world (25). In the context of an unregulated illicit drug market where supplies could be contaminated with several substances, some PWUD may engage in PSU accidentally (48, 262). However, PSU could be practiced knowingly for several individual- (e.g., recreational or therapeutic) or supply-level (e.g., shortage of certain drugs in the market) reasons (26, 28). Epidemiological studies conducted four decades ago, as well as a growing body of more recent evidence, suggest that PSU is particularly frequent among people with OUD (28, 263, 264). For example, data from the Epidemiologic Catchment Area in the 1980s reported that people who were regularly using heroin and opioids other than heroin were on average using 5 and 5.8 other drugs (excluding alcohol and tobacco), respectively (264). Similarly, in a longitudinal study of 4817 people with regular opioid use who were seeking addiction treatment in Finland from 1997 to 2008, the average number of drugs used was 3.5, and simultaneous and sequential PSU was common (265).

Despite the considerable prevalence of PSU among people with OUD and its association with several adverse mental and physical health outcomes (e.g., depression, anxiety, risky sexual practices, OD) as well as addiction treatment-related outcomes (e.g., reduced retention in addiction treatment, increased rates of relapse) in comparison with mono-substance use (27, 28, 198), the understanding of the patterns of PSU and heterogeneous risks of non-fatal ODs among different subgroups of people with OUD remains limited. The available evidence is mainly based on cross-sectional studies focusing on specific types of substance use practices and fails to capture potential nuances within longitudinal trajectories of PSU among people with OUD. We, therefore, aimed to identify longitudinal PSU classes among a cohort of PWUD in Vancouver and characterize non-fatal OD risks among different sub-classes over time.

5.2 Methods

5.2.1 Data source and participants

Data were obtained from three open, prospective cohort studies (VIDUS, ACCESS, and ARYS) of PWUD in Vancouver, BC, Canada, the details of which are described in Section 1.5. For this specific analysis, participants were limited to those who had been interviewed at least once during the study period (2005-2018). To limit the sample to people with OUD, I followed an approach previously used in the substance use literature (173, 174). I included PWUD who met the criteria for OUD at baseline defined as reporting illicit opioid use (injection or non-injection) on at least a weekly basis or having received OAT in the previous six months.

5.2.2 Measures

5.2.2.1 Outcome variable

The primary outcome of interest in this analysis was self-reported non-fatal OD during the past six months and was determined by assessing participants' responses to the following question: "In the last six months, have you overdosed on any drug by accident (i.e., had a negative reaction from using too much drugs or had a bad trip)?''. Responses were coded as yes or no.

5.2.2.2 Primary explanatory variable

The primary explanatory variable of interest was longitudinal PSU classes emerging over time among the participants and was ascertained via RMLCA (58). Details of the RMLCA modeling procedure are provided in Chapter four of the thesis. In brief, RMLCA's outcome indicators were binary variables of at least weekly illicit opioid use, cocaine use, crystal meth use, crack use, cannabis use, non-medical PO use, and heavy alcohol use (defined as >14 weekly drinks >5 daily drinks for men and for women, >7 weekly drinks or >4 daily drinks) (7). Weekly reported use of benzodiazepine, ecstasy/MDMA, speedball, and goofball were excluded from RMLCA given their low frequency (i.e., <5%). Participants with missing values for any of the key outcome indicators were excluded (i.e., 277 visits). All outcome indicators corresponded to the previous six months. A combination of selection criteria (210-212, 266) was considered to identify the final class solution (i.e., Akaike Information Criterion [AIC], Bayesian Information Criterion [BIC]), entropy, stability of classes).

5.2.2.3 Potential confounders

The selection of potential confounders in the association between PSU classes and non-fatal OD was informed by their a priori hypothesized relationship with the primary outcome

and exposure variables of interest as well as a literature review concerning substance use patterns and non-fatal OD among PWUD (25, 26). Sociodemographic covariates included age (per year older), sex at birth (male or female), ethnicity (White, Indigenous, Black and other persons of color), employment (yes or no), and cohort (ACCESS, VIDUS, or ARYS). Participants' substance use characteristics of interest included at least weekly IDU (yes or no), length of injecting career (per year older), binge drug use (yes or no), and receipt of OAT (yes or no). Lastly, potential structural confounders examined included, participants' history of incarceration (yes or no), drug dealing (yes or no), DTES residence, a neighbourhood characterized with a high concentration of substance use, poverty, and use of social services (yes or no), homelessness (yes or no), public injection (yes or no), childhood trauma (defined as a score of 13-25 [yes] or <13 [no] on the Childhood Trauma Questionnaire (267)), and depression (defined as a score of ≥22 [yes] or <22 [no] on the Center for Epidemiologic Studies Depression Scale (268)) at baseline (yes or no). All activities and experiences corresponded to the previous six months, unless indicated otherwise.

5.2.3 Data analysis

Descriptive characteristics of the sample were stratified by non-fatal OD and examined at baseline, using Pearson's Chi-square test (for categorical variables) and Wilcoxon rank sum test (for continuous variables). Participants were then assigned to different latent classes identified through RMLCA based on their highest posterior class membership probabilities. The association between PSU class membership and non-fatal OD was examined using GEE (213, 214). GEE models were fit to allow adjusting for the correlated nature of the longitudinal data through applying an exchangeable working correlation structure. Class 1 was considered as the

reference category in the regression analysis.

A bivariable GEE model was built to assess the association between non-fatal OD and the primary explanatory variable of interest as well as all secondary explanatory variables. As the objective of the study was to determine the association of membership in different PSU classes and non-fatal OD independent of potential individual, behavioural, and structural confounders, multivariable GEE models were constructed following a stepwise backward selection approach (269). First, all variables associated with non-fatal OD in the bivariable analyses at a p-value of 0.1 were considered for the multivariable analysis and used to fit a series of reduced models. At each round, the variable corresponding to the smallest relative change in the coefficients of the PSU variable was dropped in an iterative fashion until the minimum change was larger than 5% (270, 271). A sensitivity analysis was conducted to include all potential confounders in the final model and assess whether the association between PSU classes and non-fatal OD changed. AORs along with their 95% CI were reported. All analyses were conducted in SAS (Version 14.2) and R software (Version 3.6.3), and all p-values were two-sided with a significance level of 0.05.

5.3 Results

A total of 2627 participants provided 24952 observations over the study period with a median of 7 visits throughout the study (Q1-Q3: 3-16) and a median follow-up duration of 5.4 years (Q1-Q3: 2.3-10.6). Overall, 1094 (41.6%) participants had experienced at least one non-fatal OD during the study period. Baseline descriptive statistics of the participants stratified by non-fatal OD in the previous six months are presented in Table 5.1. At baseline, median (IQR) age of the participants was 35 (Q1-Q3: 24-45), and 954 (36.5%) were female. Moreover, 687

(26.3%) were living with HIV, and 1741 (66.6%) were living with HCV. The prevalence of non-fatal OD in the previous six months varied greatly across different classes at baseline. As outlined in Chapter four, RMLCA revealed five distinct longitudinal PSU classes, including low/infrequent use (Class 1; 30%), primarily opioid and meth use (Class 2; 22%), primarily cannabis use (Class 3; 15%), primarily opioid and crack use (Class 4; 29%), and persistent PSU (Class 5; 4%). Figure 4.1. provides model fit indices for RMLCA models. The five-class RMLCA model and its corresponding item response probabilities are presented in Table 5.2. Substance use patterns of people in different classes varied greatly across different groups: Class 1 were unlikely to report using different drug types during the previous six months; Class two were likely to report at least weekly use of illicit opioids and methamphetamine; Class 3 were highly likely to report at least weekly cannabis use and unlikely to use illicit opioids and methamphetamines; Class 4 were highly likely to report at least weekly use of illicit opioids and crack, but a low likelihood of using methamphetamines; and Class 5 were highly likely to report at least weekly use of several drug types. While membership in Class 5 was relatively stable across the study, membership in Class 2 had an increasing trend during the study period. Moreover, in comparison with Class 1, membership in Classes 2, 4, and 5 was significantly and positively associated with higher odds of hospitalization (Data shown in Chapter four).

The crude and adjusted longitudinal estimates of the odds of self-reported non-fatal OD across different PSU classes are presented in Tables 5.3. In bivariable GEE analyses, in comparison with Class 1, membership in all three PSU classes except Class 3 was significantly associated with increased odds of non-fatal OD: Class 2 vs. Class 1 (OR= 4.78, 95% CI: 4.13-5.54), Class 3 vs. Class 1 (OR = 1.06, 95% CI: 0.89-1.27), Class 4 vs. Class 1 (OR = 2.40, 95% CI: 2.07-2.79), and Class 5 vs. Class 1 (OR = 5.86, 95% CI: 4.35-7.89). The same three

PSU classes remained positively associated with non-fatal OD in the multivariable GEE analyses, after adjusting for potential confounders: Class 2 vs. Class 1 (AOR = 2.64, 95% CI: 2.17-3.22), Class 3 vs. Class 1 (AOR = 0.93, 95% CI: 0.76-1.13), Class 4 vs. Class 1 (AOR = 1.36, 95% CI: 1.11-1.67), and Class 5 vs. Class 1 (AOR = 2.82, 95% CI: 2.03-3.93). The findings remained relatively unchanged in the sensitivity analysis where all variables conceptually associated with non-fatal OD were included in the final multivariable model; however, the association observed for Class 4 became statistically insignificant: Class 2 vs. Class 1 (AOR = 2.20, 95% CI: 1.51 - 3.22), Class 3 vs. Class 1 (AOR = 0.86, 95% CI: 0.69-1.07), Class 4 vs. Class 1 (AOR = 1.06, 95% CI: 0.85 - 1.33), and Class 5 vs. Class 1 (AOR = 2.39, 95% CI: 1.92-2.97).

5.4 Discussion

I studied a cohort of 2627 people with OUD over a 12-year period and observed that membership in higher intensity PSU classes, despite differences among these classes, was significantly and positively associated with increased odds of non-fatal OD, independent of potential sociodemographic, behavioural, and structural confounders. The findings are consistent with an existing body of cross-sectional studies examining the association of non-fatal OD and membership in PSU latent classes among people with OUD in Australia (104), Mexico (119), Norway (108), and U.S. (130, 273, 274). I also observed that membership in Class 3 (i.e., primarily cannabis use) was not associated with increased odds of non-fatal OD, which could reflect the low use of opioids in this class.

Combining opioids and sedatives or stimulants could lead to increased consumption and enhanced adverse effects of drugs and, therefore, lead to several life-threatening

conditions, including respiratory depression, myocardial infarction, and ODs (28, 42). Given the observed relationship between the intensity of PSU and odds of non-fatal OD over time, there is a need to better understand and measure PSU not only in the context of opioids (e.g., concurrent use of PO and illicit opioids), but also in the context of simultaneous or sequential use of opioids and other types of drugs (e.g., concurrent use of opioids and different types of non-opioids) among people with OUD. Indeed, recent data from nine provinces in Canada from January to July 2020 suggest that out of all drug-related poisoning hospitalizations recorded in Canada, 29% of opioid-related cases involved non-opioid PSU and 65% of stimulant-related cases involved non-stimulant PSU (11). Restricting studies and interventions to single classes or types of drugs would not only decrease the translatability of research findings into effective practice in clinical settings, but may also contribute to lower self-perceived risk of ODs and reduced access to essential life-saving OD prevention interventions (e.g., naloxone kits) among people who engage in PSU but who do not primarily use opioids (276, 277).

The finding that more people have been using opioids and methamphetamines (i.e., Class 2) over time is consistent with an increasing body of evidence across the world. Indeed, the United Nations Office on Drugs and Crime reports that an increasing proportion of people with OUD who are entering treatment facilities across the world supplement their use with methamphetamine (278). Longitudinal analyses from over 3,500,000 treatment admission records in the U.S. suggest that the percentage of people who were primarily using heroin but also reported methamphetamine use has surged from 2.1% in 2008 to 12.4% in 2017, corresponding to a relative percentage change of 490% (279). In BC, which has seen a decline in life expectancy due to the OD epidemic (280), past-week use of methamphetamine among

clients of harm reduction sites across the province has increased from 47% in 2015 to 69% in 2018 (281). Several individual-level (e.g., prolonged opioid intoxication, enhanced euphoria, desire for experiencing a "roller coaster ride", delayed opioid withdrawal, facilitating engagement in survival activities) and supply-level (e.g., increased production, supply, and access to methamphetamine) reasons could have contributed to the increase in methamphetamine use among people with OUD (27, 139, 234). Further investments in low-threshold addiction care and harm reduction services would be an essential step in meeting the needs of these specific groups of people with OUD. In the absence of effective pharmacological treatments for methamphetamine use disorders, combining OAT medications with non-pharmacological interventions (e.g., contingency management, community reinforcement approach) has been promising for these subgroups of people with OUD. However, these interventions are often not durable or lose their benefits in the long term (282).

Consistent with an existing body of evidence (255, 272), PWUD who engaged in higher intensity PSU were more likely to have been hospitalized in the previous six months. Therefore, there is a critical opportunity for identifying people at a high risk of OD and linking them with harm reduction and addiction treatment services during their hospitalization. However, several reports have documented that people with OUD are often discriminated against in healthcare settings, undertreated for opioid-related withdrawal symptoms and pain, and leave the hospital prematurely against medical advice (283, 284). National-level statistics in Canada suggest that among PWUD admitted to hospitals for opioid-related (n = 21,824 people) and stimulant-related (n =9,869) poisonings from January 2016 to June 2020, the median length of hospital stay was three and two days, respectively (11). It is essential that healthcare providers prioritize trust and offer a non-judgmental, safe, and respectful space

when caring for PWUD. Asking people with OUD about their type, amount, and frequency of substance use during clinical examinations post-OD could help identify their specific needs and treatment requirements (285, 286). Moreover, in-hospital services for people with OUD should consider options beyond OD prevention education and abstinence-focused care. An extensive body of evidence suggests the initiation of OAT in the hospital to be associated with improved health outcomes, such as increased engagement with addiction treatment services, decreased readmissions due to non-fatal ODs, and fatal ODs (147, 286, 287). In addition, providing harm reduction services, including but not limited to take-home naloxone kits, peer support (e.g., recovery coaches), sterile needles and disposal containers, and supervised consumption facilities in hospital settings could reduce OD risks among people with OUD (284, 285, 287, 288).

5.4.1 Limitations

I would like to acknowledge the limitations of the study. First, the non-random nature of the sample limits its generalizability to all people with OUD in BC or other settings. However, given the challenging nature of recruiting a random sample of people with OUD, the longitudinal cohort and large sample size help increase the external validity of this study (290-291). Second, to include 12 years of data in the analysis, I had to rely on self-reported measures of at least weekly substance use practices in the previous six months, which might have led to measurement, recall or social desirability biases. Moreover, given the observational nature of the study, causation cannot be inferred. Third, while PSU could be simultaneous or sequential, I was unable to tease apart such differences given how variables have been measured since the initiation of data collection a few decades ago. While self-reported

measures for speedball and goofball use were available, these data were excluded from the RMLCA due to their small frequency. Fourth, I could not include benzodiazepine use in the RMLCA analysis given the small sample number of people who used illicit benzodiazepine frequently. This should not be interpreted as low frequency of benzodiazepine use among people with OUD. An extensive body of evidence has reported on the prevalence and consequences of co-using benzodiazepine and opioids among people with OUD in other settings (42, 289). Indeed, recent survey data from BC suggest a surge in the use of benzodiazepines (e.g., etizolam) among PWUD as well as its detection among illicit drug toxicity deaths in the province (292). Fifth, I could not adjust for the frequency of smoking as a confounder in the analysis, given it was unavailable in the questionnaire. Lastly, the findings should be interpreted with an eye to the changes happened in the illicit drug supply in Vancouver and various policies implemented from 2005. Indeed, the risk environment in Vancouver has been rapidly changing since the influx of fentanyl into the illicit drug market since 2015, but I was unable to include fentanyl as an outcome indicator in the analysis given the timeframe of the study.

5.5 Conclusions

This longitudinal assessment of non-fatal ODs among people with OUD in Vancouver with different PSU patterns highlighted their heterogeneous characteristics both in terms of patterns of PSU and non-fatal OD risk. These findings have important implications for OD prevention interventions and policies. Measuring and targeting OUD in isolation and investing in opioid-related interventions overlook the significance of the potential additive or multiplicative impact of using several substances on ODs and are therefore, likely to have

limited success. It is essential that the diverse nature of people with OUD in terms of both PSU and risk for ODs are reflected across the treatment continuum. In clinical practice, care provision for people with OUD needs to include comprehensive approaches that recognize the distinct needs of diverse groups of people with OUD and address their overlapping or concurrent issues. Moreover, given the high prevalence of PSU among people with OUD, in addition to identifying therapeutic options for SUD involving non-opioid drugs, there is a need to invest further in understanding and tackling the underlying social and structural drivers of PSU.

Table 5.1. Baseline characteristics of participants with opioid use disorder stratified by non-fatal overdose (2005-2018)

Characteristics	Non-fatal Overdose (Yes; n=421)	Non-fatal Overdose (No; n=2193)	P-value
PSU class			
Class 1	17 (4.0%)	321 (14.6%)	
Class 2	209 (49.6%)	568 (25.9%)	
Class 3	19 (4.5%)	258 (11.8%)	<0.001
Class 4	134 (31.8%)	972 (44.3%)	
Class 5	39 (9.3%)	68 (3.1%)	
Sociodemographic variables			
Cohort			
ARYS	199 (47.3%)	515 (23.5%)	
ACCESS	58 (13.8%)	621 (28.3%)	<0.001
VIDUS	164 (39.0%)	1057 (48.2%)	
Age (Median years [Q1, Q3])	36.51 (25.93, 45.48)	27.3 (22.59, 36.36)	<0.001
Sex (at birth)			
Female	149 (35.4%)	805 (36.7%)	0.642
Male	272 (64.6%)	1387 (63.3%)	
Ethnicity			
White	234 (55.6%)	1111 (50.7%)	
Indigenous	134 (31.8%)	705 (32.2%)	0.32
Black and other persons of color	52 (12.4%)	363 (16.6%)	
Employment (L6M)			
Yes	142 (33.7%)	567 (25.9%)	0.001
No	279 (66.3%)	1626 (74.2%)	
Substance use characteristics			
Weekly IDU (L6M)			
Yes	342 (81.2%)	1480 (67.5%)	<0.001
No	78 (18.5%)	711 (32.4%)	
Injecting career (Median years [Q1, Q3])	15.04 (6.57, 25.24)	7.15 (2.55, 15.44)	<0.001
Binge drug use (L6M)			
Yes	258 (61.3%)	1016 (46.3%)	<0.001
No	161 (38.2%)	1172 (53.4%)	
OAT (L6M)			
Yes	162 (38.5%)	1127 (51.4%)	<0.001

No	254 (60.3%)	1061 (48.4%)	
Structural-level characteristics			
Incarceration (L6M)			
Yes	116 (27.6%)	386 (17.6%)	<0.001
No	302 (71.7%)	1800 (82.1%)	
Drug dealing (L6M)			
Yes	206 (48.9%)	866 (39.5%)	<0.001
No	214 (50.8%)	1324 (60.4%)	
DTES residence (L6M)			
Yes	269 (63.9%)	1404 (64.0%)	0.956
No	152 (36.1%)	789 (36.0%)	
Homelessness (L6M)			
Yes	280 (66.5%)	924 (42.1%)	<0.001
No	136 (32.3%)	1261 (57.5%)	
Public injection (L6M)			
Yes	288 (68.4%)	943 (43.0%)	<0.001
No	130 (30.9%)	1240 (56.5%)	
Childhood Trauma			
Yes	290 (68.9%)	1409 (64.3%)	0.004
No	80 (19.0%)	579 (26.4%)	
Depression (baseline)			
Yes	267 (63.4%)	1277 (58.2%)	<0.001
No	106 (25.2%)	791 (36.1%)	

Notes: PSU: Polysubstance Use; Class 1 (Low/Infrequent substance use); Class 2 (Primarily opioids and methamphetamine use); Class 3 (Primarily cannabis use); Class 4 (Primarily opioids and crack use); Class 5 (Persistent PSU); L6M: Last six months; DTES: Downtown East side. Data are n (%) unless otherwise specified and percentages are rounded.

Table 5.2. Item response probabilities across different latent classes during the study period (2005-2018)

Characteristics (L6M)	Class 1 (30%)	Class 2 (22%)	Class 3 (15%)	Class 4 (29%)	Class 5 (4%)
Weekly Illicit Opioid Use	11%	**64%**	4%	**71%**	**73%**
Weekly Cocaine Use	9%	3%	10%	32%	**54%**
Weekly Meth Use	0%	**63%**	3%	8%	44%
Weekly Crack Use	31%	2%	38%	**73%**	**59%**
Weekly Cannabis Use	1%	45%	**97%**	31%	**76%**
Weekly Prescription Opioid use	4%	13%	9%	20%	35%
Heavy Alcohol Use	9%	13%	14%	10%	46%

Notes: Class 1 (Infrequent substance use); Class 2 (Primarily opioids and methamphetamine use); Class 3 (Primarily cannabis use); Class 4 (Primarily opioids and crack use); Class 5 (Primarily opioids, cocaine, crack, and cannabis use); L6M (4.04%): Last six months; Bold fonts indicate item-response probabilities of >0.50; Percentages refer to probability/chance of using each drug in each class (e.g., the members in Class 3 had a 97% chance of reporting weekly cannabis use in L6M). Weekly use refers to at least weekly use.

Table 5.3. Bivariable and multivariable GEE analysis of factors associated with non-fatal overdose

Characteristics	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
PSU class				
Class 2 vs. Class 1	4.78 (4.13 - 5.54)	<0.001	2.64 (2.17 - 3.22)	<0.001
Class 3 vs. Class 1	1.06 (0.89 - 1.27)	0.511	0.93 (0.76 - 1.13)	0.475
Class 4 vs. Class 1	2.40 (2.07 - 2.79)	<0.001	1.36 (1.11 - 1.67)	0.003
Class 5 vs. Class 1	5.86 (4.35 - 7.89)	<0.001	2.82 (2.03 - 3.93)	<0.001
Sociodemographic variables				
Cohort				
ACCESS vs. ARYS	0.31 (0.26 - 0.38)	<0.001	0.50 (0.41 - 0.60)	<0.001
VIDUS vs. ARYS	0.39 (0.34 - 0.46)	<0.001	0.52 (0.44 - 0.61)	<0.001
Age (per year older)	0.96 (0.96 - 0.97)	<0.001		
Sex (at birth)				
Male vs. Female	1.09 (0.94 - 1.26)	0.255	-	-
Ethnicity				
Indigenous vs. White	0.96 (0.83 - 1.12)	0.630	-	-
Black and other persons of color vs. White	0.64 (0.52 - 0.79)	<0.001	-	-
Employment (L6M)				
Yes vs. No	1.11 (1.02 - 1.21)	0.021	-	-
Substance use characteristics				
Weekly IDU (L6M)				
Yes vs. No	2.73 (2.46 - 3.04)	<0.001	1.40 (1.17 - 1.67)	<0.001
Injecting career (per year longer)	0.97 (0.96 - 0.97)	<0.001	-	-
Binge drug use (L6M)				
Yes vs. No	1.81 (1.67 - 1.96)	<0.001	-	-
OAT (L6M)				
Yes vs. No	0.68 (0.61 - 0.75)	<0.001	-	-
Structural-level characteristics				
Incarceration (L6M)				
Yes vs. No	2.02 (1.78 - 2.28)	<0.001	-	-
Drug dealing (L6M)				
Yes vs. No	1.78 (1.63 - 1.95)	<0.001	1.38 (1.24 - 1.53)	<0.001

DTES residence (L6M)				
Yes vs. No	1.11 (1.01 - 1.22)	0.031	-	-
Homelessness (L6M)				
Yes vs. No	2.13 (1.92 - 2.35)	<0.001	-	-
Public injection (L6M)				
Yes vs. No	2.89 (2.61 - 3.21)	<0.001	1.94 (1.72 - 2.18)	<0.001
Childhood Trauma				
Yes vs. No	1.41 (1.18 - 1.67)	<0.001	-	-
Depression (baseline)				
Yes vs. No	1.64 (1.40 - 1.92)	<0.001	-	-

Notes: PSU: Polysubstance Use; Class 1 (Infrequent substance use); Class 2 (Primarily opioids and methamphetamine use); Class 3 (Primarily cannabis use); Class 4 (Primarily opioids and crack use); Class 5 (Persistent PSU); OAT: Opioid agonist treatment; L6M: Last six months; DTES: Downtown East side.

Chapter 6: Conclusion

6.1 Summary of findings

Through this thesis research, I sought to improve the understanding of longitudinal PSU practices, risk factors, and associated adverse health outcomes among people with OUD. Chapter two presented a systematic review of the literature on latent patterns of PSU among people with OUD in studies that utilized person-centred statistical approaches. The review found 30 eligible studies and identified five distinct PSU patterns, including infrequent/low PSU, primarily heroin use, primarily heroin and stimulant use, primarily stimulant use, and frequent PSU. The review suggested PSU to be often the norm rather than an occasional practice among a minority group of people with OUD. Membership in higher intensity PSU classes was positively associated with a range of individual- (e.g., sharing needles, frequent IDU), and socio-structural-level exposures (e.g., history of incarceration, homelessness). Several studies included in the review associated higher-intensity PSU with several adverse mental and physical health outcomes. The review also highlighted some of the methodological shortcomings in how latent analyses aiming at characterizing PSU have been conducted. For example, several studies were descriptive in nature, and most included studies (i.e., 27 out of 30) assessed cross-sectional associations between particular behavioural characteristics and membership in PSU classes. Moreover, PSU operationalization varied substantially among the studies and was measured based on an array of clinical or self-reported metrics across different timeframes, a methodological approach that made comparing study findings very challenging.

Chapter three presented the findings of a series of ITS analyses that used self-reports of regular (i.e., at least weekly) substance use practices among a cohort of people with OUD

in Vancouver and provided a quantitative assessment of how their substance use patterns changed after a national supply reduction intervention (i.e., delisting of OxyContin from provincial drug formularies) was implemented in Canada in March 2012. These analyses that were adjusted for potential biases, such as seasonality and autocorrelation, estimated that following the policy implementation, illicit opioid use did not decrease among the participants. Indeed, the policy change was significantly associated with an increase in the level and trend of regular heroin and illicit PO use. Moreover, although the policy change was not associated with significant increases in PWUD's crack or cocaine use, it was significantly associated with an upward trend in the regular use of methamphetamine. Overall the findings suggested that delisting OxyContin from the public drug formulary in BC did not seem to have played an important role in reducing illicit opioid use among people with OUD, some of whom may have shifted their drug of choice or supplemented their substance use with other drugs.

Chapter four presented an epidemiological study that used data from three prospective cohorts of PWUD (i.e., VIDUS, ACCESS, ARYS) in Vancouver and identified the longitudinal latent classes of PSU among people with OUD and its predictors via RMLCA and GEE models. The analysis found five distinct classes of PSU over the course of the study (2005-2018), which were distinguished by people's low/infrequent use, primarily opioid and methamphetamine use, primarily cannabis use, primarily opioid and crack use, and persistent PSU. The findings also highlighted the heterogeneous characteristics of people with OUD. In multivariable analyses, membership in higher-frequency PSU classes was positively associated with younger age, male sex, and several behavioural (e.g., frequent IDU practices, unprotected sex) and socio-structural (e.g., homelessness, residence in DTES, incarceration) adversities. Moreover, membership in higher-frequency PSU classes was negatively

associated with having accessed OAT at any point during the follow-up. The findings underscored that research and clinical practices aimed at characterizing and addressing risk factors of PSU among people with OUD should recognize the unique individual needs of people with OUD and go beyond siloing them into specific groups based on their primary substance of choice. Preventing harms associated with PSU would benefit most from addressing socio-structural inequities experienced by people with OUD rather than focusing exclusively on individual-level outcomes that are often not client-centred.

Chapter five presented a longitudinal assessment of odds of non-fatal ODs among different classes of PSU among people with OUD. It was hypothesized that people in higher-intensity PSU are at a higher risk of non-fatal OD over time. Out of the 2627 participants who were followed up for a median of 5.4 years, 41.6% had experienced at least one non-fatal OD over the course of the study (2005-2018). In the multivariable analyses and after adjusting for potential confounders, membership in all PSU classes, except Class 3 (i.e., primarily cannabis use), was significantly associated with increased odds of non-fatal OD, when compared with the low/infrequent use class. The findings also showed that participants who engaged in higher-intensity PSU were more likely to have been recently hospitalized, which provides a critical opportunity for identifying high-risk subgroups for non-fatal OD and linking them with harm reduction and addiction treatment services during hospitalization and post-discharge. These findings suggest that measuring and targeting OUD in isolation overlooks the significance of the potential additive or multiplicative impact of using several substances on ODs. Therefore, the diverse and individualized risk of people with OUD for non-fatal ODs should be reflected across their care and treatment continuum.

6.2 Strengths and unique contributions

This thesis has several strengths and unique contributions to the field of substance use research. First, the systematic review of PSU classes among people with OUD is an important contribution to the substance use literature. This systematic review provided a comprehensive and critical assessment of the studies using person-centred methodologies and identified the gaps and limitations in the existing body of evidence, and highlighted methodological and contextual priority areas for future PSU research. Second, the ITS analysis of people with OUD's substance use practices before and after reformulation of Oxycontin in Canada is the first of its kind to assess potential modifications in substance use patterns of people with OUD after this supply reduction policy in Canada. Previous analyses on this policy have been primarily ecological or used aggregate-level data on population-level PO consumption (152, 158). This study provides further evidence that highlights the unintended consequences of supply reduction interventions and their limited meaningful contribution to efforts aimed at addressing the opioid epidemic. Lastly, the longitudinal assessment of trajectories of PSU classes and associated health outcomes (i.e., non-fatal OD) within each class over time is an important novel contribution to opioid-related research. As outlined in Chapter two of the thesis, the existing evidence on this topic is restricted to small-scale cross-sectional studies that often suffer from several methodological limitations. Specifically, this research helped identify the latent longitudinal patterns of PSU and associated predictors among people with OUD as well as the diverse risk of people in each subclass for non-fatal OD. Collectively, the findings of the two studies presented in Chapters four and five highlighted significant heterogeneities within the population of people with OUD. These findings have significant implications for future research, clinical practice, and policy development.

6.3 Limitations

The limitations of each specific analysis are discussed in their respective chapter. Overall, there are several specific limitations to this research that need to be acknowledged, most of which are common among studies on PWUD. First, several variables used in the analyses in this thesis were self-reported in nature and are subject to potential recall and social desirability biases. However, although previous studies have shown that using a combined measure using self-report as well as objective metrics is ideal, self-reported substance use practices among PWUD have reasonable validity and reliability (194, 290). Moreover, several procedures and techniques were applied to reduce the above-mentioned biases during data collections (e.g., ensuring confidentiality and anonymity of the responses, establishing rapport with the participants, placing more sensitive questions towards the end of the research interview, and asking participants about their recent substance use behaviours). Second, the cohort studies in this thesis research include a non-random group of PWUD which limits the generalizability of the findings to PWUD not enrolled in the cohorts as well as those living outside Vancouver. However, the hard-to-reach nature of PWUD and the lack of a population-based registry of PWUD make collecting a longitudinal probability-based sample very challenging. It is worth noting that several measures were utilized to increase the generalizability of the non-random sample of the participants. For example, peer researchers are involved in the recruitment process, and participants are recruited through snowball sampling and street outreach from various neighbourhoods known to include a large population of PWUD. Moreover, participants of the above-mentioned cohorts have been shown to be comparable with other samples of PWUD in BC (291). Third, although potential

confounders were thoroughly conceptualized *a priori* and accounted for in the multivariable regression analyses included in this thesis, residual confounding cannot be ruled out. Moreover, similar to other studies of observational nature, causality cannot be inferred in the associations reported. Fourth, while PSU could be concurrent or consecutive, I was unable to tease that apart in these analyses given how data had been collected since the establishment of the cohorts a few decades ago. To help reduce potential biases on this front, I included regular substance use patterns (i.e., at least weekly use) over the course of the previous six months. Lastly, although the opioid toxicity epidemic in BC is primarily driven by the influx of fentanyl and its analogues in the illicit drug supply since 2014 (1, 2), I was unable to include regular illicit fentanyl use in these longitudinal analyses, given the period of the study (2005-2018) and its low self-reported use among the participants. Of note, this could be due to the fact that PWUD may have been uncertain about their exposure to fentanyl. Future studies on measuring substance use patterns would benefit from looking at how PSU classes may have evolved in the context of a toxic drug supply where PWUD may be exposed to synthetic opioids knowingly or accidentally (47,48,187).

6.4 Future Directions of Research and Clinical Practice

Although specific recommendations for future research are provided in each chapter, there are three specific suggestions that are briefly mentioned here. First, while an increasing body of evidence that have used person-centred approaches to determine different PSU classes is encouraging, there is a need to ensure the utilized methods and decisions made in identifying different PSU classes or profiles are transparent and reproducible. Including various subjective groups of variables as outcome indicators in latent class analyses would make comparisons

across different studies difficult, if not impossible. Following the existing guidelines and checklists could help alleviate the historical concerns about the statistical rigour of using person-centred approaches. The scientific publishing industry (i.e., academic journals) could also help improve the quality of such analyses by requiring a standardized checklist for latent analyses to be included in the submission process, as they do for variable-centred empirical analyses (e.g., strengthening the reporting of observational studies in epidemiology [STROBE]) or systematic reviews (e.g., PRISMA). Moreover, given the changing nature of substance use patterns among PWUD, there is a need to account for time in determining substance use latent classes and conduct further longitudinal latent analyses.

Second, there is significant heterogeneity among people with OUD and their PSU patterns are quite different from substance use patterns among the general population. These heterogeneities are not just reflected in their individual- and structural-level risk factors but also adverse health outcomes (e.g., non-fatal OD). The considerable diversities among people with OUD should be reflected in addiction research, which often focuses on mono-substance use practices that are not compatible with the reality of substance use practices among people with OUD. Indeed, there is a need to study multiple substances and their synergies to help understand their individual and combined impacts on substance use-related trajectories and adverse health outcomes. Moreover, the underlying reasons for practicing PSU should be further understood to help inform OD prevention interventions. These approaches should inform not only substance use prevention and treatment research but also public health surveillance efforts. Implementing practices that are not client-centred or focus on complete abstinence from all substances, put all people with OUD into a single category, and simplify their substance use treatment practices by concentrating on the primary drug of choice/use, fail

to acknowledge the specific needs and risks of different subgroups among people with OUD and would be of limited success in addressing the opioid epidemic.

Third, although measuring PSU is methodologically challenging, future research could benefit from improving the instrumentation of and screening for PSU in clinical settings. Developing pilot-tested and standardized screening tools for PSU that can measure different types of PSU (e.g., concurrent, consecutive), routes of administration (e.g., injection, non-injection), reasons for practicing PSU (e.g., recreational, withdrawal management, countering OAT's sedating impacts), and recent experiences (e.g., last week, current) is needed to help fully understand the impacts and interactions of PSU among people with OUD and inform addiction research and clinical practice. Such screening tools could aid in better identification of people engaged in higher-risk PSU practices, help define relevant treatment-related outcomes (i.e., client-centred non-abstinence focused), and tailor care and treatment plans accordingly. Moreover, given that stimulants are commonly used among a sizeable sub-population of people with OUD, it is important to ensure that treatment approaches embrace a holistic view of SUD, rather than an opioid-focused perspective. It is also essential to understand why people with OUD practice PSU and tackle the underlying influences or motivations. Providing people with OUD with educational interventions around stimulant use-related harms and its potential adverse impacts on OUD treatment-related outcomes could also be beneficial (293). In addition, in the absence of effective and approved pharmacological interventions for stimulant use disorder, OAT services should also offer behavioural (e.g., contingency management, cognitive behavioral therapy) and harm reduction interventions (e.g., safer pipe and smoking supply distribution, supervised consumption facilities, overdose prevention services including facilities where inhalation is allowed) tailored towards treating

stimulant use disorder (282) and minimizing its associated harms. Moreover, given the considerable increase in stimulant use in recent years, efforts to identify potential pharmacological interventions to treat stimulant use disorder need to be expanded. Therapeutic approaches should go beyond targeting a single cellular pathway for a particular substance and incorporate novel and promising models of care, such as collaborative care strategies that help deliver evidence-informed interventions for multiple SUD and address the diverse needs of patients with complex comorbid SUD (294). Lastly, future experimental research on clinical management of PSU among people with OUD is required to develop optimal clinical interventions that clarify whether treatment approaches for these patients should consider managing all disorders concurrently or one at a time.

6.5 Implications for Substance Use Policies

Considering the ongoing opioid overdose epidemic, the findings of this research have two important implications for Canada's substance use-related policies. First, a meaningful, sustainable, and successful response to the opioid epidemic is multifaceted and cannot be achieved by enforcing a war on the supply of prescription or non-prescription opioids. Annually, Canada is spending billions of dollars on the direct and indirect costs of the opioid epidemic; however, most resources are distributed disproportionally to fight the supply side of the epidemic (261). Supply-reduction interventions may be indeed successful in reaching their intended impact of reducing access to certain drugs; however, they do not necessarily lead to reduced consumption or drug-related harms among people with OUD (163-169). Focusing on targeting access to the opioids' supply is unwise and, as shown before in numerous international settings (160-162), would have unintended consequences, such as increasing the

toxicity of the opioid supply, forcing people with OUD to shift to riskier substances, or engaging in PSU practices. It is important to remember that supply reduction is only part of the comprehensive strategies needed to address SUD, and focusing on the opioid supply fails to address the demand side of the drug market, which continues to grow and will be met one way or another. There is also a need to develop a coordinated infrastructure that facilitates the continuity of prevention and treatment interventions.

Second, as outlined throughout the thesis, the heterogeneities within the population of people with OUD need to be reflected across the policies and programs aimed at addressing the opioid epidemic. Indeed, there is a need to move from opioid-centric policies and programs towards a holistic view of substance use among people with OUD. Substance use policies would be most impactful if they try to better assess and understand PSU practices over time, and recognize that PSU is the norm among a majority of PWUD, particularly those who are at a high risk of OD. While providing numerous resources for reducing access to prescription opioids (e.g., prescription drug monitoring programs), treating OUD (e.g., OAT services), or preventing opioid-related OD deaths (e.g., take-home naloxone) is important, additional support is needed to address the increasing rates of PSU among people with OUD and the involvement of multiple drugs in fatal and non-fatal ODs (202, 256, 263). In the context of the ongoing overdose epidemic, public health messaging should also highlight that ODs involving multiple substances may not respond well to naloxone, and additional supports may be required (27, 28). Further investments in PSU-related research, tackling universal risks across various substances, understanding the underlying reasons for engaging in PSU, and developing novel interventions tailored towards SUD other than OUD are warranted.

6.6 Conclusions

This thesis tried to contribute to the body of evidence on PSU practices and its associated harms among people with OUD to help inform future research, policies, and practices tailored towards addressing the opioid epidemic in Canada. This research highlighted the diverse nature of people with OUD in terms of longitudinal substance use patterns and long-term risk for non-fatal OD. The findings also underscored that tackling the supply side of opioids would not necessarily lead to reduced consumption of opioids among people with OUD and could instead have unintended adverse consequences. Moreover, interventions heavily focused on substance use cessation, abstinence, and individual behaviour change, fail to recognize people's dissimilar needs and motivations for substance use, and are often disconnected from the reality of PWUD's lives. While the need to support treatment of OUD remains evident, support should go to evidence-based policies, and additional attention should be given to interventions and policies that address PSU and not OUD only. Indeed, given the extent of PSU practices among people with OUD, the opioid specificity of existing prevention and treatment interventions has limited ability to tackling the opioid epidemic in Canada. Collectively, these findings underline that the heterogeneities observed within the people with OUD and their behaviours need to be reflected in substance use research, practice, and policy implementation.

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Appendices

Appendix A Preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	15
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	NA (in thesis)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	16
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	17
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Table 2.1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	17
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Table 2.1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix B
Study selection	9	State the process for selecting studies (i.e., screening,	17

		eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	18
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	18
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	18
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Table 4.2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Appendix C
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 2.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2.2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2.2,
Results of individual	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention	Table 2.4

studies		group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	19-24
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix C
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	28
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	29
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix B Sample search strategy (Medline)

1. substance-related disorders/ or alcohol-related disorders/ or alcohol-induced disorders/ or alcoholic intoxication/ or alcoholism/ or binge drinking/ or amphetamine-related disorders/ or cocaine-related disorders/ or drug overdose/ or inhalant abuse/ or marijuana abuse/ or narcotic-related disorders/ or opioid-induced constipation/ or opioid-related disorders/ or heroin dependence/ or morphine dependence/ or opium dependence/ or phencyclidine abuse/ or psychoses, substance-induced/ or substance abuse, intravenous/ or substance abuse, oral/ or substance withdrawal syndrome/ or alcohol withdrawal delirium/ or alcohol withdrawal seizures/
2. ((Opioid adj2 Disorders) or opioid addiction or opioid dependence).ti,ab.
3. (opioid adj2 analgesics).ti,ab. or Analgesics, Opioid/
4. exp Narcotics/
5. exp Methadone/
6. exp Fentanyl/
7. (Heroin Dependence or Morphine Dependence or Opium Dependence).ti,ab.v
8. (prescription adj2 opioid*).ti,ab.
9. exp opioid substitution treatment/ or exp Naloxone/ or Substance Abuse Treatment Centres/ or MMT.ti,ab.
10. (opioid* or opiate* or opioid dependen* or opioid substitution or heroin dependen* or opiate dependen*).tw. or buprenorphine.ti,ab. or suboxone.ti,ab. or opioid maintenance.ti,ab. or opiate maintenance.ti,ab. or opioid?agonist*.ti,ab. or maintenance therap*.ti,ab. or maintenance treatment.ti,ab. or heroin maintenance.ti,ab. or morphine maintenance.ti,ab. or Opiate Replacement.tw. or Medication?Assisted Treatment.ti,ab.
11. (Fentanyl or Sufentanil or Sufenta or Carfentanil or Carfentanyl or Hydrocodone or Methadose or Methadon$ or Metadol or Suboxone or Tramadol or Dihydromorphine or Hydromorphone or Morphin* or Morfin* or Oxycontin or Oxycodone or Tapentadol or Heroin or Opium or Subutex or Buprenex or Buprex or Buprine or Buprenorphine or Clonidine).ti,ab.
12. ("poly?substance use" or "poly?drug use" or poly?substance or poly?drug or "multiple drug*" or "multiple substance*").ti,ab.
13. (concurrent or co-use or simultaneous or co-occurring or co-abuse).ti,ab.
14. or/1-13
15. (latent transition analysis or latent class or profile analysis or latent class growth model* or person cent?red or person?oriented or LCA or LPA or LTA or latent variable or latent profile or mixture model*).ti,ab.
16. Latent Class Analysis/

17. 15 or 16
18. 14 and 17
19. limit 18 to humans

Notes: exp: explode terms; ti,ab: title & abstract; adj: adjacent

Appendix C Quality assessment of the included studies using the Newcastle-Ottawa quality assessment scale

	Selection				Comparability	Outcome			
Author (Year)	**Representativeness**	**Sample size**	**Non-respondents**	**Exposure ascertainment**	**Comparable subjects**	**Outcome assessment**	**Statistical test**	**Total Score**	**Overall Assessment**
Afshar (2019)	1	1	1	2	2	2	1	10	Very good
Anderson (2018)	0	1	1	2	1	2	1	8	Good
Betts (2016)	1	1	1	1	2	1	1	8	Good
Bobashev (2018)	0	0	1	1	2	1	1	6	Satisfactory
Bunting (2020)	1	1	1	1	2	1	1	8	Good
Carlson (2014)	1	1	1	2	2	1	1	9	Very good
Chen (2018)	0	1	1	1	2	1	1	7	Good
Daniulaityte (2019)	1	1	1	2	2	1	1	9	Very good
De Nadai (2019)	1	1	1	1	1	1	1	7	Good
Eastwood (2017)	1	1	1	1	2	1	1	8	Good
Eastwood (2019)	1	1	1	1	2	1	1	8	Good
Fong (2015)	1	1	1	1	2	1	1	8	Good
Gicquelais (2019)	1	1	1	1	2	1	1	8	Good
Gjersing (2018)	1	1	1	1	2	1	1	8	Good
Harrell (2012)	0	1	1	1	2	1	1	7	Good
Hautala (2017)	0	1	1	1	1	1	1	6	Satisfactory
Kuramoto (2011)	1	1	1	1	2	1	1	8	Good
Liu (2020)	1	1	1	1	0	1	1	6	Satisfactory
Meacham (2018a)	1	1	1	1	2	1	1	8	Good

Meacham (2018b)	1	1	1	1	2	1	1	8	Good
Meacham (2015)	1	1	1	1	2	1	1	8	Good
Monga (2007)	1	1	1	1	1	1	1	7	Good
Nielsen (2011)	0	0	1	0	0	1	1	3	Unsatisfactory
Patra (2009)	1	1	1	1	2	1	1	8	Good
Peacock (2015)	1	1	1	2	2	1	1	9	Very good
Roth (2015)	1	1	1	1	2	1	1	8	Good
Schneider (2019)	0	0	1	1	1	1	1	5	Satisfactory
Schneider (2020)	0	1	1	1	1	1	1	6	Satisfactory
Tavitian-Exley (2018)	1	1	1	1	2	1	1	8	Good
Wu (2011)	1	1	1	1	2	2	1	9	Very good

Very Good Studies: 9-10 points; Good Studies: 7-8 points; Satisfactory Studies: 5-6 points; Unsatisfactory Studies: 0 to 4 points; Sample sizes less than 300 were deemed insufficient (See Nylund-Gibson et al. 2018); Risk of bias range: 0–10; Selection: (Maximum 5 points); Comparability: (Maximum 2 points); Outcome: (Maximum 3 points); Median score: 8 (IQR=1)

Appendix D Quality assessment results based on items from the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS) checklist

Author (Year of publication)	Reports missing data mechanism	Describes variables related to missing data	Describes how missing data dealt with	Distribution of the observed variables reported	Software mentioned	Parameter restrictions reported	Covariate analyses can be [illegible]	Random start values and final iterations reported	Model selection tools described statistically	Number of fitted models reported, including 1-class	Number of cases per class reported for each model	Entropy reported	Plots/bar charts included for the final solution	Plots/bar charts included for each model	Final class solution numerically described	Syntax files available
Afshar (2019)	N	N	N	N	Y	N	Y	N	Y	Y	Y	N	Y	N	Y	Y
Anderson (2018)	N	N	N	N	Y	N	Y	N	Y	Y	Y	Y	N	N	Y	N
Betts (2016)	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	N
Bobashev (2018)	N	N	N	N	Y	N	Y	N	Y	Y	Y	N	Y	N	Y	N
Bunting (2020)	N	N	N	N	Y	N	Y	N	Y	Y	Y	Y	N	N	Y	N
Carlson (2014)	N	N	N	N	Y	N	Y	N	Y	Y	Y	N	N	N	Y	N
Chen (2018)	N	N	N	N	Y	N	Y	N	Y	Y	Y	N	N	N	Y	N
Daniulaityte (2019)	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	N	N	Y	N
De Nadai (2019)	N	N	N	N	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	N
Eastwood (2017)	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	N	N	Y	N
Eastwood (2019)	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	N
Fong (2015)	N	N	N	N	Y	N	Y	N	Y	Y	Y	N	Y	N	Y	N
Gicquelais (2019)	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	N	N	Y	N

Gjersing (2018)	N	N	N	N	Y	N	Y	N	Y	Y	Y	Y	N	N	Y	N
Harrell (2012)	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	N
Hautala (2017)	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	N
Kuramoto (2011)	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	N	N	Y	N
Liu (2020)	N	N	N	N	Y	N	N	N	Y	Y	Y	N	Y	N	Y	N
Meacham (2018a)	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	N
Meacham (2018b)	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	N
Meacham (2015)	N	N	N	N	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	N
Monga (2007)	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	N	Y	N	Y	N
Nielsen (2011)	N	N	N	N	Y	N	N	N	Y	Y	Y	Y	N	N	Y	N
Patra (2009)	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	N	N	Y	N
Peacock (2015)	N	N	N	N	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	N
Roth (2015)	N	N	N	N	Y	N	Y	N	Y	Y	Y	Y	N	N	Y	N
Schneider (2019)	N	N	N	N	Y	N	Y	N	Y	Y	Y	Y	N	N	Y	N
Schneider (2020)	N	N	N	N	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	N
Tavitian-Exley (2018)	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	N
Wu (2011)	N	N	N	N	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	N

Notes: N: No; Y: Yes