SUBSTANCE USE AND PSYCHIATRIC CHARACTERISTICS OF PRESCRIPTION OPIOID USERS IN A LOW-THRESHOLD METHADONE MAINTENANCE TREATMENT PROGRAM IN NOVA SCOTIA

by

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Submitted in partial fulfilment of the requirements
for the degree of Doctor of Philosophy

at

Dalhousie University
Halifax, Nova Scotia
November 2011

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DALHOUSIE UNIVERSITY

DEPARTMENT OF PSYCHOLOGY

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DALHOUSIE UNIVERSITY

DATE: November 30 2011

AUTHOR: Heather Grace Fulton

TITLE: Substance Use and Psychiatric Characteristics of Prescription Opioid Users in a Low-Threshold Methadone Maintenance Treatment Program in Nova Scotia

DEPARTMENT OR SCHOOL: Department of Psychology

DEGREE: PhD CONVOCATION: October YEAR: 2012

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ABSTRACT

Prescription opioid use is highly prevalent and may be replacing heroin as the predominant illicit opioid that is used. Little is known about specific prescription opioid use characteristics, or issues faced by these individuals in treatment. The major aims of the two studies comprising this thesis were: 1) to systematically and quantitatively assess different occasions of use for the prescription opioid hydromorphone; and 2) to evaluate how current substance use and psychiatric symptoms may be related in a population of prescription opioid users enrolled in a low-threshold Methadone Maintenance Treatment (MMT) program. Eighty-two participants from a low-threshold MMT program in Halifax, Nova Scotia were interviewed regarding their lifetime and current substance use, specific past occasions of hydromorphone use, and current psychiatric symptoms. A subsample of 26 participants was interviewed a second time, one day later, to assess reliability of participants' self-report on the above-mentioned study measures. It was found that many variables were reliably reported between the two interviews by the subsample. With regards to the first major thesis aim, hydromorphone was found to be a prevalent, highly-favoured prescription opioid in the sample. Characteristics of initial, but not later, hydromorphone use varied by prescription status at initiation. Later use of hydromorphone shared many characteristics previously documented with heroin. With regards to the second major thesis aim, participants reported high rates of current substance use and psychiatric symptoms. Current substance use and psychiatric symptoms appeared to be related; notably, non-prescribed benzodiazepine use predicted depression and anxiety symptoms, and general anxiety predicted non-prescribed benzodiazepine use. In summary, while the results may not be representative of all prescription opioid users, or MMT clients, the thesis presented novel findings with a unique and vulnerable population. The findings supplement the existing literature in terms of describing how prescription opioids may be used during specific occasions, and in describing psychiatric and substance use issues faced by prescription opioid users enrolled in low-threshold MMT in Nova Scotia.

LIST OF ABBREVIATIONS USED

α	alpha, probability of Type I error
APA	American Psychiatric Association
CI	Confidence Interval
df	degrees of freedom
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Version, Fourth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Version, Fourth Edition, Text Revision
e-CPS	Electronic Version of the Compendium of Pharmaceuticals and Specialities
F	Fisher's F-ratio
GAD	Generalized Anxiety Disorder
GHB	Gamma-hydroxybutyrate
HIV	Human Immunodeficiency Virus
ICD-9-CM	International Statistical Classification of Disease, Ninth Edition, Clinical Modification
ICD-10	International Statistical Classification of Disease, Tenth Edition
INCB	International Narcotics Control Board
κ	Cohen's Kappa, a statistical estimate of agreement between raters for coding of categorical data
LSD	Lysergic acid diethylamide
M	Mean
MDA	3,4-Methylenedioxyamphetamine
MDMA	3,4-Methylenedioxymethamphetamine
mg	milligram
MMT	Methadone Maintenance Treatment
n	Sample size
N	Population size
NAOMI	North American Opiate Medication Initiative
NSDUH	National Survey on Drug Use and Health
ϕ	phi, measure of association
p	Probability of Type-1 error
PABAK	Partial and Bias Adjusted Kappa (κ)
PCP	Phencyclidine
PDSQ	Psychiatric Diagnostic Screening Questionnaire
PTSD	Post-Traumatic Stress Disorder
OCD	Obsessive Compulsive Disorder
OR	Odds Ratio
r	Pearson product-moment correlation
®	Registered trademark
R^2	Multiple correlation squared
SAMHSA	Substance Abuse and Mental Health Services Administration
SD	Standard Deviation

SPSS	Statistical Package for the Social Sciences
t	Computed value for t-test
USA	United States of America
X^2	Computed value of Chi Square

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my parents for their emotional, as well as financial, assistance throughout my lifetime of education to date. I could not have done it without your advice, encouragement, coaching and support throughout this very long process. Thank you to you both, and Sarah, for cheering me on towards all the different finish lines.

To Marcus Juodis: you know how much you mean to me. You've been there throughout the hard times, as well as the good times. Thank you for being the voice of reason- whether it was to "stop and smell the roses", to consult with other literature, or to consider implications that were outside my narrowed view at the time.

To my classmates: I feel lucky to have known you and to have spent so much time together. Thank you for the shared laughs, support, and motivation.

To my supervisors, Sean P. Barrett and Sherry H. Stewart: Thank you so much for your time, your expertise, your careful attention to detail, your "big picture" ideas, your encouragement and your support throughout so many different endeavors. I am incredibly grateful that we chose to spend that past six years together. I feel I have been given extraordinary opportunities by you both. I hope to continue to make you proud as I move forward in the future.

To my valued and indispensable dissertation committee, Simon Sherry and Jennifer Stamp: Thank you for all your suggestions, edits and support. It

was a pleasure to work with you both and an honour to benefit from your insightful comments and hard work.

I am very grateful to the Canadian Institutes of Health Research who generously funded three years of my graduate school training. I would also like to extend sincere thanks to the Killam Foundation for their generous Killam Doctoral Scholarships, and the Natural Sciences and Engineering Research Council who also provided substantial financial support in the completion of my PhD. Financial support for the present dissertation research projects was also generously provided by research grants from the Dalhousie Department of Psychiatry and Canadian Institutes of Health Research.

I would like to extend a special thank you to Cindy MacIsaac who provided me with invaluable feedback on measures, protocols and manuscripts. I am proud to have known you as a research collaborator, as well to call you my friend. Thank you to Jill, Frances, Anne, Darlene, Donnie, John and the many other staff members who helped me during my time at Direction 180. Your flexibility, patience and feedback while I completed the research projects was invaluable. You consistently provided me wonderful, “real world” experiences and advice; for that I am very grateful.

Last, but certainly not least, I would like to sincerely thank the clients of Direction 180, to whom this dissertation is dedicated. Your perseverance, strength and openness, is a continuing inspiration for me. Nothing motivated me more to finish my thesis than wanting to work with clients like you in the future. You have been an essential part in my education, and have entrusted to me

invaluable information and experience. While only a small part of what you shared with me is documented in this dissertation, what you taught me through our informal chats, anecdotes and shared experiences together is just as valued. I am forever indebted to you for the knowledge and wisdom that you shared with me. I will not forget it- or you. John F. Kennedy said, “As we express our gratitude we must never forget that the highest appreciation is not to utter words, but to live by them”. I hope, as a future researcher and clinician, to work in ways that will continue to express my gratitude to you all.

CHAPTER 1 INTRODUCTION

1.1 Introduction Overview

The focus of this thesis is to investigate the phenomenon of prescription opioid misuse and the challenges encountered in treatment by individuals who develop problems with these substances. This introductory chapter will provide an overview of the existing literature on the use and misuse of opioid medications. It will also summarize the existing literature on the treatment of opioid dependence and ongoing challenges faced by individuals in treatment. The following chapter (Chapter 2) will outline the methods for collection of thesis data. Chapter 3 will outline the results of the reliability assessment of the measures used in the later thesis studies. Chapters 4 and 6, respectively, present the results of the two empirical thesis studies investigating a) initiation and later use of a commonly misused prescription opioid medication, and b) ongoing mental health symptoms and substance use behaviours of individuals in treatment for their opioid use. Each publication-style manuscript within Chapters 4 and 6 is preceded by sections outlining specific study questions and hypotheses, and succeeded by additional sections of supplemental analyses and discussion that could not be included in each manuscript publications due to space limitations. Chapter 5 will explain how the first thesis study (Chapter 4) extends to the second thesis study (Chapter 6). Chapter 7 will discuss the novel

research contributions of the thesis studies, general limitations across both studies, directions for future research, and clinical implications.

1.2 Overview of Opioid Substances

The term *opiate* refers to substances naturally derived from the poppy plant (e.g., morphine). The term *opioid* is more inclusive and refers to opiates as well as substances that have been artificially synthesized (partially or fully) and have opiate-like properties (e.g., oxycodone). Opioids act on the opioid receptors in the body to produce many physical and subjective effects, such as respiratory depression, disruption of digestive activity and increased lethargy. Opioids are most well known, and medically utilized, for their pain-relieving effects. Terms such as *narcotic* and *analgesic* are also frequently used to refer to opioid substances. However, *narcotic* is occasionally used to refer to the general category of illicit substances (e.g., cocaine), and *analgesic* can also be used to describe non-opioid medications with pain-relieving properties (e.g., acetaminophen; McKim, 2006). Consequently, the term *opioid* is used throughout this document due to its inclusivity of describing substances such as morphine, heroin, oxycodone, as well as its specificity in excluding substances such as cocaine or acetaminophen.

Opioids are often prescribed by medical professionals for their strong analgesic properties (Winger, Woods, & Hoffmann, 2004). However, long term ingestion of such medications can lead to tolerance and/or unpleasant withdrawal

symptoms; that is, physical dependence. Tolerance is defined as occurring when increasing amounts of a substance are required to obtain a desired effect, or when the use of the same amount of a substance produces a notably reduced effect compared to previous use occasions. Withdrawal symptoms for opioids can include flu-like symptoms of a runny nose, nausea, chills, fatigue, and/or diarrhea (American Psychiatric Association [APA], 2000).

Opioid substances and medications can also be used and/or misused by individuals to achieve a euphoric state (Davis & Johnson, 2008; Wise & Bozarth, 1985). However, as one continues to use opioids to achieve this state, one may be less able to do so because of tolerance effects. Consequently, increasing amounts of the substance or increasingly risky administration practices (e.g., intravenous administration) may be used. The escalation in the amount of the substance administered and changes in the method of use in order to alleviate withdrawal symptoms and overcome tolerance effects is considered to be a major factor in the development of addiction (i.e., psychological dependence) to opioids (Frantz & Koob, 2005; Koob & LeMoal 1997; 2008)

1.3 Trends and Problems Associated with Opioid Use

Heroin has historically been one of the primary substances of concern by law enforcement and treatment agencies (Lafrenière & Spicer, 2002). Its use has been found to be associated with many costs to society such as medical complications, crime/legal issues, and lost employment/productivity (see Mark,

Woody, Juday & Kleber, 2001, for review). However, recent research in both Canada and the United States of America (USA) suggests that heroin use may be decreasing in prevalence. Epidemiological research in the USA with both adolescents and the general population (Johnston, O'Malley, Bachman & Schulenberg, 2010a; Substance Abuse and Mental Health Services Administration [SAMHSA], 2010a), and a Canadian study surveying illicit opioid users (Fischer, Rehm, Patra, & Firestone Cruz, 2006) noted decreases in self-reported use of heroin. Researchers from these studies noted that prescription opioid use and misuse was becoming increasingly common, and appeared to be more prevalent than heroin use in many areas. Some researchers (e.g., Fischer & Rehm, 2007; Fischer, Rehm, Goldman, & Popova, 2008) have further suggested that prescription opioid misuse may be replacing heroin as the predominant illicit opioid used in North America.

Canada is the third greatest per capita consumer in the world of opioid medications, slightly below Germany and the USA. However, Canada is the greatest per capita consumer of many specific opioid medications (e.g., hydromorphone/Dilaudid®/Hydromorph Contin®; International Narcotics Control Board [INCB], 2009). Research conducted investigating opioid prescriptions in Ontario found that prescription rates for opioids have increased by 29% between 1991 and 2007 (458 to 591 prescriptions per 1000 people annually) and newer formulations, specifically, the extended release formulation of oxycodone (Oxycontin®), have increased by over 850% during this time period (23 to 197 prescriptions per 1000 people annually; Dhalla et al., 2009). This is particularly

of note given that some research has found approximately 5-24% of individuals prescribed opioids for pain use their opioid medications in aberrant ways (e.g., increasing dose/taking more than prescribed; see Martell et al., 2007 for review).

1.4 Trends in Non-Medical Prescription Opioid Use and Misuse

1.4.1 Definitions of Non Medical Use and Misuse

Prescription drug misuse has not been consistently defined across studies (see Barrett, Meisner & Stewart, 2008 for review). Some studies (e.g., Poulin, 2002; McCabe, Cranford, Boyd & Teter, 2007; Boyd, McCabe & Teter, 2006) have defined prescription drug misuse as "any use without a prescription", whereas others have used this term to denote use of prescribed medications "without a prescription or without a doctor telling you to take them" (e.g., Brands, Paglia-Boak, Sproule, Leslie & Adlaf, 2010, p. 258) or using "only for the experience or feeling they [the prescription opioids] caused" (SAMHSA, 2006, p. 166). That is, some studies have defined misuse as any use without a prescription as well as use with a prescription-but for reasons that are not medically indicated and/or in non-prescribed ways. The present document defines the term "misuse" as any use without a prescription. "Non-medical use" is used to denote use of a prescribed medication in a manner (e.g., intranasal, intravenous administration) or for a reason (e.g., to get high) that was not indicated by the prescribing physician.

1.4.2 Increased Prevalence of Non-Medical Prescription Opioid Use and Misuse

Non-medical prescription opioid use and misuse has increased in prevalence across many different segments of the population: adolescents (i.e., individuals aged 12-17 years), individuals seeking substance use treatment, as well as the population in general (i.e., all adolescents and adults aged 12 years and older). Investigation of substance use in adolescents is important because this population is a good indicator of future societal substance use problems and treatment needs (Bachman, Johnston & O'Malley, 2001). Additionally, an earlier age of using substances is a major risk factor for later substance use problems (e.g., Grant & Dawson, 1997). Thus, adolescent data can be used to anticipate possible future treatment challenges.

Non-medical prescription opioid use and misuse by adolescents has increased sharply in the past 20 years in the USA (Johnston, O'Malley, Bachman, & Shulenberg, 2010b); some estimates report non-medical prescription opioid use and misuse has increased by 618% between 1990 and 2002 (Sung, Richter, Vaughan, Johnson, & Thom, 2005). Recent epidemiological investigations conducted in 2009 in the USA estimated that over 13% of grade 12[1] students have non-medically used and/or misused prescription

[1] Researchers omitted data from secondary students in grades 7-11 due to researcher beliefs that the younger grades were over-reporting and/or unable to discriminate which substances should be included/excluded in the category of prescription opioids

opioids in their life and approximately 9% have non-medically used and/or misused these medications within the past year. This is the highest prevalence rate recorded since assessment first began in the USA in 1977 (Johnston et al., 2010a). Even higher prevalence statistics have been found in Canada, with 21% of Ontario students between grades 7-12 reporting non-medical opioid use and/or misuse in the past year. Seventy-three percent of the students reporting past year use said that they had obtained the opioid medication from their home (Adlaf & Paglia-Boak, 2007).

Non-medical use and misuse of prescription opioids in the USA and Canada is the third most common form of substance use, after alcohol and cannabis, reported by adolescents. That is, non-medical prescription opioid use and misuse is more common than tobacco use (Adlaf & Paglia-Boak, 2007; Brands et al., 2010; Sung, et al., 2005). Additionally, adolescents who report non-medical prescription opioid use and/or misuse have been found to be more likely than non-users to report using alcohol, cannabis and other illicit substances, and to be more likely to report experiencing symptoms of drug abuse (Boyd et al., 2006; Wu, Ringwalt, Mannelli & Patkar, 2008).

In terms of the general population (i.e., individuals aged 12 years and older), non-medical opioid use and misuse in the USA rose by 300% between 1991 and 2002 (Manchikanti & Singh, 2008). Currently it is estimated that approximately 5.2 million individuals aged 12 and older (2.1% of the population) in the USA have non-medically used or misused a prescription opioid in the past 30 days (SAMHSA, 2009a). The population of non-medical oxycodone users

and misusers in the USA has been estimated to be greater than the estimated population of heroin users (SAMHSA, 2005). Popova, Patra, Mohapatra, Fischer and Rehm (2009) extrapolated data from the USA regarding the prevalence of non-medical prescription opioid use and misuse to estimate the number of non-medical prescription users and misusers in Canada. They estimated that between 321 009 (1 961 individuals per 100 000) and 913 905 (5 582 individuals per 100 000) individuals in Canada misused and/or used prescription opioids non-medically in 2003.

Between 2001 and 2005 the OPICAN study surveyed illicit opioid users, who were not receiving substance use treatment, in seven different Canadian cities (Vancouver, Edmonton, Toronto, Montréal, Québec City, Fredericton, and Saint John). It was found that, outside of Montreal and Vancouver, heroin use was almost completely absent; prescription opioids were the predominant opioids used by participants. Additionally, heroin use at the study sites within all seven cities was found to have significantly decreased between 2001 and 2005 (Fischer et al., 2006).

1.5 Problems Associated with Prescription Opioid Use, Nonmedical Use and Misuse

As prevalence of the use, non-medical use and misuse of prescription opioids has increased, so have the problems associated with these medications.

1.5.1 Morbidity and Mortality

In 2002, the number of prescription opioid-related deaths in the USA was greater than the number of deaths related to either cocaine or heroin (Paulozzi Budnitz & Xi, et al., 2006). Between 1996 and 2006, the number of poisonings related to prescription opioids (i.e., accidental or intentional overdoses) increased over 300% from 4,000 to 13,800 deaths. This represented 40% of all poisoning related deaths in the USA in 2006 (Warner, Chen & Makuc, et al., 2009). In terms of morbidity, visits to the emergency room related to prescription opioid use increased 111% between 2004 and 2007 to over 300,000 visits per year in the USA (Centers for Disease Control and Prevention, 2010). Additionally, the number of children's deaths and hospitalizations related to accidental ingestion of a caregiver's or relative's prescription opioid medications have been identified as a notable public health concern (Bailey, Campagna, Dart & The RADARS System Poison Centre Investigators, 2009).

Prescription opioid-related morbidity and mortality has also substantially increased in Canada. Between 1991 and 2004, opioid-related deaths in Ontario increased by almost 100% from 13.7 deaths to 27.2 deaths per million people. This is greater than the incidence of death from Human Immunodeficiency Virus (HIV) infection (Dhalla et al., 2009).

1.5.2 Substance Abuse, Dependence and Treatment Admissions

In addition to health-related problems, there have been noted increases in psychological problems associated with use, non-medical use and misuse of prescription opioid medications, namely, substance abuse and dependence. Substance abuse and dependence, as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision* (*DSM-IV-TR*; APA, 2000), are the two main substance use disorders. Each disorder is defined by criteria describing maladaptive patterns of substance use that are associated with significant impairments in functioning and/or distress. The disorder of substance dependence is also known as "addiction" (McKim, 2006). It is important to note that substance dependence, as defined by the *DSM-IV-TR*, can occur with or without physical dependence symptoms (i.e., tolerance and/or withdrawal; APA, 2000).

In terms of the general population, approximately one third of adolescents (12-17 years) in the USA reporting non-medical use of prescription opioids in the past year reported experiencing symptoms of substance abuse and/or dependence (as defined by the *DSM-IV*[2] [APA, 1994]). Seven percent met criteria for opioid abuse, 20% were subthreshold for an opioid dependence diagnosis, and an additional 9% met criteria for an opioid dependence diagnosis (Wu et al., 2008). In a study of individuals prescribed codeine in Canada, over

[2] Note: The diagnostic criteria for substance dependence and abuse did not change between the *DSM-IV* and *DSM-IV-TR* versions.

37% of those surveyed met *DSM-IV* (APA, 1994) criteria for opioid dependence and 4% met criteria for abuse (Sproule, Busto, Somer, Romach, & Sellers, 1999).

Treatment centres have reported a notable increase in the number of admissions related to prescription opioids. In the USA, a 1998 nationwide survey found that 2.2% of individuals admitted to substance use treatment (translating to approximately 9 admissions per 100,000 people in the general population in 1998) reported a prescription opioid as their primary, secondary, or tertiary substance of abuse. By 2008, this figure increased by over 400% to 9.8% of all individuals admitted to substance use treatment (translating to approximately 45 admissions per 100,000 people in the general population in 2008; SAMHSA, 2010b; 2010c).

Similar increases in prescription opioid-related admissions have been observed in Canada. In a study of clients presenting for opioid detoxification services in Toronto between 2000 and 2004, researchers found that the number of individuals presenting for assistance related to their prescription opioid use steadily increased over time (e.g., extended release oxycodone-related admissions increased from 3.8% to 55.4% of total admissions), while individuals presenting for assistance related to their heroin use remained consistently low in prevalence (approximately 5-18% of total admissions; 10-20 individuals each year; Sproule, Brands, Li, & Catz-Biro, 2009).

1.5.3 Other Costs Associated with Prescription Opioid Use, Nonmedical use and Misuse

Unsurprisingly, the observed increases in prescription opioid-related morbidity, mortality, abuse, dependence, and treatment admissions come at great cost to society. First, there are the unquantifiable personal costs to individuals as well as to their families and friends related to the distress experienced by those who have been hospitalized, become ill, become psychologically dependent, had to enter treatment, and/or died related to their use of prescription opioids.

Second, there are societal losses related to crimes committed in order to obtain prescription opioid medications (e.g., pharmacy robberies) or to obtain money to buy prescription opioid medications (e.g., break and enter, prostitution; Cook & Caverson, 2010). There are also increased health care costs related to the above mentioned increases in morbidity and mortality as well as lost productivity. One study of insured individuals in the USA found that individuals who met criteria for opioid abuse (as defined by the *International Statistical Classification of Disease - Ninth Edition, Clinical Modification* [*ICD-9-CM*; USA National Centre for Health Statistics, 2010] – a similar diagnosis to opioid abuse as defined by the *DSM-IV*; APA, 1994) had a greater number of comorbidities and health care expenses than those who did not meet *ICD-9-CM* opioid abuse criteria ($15,884 vs. $1,830 in costs per year respectively; White et al., 2005). In the USA, it was estimated that the social costs of nonmedical prescription opioid

use and misuse was $53 billion for the year of 2006 alone (Hansen, Oster, Edelsberg, Woody & Sullivan, 2010).

Such nation-wide cost-estimation data is not available for Canada. However, a recent study put the cost of an untreated individual with opioid dependence in Toronto as $45,000 per year. When all estimated affected individuals (based on prevalence statistics for untreated opioid dependence) were summed together, the researchers estimated this translated to a cost to metropolitan Toronto of $105 to $171 million dollars per year. When estimates for all affected individuals in the province of Ontario were summed together in a similar manner, the researchers determined that this likely translated to a cost of approximately $660 million per year to the province of Ontario (Wall et al., 2000). This cost estimate was considered by some be greatly underestimated because of the increasing prevalence of prescription opioids (and thus a greater prevalence of untreated opioid dependence than the figure used by Wall and colleagues), and the failure of the researchers to include costs such as those related to the treatment of opioid-dependent individuals with HIV and/or Hepatitis C, social assistance programs, and some health services (Ontario Addiction Treatment Centres, 2001).

In addition to unquantifiable personal costs and economic estimations of social costs, nonmedical prescription opioid use and misuse also have detrimental downstream effects on individuals in society experiencing acute or chronic pain. Non-medical use and misuse of opioid medications may negatively affect the development of new medications and clinical trials. For example,

clinical trials/pharmaceutical companies need to demonstrate not just that their new medication is effective in treating pain, but new abuse-deterrent formulations need to developed and tested and abuse-risk reports need to be filed before a medication can be released. This can add greatly to the research and development costs for a medication (Katz et al., 2007). Releasing a medication without an effective abuse-deterrant formulation can result in extensive negative publicity (e.g., Oxycontin® misuse and Purdue Pharma; Jayawant & Balkrishnan, 2005). Further, widespread non-medical use and misuse of these medications are thought to contribute to "opiophobia" (i.e., fear of prescribing opioids) by those in the health professions. This can result in some individuals with pain not receiving adequate pain treatment (Gilson & Kreis, 2009; Kirsh, Vice & Passik, 2008; Strassels, 2009). Indeed, one study found the most common dilemmas reported by physicians in deciding to prescribe opioids to their patients were concerns regarding opioid-seeking behaviour and abuse (Bendtsen, Hensing, Elebing & Shadin, 1999). In addition, many pharmacies refuse to stock commonly misused opioid medications for fear of robbery (Jayawant & Balkrishnan, 2005). Thus, even if an individual with pain receives an opioid prescription, obtaining the medication can be very difficult.

1.6 Etiology of Prescription Opioid Use, Non-medical Use, Misuse and Addiction

Etiology is the investigation of probable causes and correlates of different behaviours and/or conditions (Committee on Opportunities in Drug Abuse Research, 1996). Etiological models of substance use behaviour may focus on substance use and initiation, or on the development of a substance use disorder (e.g., addiction, see Section 1.5.2 for a brief overview of the terminology of abuse, dependence and addiction to prescription opioids). While the above outlined changes in the patterns and issues related to prescription opioid use have occurred relatively recently, a number of possible factors have been proposed and investigated regarding the etiology of prescription opioid use, non-medical use, misuse and addiction.

To explain the observed increases in prescription opioid use there are two primary reasons that have been posited and investigated to date (Manchikanti, Fellows, Ailani & Pampati, 2010). Firstly, there have been documented increases in chronic non-cancer pain conditions in the general population (e.g., musculoskeletal pain such as lower back pain in recent decades; Freburger, Holmes, Agans et al., 2009; Harkness, Macfarlane, Silman & McBeth, 2000). Second, many of the pain treatment protocols and prescribing practices advocated by professional bodies have changed to address under-treatment of pain conditions (Manchikanti, 2007; Manchikanti et al., 2010; Manchikanti & Singh, 2008). The combination of increased prevalence of pain conditions in

combination with prescription practices regarding powerful opioids may account for much of the observed increases in opioid use/dispensing in Canada and the USA.

Observed increases in non-medical prescription opioid use and misuse have been posited by some researchers (Cicero, Inciardi & Munoz, 2005; Cicero, Lynskey & Todorov, 2008) to be due to: 1) The comparative ease of acquiring prescription opioids compared to heroin, particularly given the high prevalence of those who are prescribed such medications (Manchikanti & Singh, 2008). The ease of obtaining prescription opioids has been hypothesized to be particularly important to the rise of nonmedical use and misuse in less urban areas where heroin is typically unavailable (Cicero, Inciardi & Munoz, 2005; Cicero, Lynskey & Todorov, 2008). This assertion regarding availability contributing to prevalence of non-medical use and misuse is supported by research with adolescents where 73% of individuals who had non-medically used or misused an opioid in the past year reported that they had obtained the substance from their home (Adlaf & Paglia-Boak, 2007). 2) Law enforcement agencies attempt to closely monitor and prevent the production, transportation, buying and selling of illicit substances, like heroin. Thus the perceived risk of arrest and/or prosecution may be increased when attempting to sell and/or purchase heroin relative to the perceive risk of attempting to sell and/or purchase illicit prescription opioids. 3) The use, non-medical use and/or misuse of prescription opioids is less stigmatized and therefore considered to be more socially accepted than heroin. 4) The purity and dosage of prescription opioids are considered to be constant

and therefore predictable relative to illicit substances like heroin which can be diluted to low purity levels (e.g., through the addition of diluents like glucose, talc), or laced with other potentially harmful adulterants (Cicero et al., 2005; Gomez & Rodriguez, 1989). Additionally, with a consistent and predictable amount of a substance, the perceived danger of use and/or risk overdose may be considered by users to be reduced relative to heroin or other substances (Cicero et al., 2005; Cicero et al., 2008).

In addition to the above hypothesised attitudinal factors, a number of other demographic etiological variables have been identified in the literature as associated with nonmedical prescription opioid use and misuse. Adlaf and Paglia-Boak 's 2007 survey of adolescents in Ontario found that non-medical prescription opioid users and misusers, relative to non-users, were more likely to be female, be in a higher grade, and live in Northern Ontario. Research in the USA identified adolescent non-medical prescription opioid users and misusers as more likely than non-users to be female, in late adolescence, non-Hispanic Caucasian, and from lower income families. Additionally, a history of alcohol and other substance use (particularly non-medical use and misuse of other prescription drugs), history of selling illicit substances, and pro-drug use attitudes were identified as risk factors associated with increased non-medical prescription opioid use and misuse (Sung et al., 2005). Sung and colleagues (2007) identified parental influence, namely disapproval of cannabis use, frequent checking-in regarding homework, and provision of compliments to their children, as protective factors against teenagers non-medically using or misusing prescription opioids.

In terms of etiological investigations into risk factors associated with the development of an addiction to prescription opioids, research has primarily investigated pain-affected populations and risk factors associated with these opioid-prescribed individuals to develop an addiction to their medication. Across studies, the greatest risk factor for individuals developing an addiction to their opioid medication is a prior history of another substance use disorder (e.g., alcohol dependence; Hojsted & Sjorgen, 2007; Wells, 2007). Many measures that have been developed to identify individuals who are most at risk for misusing and/or becoming addicted to their opioid medications (e.g., Screener to Predict Opioid Misuse in Chronic Pain Patients; Butler, Budman, Fernandez, Fanciullo & Jamison, 2009) ask about this characteristic.

Another factor that has been proposed to denote an increased risk for an opioid-prescribed individual to develop an addiction to their medication is the initial subjective effect experienced by an individual after first using the medication. In a small case-control study of chronic pain patients, all of whom first used opioids in the treatment of their chronic pain, participants were asked to recall their initial subjective experiences after taking opioids. One half of the sample were individuals who had later gone on to develop opioid use disorders and enter treatment for their prescription opioid use, and the other half of the sample were controls receiving opioid maintenance therapy for chronic pain and had never developed problems with their use of opioids. Those who had later developed problems were significantly more likely to report that they had initially experienced euphoria after using their opioid medication than the control group

(Bieber et al., 2008). This suggests that there may be important biological risk factors associated with development of problems with prescription opioid use.

Many researchers have proposed that presence of psychiatric symptoms is also an important etiological risk factor in the development of addiction to prescription opioids. That is, it has been proposed that some individuals with chronic pain will use their opioid medication to cope with stress and/or to self-medicate painful emotions. Engaging in such "chemical coping" behaviour is considered to be a contributing factor in the development of an addiction to opioids (Savage 2002; Wells, 2011). However, while there is evidence that psychiatric symptoms (e.g., history of a mood or anxiety disorder) are associated with an increased risk for misuse of opioid medication by chronic pain patients (Ajay et al., 2007; Edlund, Steffick, Hudson, Harris & Sullivan, 2007), no studies to date have clearly demonstrated a causal relationship. There is insufficient data to date to determine if prescription opioid use (and/or non-medical use and misuse) is an antecedent, concomitant, or consequent of psychiatric distress.

1.7 Limitations in the Literature of Prescription Opioid Use and Misuse

While several epidemiological studies have investigated the prevalence of prescription opioid use, non-medical use, misuse, and related problems, few details are known about the specific use characteristics associated with

prescription opioids. That is, little is known about the contexts in which individuals who later receive treatment for prescription opioid use first begin using prescription opioid medications (e.g., do they have a prescription for the medication?), how they use these substances (e.g., routes of administration, co-use with other substances), or why (e.g., are they using to get high? To decrease pain?). Substances are often used in polysubstance context (e.g., Barrett, Darredeau, & Pihl, 2006; Gossop, Manning, & Ridge, 2006) - including opioids (e.g., heroin with cocaine to "speedball"; Leri, Bruneau & Stewart, 2003). However, no studies, to the knowledge of the author, have systematically, quantitatively investigated how prescription opioids may be initiated and/or later used with other substances as well as the context of such use occasions.

Quantitatively and systematically evaluating specific occasions of prescription opioid use by individuals who develop problems with these substances is important not only for having a better idea of how these medications are initially used, and possible ways to prevent or delay initiation, but also to determine if the nature of first exposure is important to harm/risks associated with later (more recent) use, such as the likelihood to use via injection drug use or co-use with substances that may increase risk of overdose. Obtaining such knowledge would be beneficial in order to develop possible ways to reduce harm associated with prescription opioid use and misuse (e.g., tailored education regarding overdose risk when co-using substances). Previous studies have found that reasons for initiating a behaviour may be different from the reasons for continuing to engage in that behaviour (e.g., Chapman, 1995;

DiClemente, 2003; Planalp & Trost, 2009). Thus investigating more recent use in addition to initial use would elucidate possible reasons for use, and any changes in reasons for use, that may help in better tailoring treatment programs to meet these clients' needs.

1.7.1 Hydromorphone- A Prescription Opioid of Particular Interest

Hydromorphone, also known as hydromorphone hydrochloride, Dilaudid®, and Hydromorph Contin®, is a semi-synthetic opioid medication intended for the treatment of both acute and chronic forms of moderate to severe pain (Purdue Pharma, 2008, 2010; Quigley, 2002; see also the electronic version of the Compendium of Pharmaceuticals and Specialties [e-CPS], 2007). Hydromorphone is a particularly interesting prescription opioid because it shares many pharmacological similarities with the illicit opioid heroin. Heroin is also a semi-synthetic opioid and both substances are potent μ-opioid receptor agonists (Epstein, Renner, Ciraulo, Knapp & Jaffe, 2005; Purdue Pharma, 2008; 2010; Sarhill, Walsh & Nelson, 2001). Both substances are stronger than morphine: heroin is considered to be twice as strong on a milligram basis [Kaiko, Wallenstein, Rogers, Grabinski & Houde, 1981], whereas hydromorphone is considered to be approximately eight times as strong as morphine on a milligram basis [Purdue Pharma, 2008]. Heroin and hydromorphone also have similar onsets and durations of action (i.e., 3-4 hours) based on physiological measures (e.g., pupil diameter, blood oxygen saturation; Brands, Marsh, Busto &

MacDonald, 2004). Hydromorphone and heroin both have relatively high lipid solubility[3] relative to morphine; Sarhill et al, 2001; Wallenstein et al., 1990; Winger et al., 2004). While not well studied in humans, in animal studies, rats have been found to have similar physical dependence profiles to heroin and hydromorphone salts, such as abnormal posturing, teeth chattering, and body temperature decrease, when administered naloxone after chronic administration of either drug (Brands, Baskervill, Hirst & Howdey, 1979).

In addition to the pharmacokinectic similarities, hydromorphone and heroin have also been found to have many similarities in the reported subjective effects when each drug is used. In a study by Brands, Marsh and colleagues (2004), casual heroin users were given intravenous and subcutaneous infusions of heroin and hydromorphone. Participants reported similar scores for both drugs for both intravenous and subcutaneous injections on subjective measures such as feeling of "drug effect" and "rush" and the time course (time to onset and peak) for such subjective effects was similar for the two drugs. However, the researchers found that hydromorphone was approximately 3-4 times more potent than heroin. In a similar study with cancer patients, Wallenstein and colleagues (1990) also found that participants reported similar subjective effects to both substances (e.g., sleepiness, analgesia), and the onset to action and time effect curves of the subjective responses were also very similar between the two substances. Overall, the researchers concluded, on a milligram basis,

[3] Lipid solubility of a substance determines how quickly a substance is able to enter and exit the blood-brain barrier. Thus, lipid solubility influences the potency, onset, and duration of action of a substance in the body.

hydromorphone was approximately five times as potent as heroin, but both substances produce very similar clinical effects and could be used as substitutes for each other.

Another study to find similar effects between heroin and hydromorphone was the North American Opiate Medication Initiative (NAOMI) study trial that examined the utility of injectable heroin and hydromorphone as possible treatments for heroin dependence (Schechter, 2002; Oviedo-Joekes et al., 2008). Of all the participants, a subset (n = 25) were randomly assigned to receive injectable hydromorphone, whereas the majority (n = 115) were randomly assigned to receive injectable heroin. Both participants and researchers were double blinded as to which substance the participant received. At completion of the study, none of the participants in the hydromorphone group reported that they "definitely" received hydromorphone, 12.0% indicated they "possibly" received hydromorphone, and 32.0% reported they "definitely" received heroin. The distribution of these responses were not statistically different from the heroin group where 2.6% of participants reported they "definitely" received hydromorphone, 7.8% reported they "possibly" received hydromorphone, and 46.1% reported they "definitely" received heroin (Oviedo-Joekes et al., 2010). These findings are particularly interesting given that individuals in this study were extensively experienced opioid users in Vancouver. Thus participants would presumably be very familiar with the subjective effects of heroin and possibly hydromorphone as well (Oviedo-Joekes et al., 2008). Participants' inability to correctly determine which substance they were given suggests that the

subjective effects are extremely similar - even to experienced users of opioid substances. A number of countries are currently developing or conducting trials to assess hydromorphone as a possible treatment for heroin dependence because of the reported subjective and pharmacokinectic similarities between the two substances, and because hydromorphone does not have the same legal and political barriers as heroin (Bammer, Dance, & MacDonald, 2004).

In addition the pharmacokinetic and subjective similarities to heroin, hydromorphone is a substance of particular interest given the high prevalence of the use and misuse of this medication. Canada is the leading consumer in the world of hydromorphone (INCB, 2009) and Nova Scotia has the highest per capita consumption of hydromorphone of all Canadian provinces (IMS Health, 2008). While Canada far exceeds the USA in hydromorphone consumption, with 2579 daily doses compared to 503 daily doses per million inhabitants during 2006-2008 (INCB, 2009), studies in the USA have indicated that hydromorphone use has increased 319% between the years of 1997 and 2007 ((Manchikanti et al., 2010). Statistics are not available for Canada. But, based on the similarity of previous prescription opioid statistics between the two countries (see Sections 1.3-1.5), similar increases in consumption may also be occurring in Canada. Moreover, hydromorphone was the most common prescription opioid used by illicit opioid users in a survey across Canada (Leri et al., 2005), it was the most common opioid of choice listed by MMT clients in Halifax, Nova Scotia (Marshall, 2004), and non-medical hydromorphone users and/or misusers have been found to engage in more serious substance use behaviours than non-medical users

and/or misusers of other prescription opioids (Smith, Haddox, & Di Marino, 2007).

1.7.2. Summary of Rationale for Study One

As mentioned above (see Section 1.7), while several epidemiological studies have investigated the prevalence of prescription opioid misuse (e.g., Fischer et al., 2006; SAMHSA, 2010a), few details are known about the specific characteristics associated with the misuse of these medications. For example, little is known about the context in which individuals who go on to develop problems begin using prescription opioids, or how their use might change over time.

Hydromorphone is a substance of particular interest because several previous investigations have suggested this medication has a similar pharmacokinetic profile (e.g., onset of action, time to peak levels) to heroin and may be subjectively indistinguishable from heroin when injected (Brands, Marsh et al., 2004; Oviedo-Joekes et al., 2010; Wallenstein et al., 1990). Moreover, previous studies with illicit opioid users (Leri et al., 2005) and MMT clients (Marshall, 2004) indicate hydromorphone is a commonly used and favoured prescription opioid.

1.8 Treatment of Opioid Dependence

There are a number of empirically supported treatment options for opioid dependence such as short-term detoxification, antagonist treatment (e.g., naltrexone), therapeutic communities, outpatient drug-free treatments (e.g., relapse prevention programs), residential programs, and opioid substitution therapy (see Epstein et al., 2005 for review). Opioid substitution therapy is typically conducted using methadone, or buprenorphine (e.g.., Suboxone®). Methadone, however, is the most widely used of the opioid substitution medications (Lobmaier, Gossop, Waal & Bramness, 2010).

1.8.1 Methadone Maintenance Treatment (MMT)

Methadone was developed first by Dole and Nyswander (1965) for the treatment of heroin dependence. Methadone is a μ-opioid receptor agonist with a relatively long half-life (i.e., 22 hours [Eap, Buclin & Baumann, 2002] in comparison to other opioids such hydromorphone or oxycodone with half lives of 2-3 hours; Epstein et al., 2005; Inturrisi, 2002). Methadone administration has been found to be beneficial for opioid dependence because high doses alleviate cravings and withdrawal symptoms related to opioid use, and such doses induce cross-tolerance to other opioids (i.e., euphoria is unable to be achieved if other opioids are administered due to methadone occupying the opioid-receptors; Epstein et al, 2005; McKim, 2006). That is, by alleviating opioid withdrawal

symptoms methadone-maintained individuals are provided with negative reinforcement for remaining abstinent from other opioid use (instead of punishment) and positive reinforcement (i.e., euphoria) is prevented from being experienced when using other opioids.

MMT can be offered through “high-” or “low-threshold” clinics. “Threshold” refers to the criteria by which clients need to abide in order to remain in treatment. “High-threshold” clinics have stricter criteria, such as clients needing to maintain negative urine screens (i.e., abstinence from all substances), and/or attending a certain number of adjunct programs/groups. “Low-threshold” clinics typically do not require clients to remain abstinent from substances in order to receive methadone treatment (Royal College of Psychiatrists, 2000). Instead, a conditional, positive reinforcement method is used. That is, if negative urine drug screening test results are obtained then the client gains certain privileges. Privileges can include receiving take-home doses of methadone or receiving methadone doses at a local pharmacy. These privileges are highly valued by clients given the inconvenience and long possible travel times required to attend the clinic on a daily basis (Marshall, 2004). Thus if the client is able to maintain negative urine screens then s/he is rewarded for abstaining from substances as opposed to being punished (e.g., loss of privileges, access to treatment) for using substances. Typically clients enrolled in low-threshold programs have previously been enrolled in other, higher threshold programs and were unable to abide by their stricter guidelines. Other low-threshold MMT clients may have resisted enrolling in “traditional”, high-threshold programs due to fear of prosecution or the

perceived unattainable barriers of “absolute abstinence”. Low-threshold treatment programs typically aim to reduce the harms associated with substance use through enabling individuals, who might otherwise have little to no contact with or access to health professionals and treatment services, to improve their physical and mental health (Marlatt & Tapert, 1993).

Although some have debated the efficacy of MMT (Kleber, 2008; Fischer, Rehm, Kim & Kirst, 2005), it is still considered the most effective (Centers for Disease Control and Prevention, 2002), and remains one of the most researched, therapies for opioid dependence (Mattick, Breen, Kimber & Davoli, 2002). Additionally, MMT has been repeatedly demonstrated to be a highly cost-effective strategy to treat opioid dependence and its related harms (Kerr, Marsh, Li, Montaner & Wood, 2005). It has been found to be more cost-effective than many other common medical interventions (e.g., cardiac bypass surgery, haemodialysis; Barnett, 1999). MMT has been found to significantly reduce opioid use compared to control treatment (e.g., detoxification, placebo, drug-free treatment, waitlist) in clinical trials (see Marsch, 1998 and Mattick et al., 2009 for review). Individuals enrolled in MMT have been found to engage in significantly less HIV and Hepatitis C risk behaviours, such as injection drug use, and risky sexual behaviour (Dolan et al., 2005; see Gowing, Farrell, Bornemann, Sullivan, & Ali, 2008 and Marsch, 1998 for reviews). Some evidence also suggests individuals in MMT have decreased mortality (Mattick et al., 2009) and criminal activity (Dolan et al., 2005; Marsch, 1998; Mattick et al., 2009).

1.8.1.1 Prevalence of Psychiatric Symptoms in MMT Clients

Clients' mental health appears to be an important factor in substance use treatment success (McLellan, Luborsky, Woody, O'Brien & Druley, 1983; McLellan, Childress, Griffith & Woody, 1984). While estimates greatly vary, approximately 28-76% of clients in MMT have a current comorbid psychiatric disorder other than substance abuse or dependence (Astals et al., 2009; Batki et al., 1996; Cacciola, Alterman, Rutherford, McKay, & Mulvaney, 2001; Callaly, Trauer, Munro, & Whelan, 2001; Gelkopf, Weizman, Melamed, Adelson, & Bleich, 2006; King & Brooner 1999; Marion, 2005; Schreiber, Peles. & Adelson, 2008; Ward, Mattick, & Hall, 1998a). Differences in comorbidity estimates among MMT client samples are likely due to differences in the inclusion/exclusion of personality disorders, types of measures used (e.g., retrospective file review, structured clinical interview, questionnaire) and whether clients were assessed at admission to MMT or later in treatment after a period of stabilisation.

Comparisons of these MMT client sample prevalence rates are difficult to make to base rates for psychiatric disorders in the general population due to different measures and assessment periods being used. For example, some studies examined and reported prevalence of psychiatric diagnosis at the time of admission to MMT versus prevalence of psychiatric diagnosis in the past 12 months for the general population. Some studies used structured clinical interviews that make psychiatric diagnoses based on DSM criteria, whereas

others used World Health Organization Composite International Diagnostic Interviews that use slightly different diagnostic criteria. Across the different studies of MMT client samples and the general population, the observed prevalence rates of different psychiatric disorders in MMT client samples tend to be similar or elevated in comparison to the general population. For example, Gelkopf and colleagues (2006) found 21.6% of MMT clients met current *DSM-IV* criteria for PTSD. Conversely, 3.5% of the general population have been found to meet *DSM-IV* criteria for PTSD at some point during the past 12 months (Kessler, Chiu, Demler and Walters, 2005).

Current psychiatric comorbidity in MMT clients is associated with decreased quality of life (Carpentier et al., 2009), poorer psychosocial and medical status (Cacciola et al., 2001), and increased HIV risk behaviours (Metzger et al., 1991; Woody, Metzger, Navaline, McLellan, & O'Brien, 1997). History of psychiatric admission is associated with an increased risk of mortality among MMT clients (McCowan, Kidd, & Fahey, 2009). Psychiatric severity has been found to be predictive of decreased counselling attendance by MMT clients (Craig & Olson, 2004), and psychiatric distress appears to generally be predictive of poorer treatment outcome (Darke, 1998a). However, this finding is not consistent across all studies (e.g., Ball & Ross, 1991; Gelkopf et al., 2006; Pani, Trogu, Contu, Agus, & Gessa, 1997).

1.8.1.2 Prevalence of Substance Use and Related Problems in MMT Clients

Despite the many benefits associated with MMT, a number of individuals enrolled in MMT programs continue to use/misuse substances (see Darke, 1998a and Stitzer & Chutuape, 1999 for reviews), such as cocaine (e.g., Gollnisch, 1997; Maremmani et al., 2007; see Condelli, Fairbanks, Dennis, & Rachal, 1991 for review), non-prescribed benzodiazepines (e.g., Gollnisch, 1997; Schreiber et al., 2008), or other opioids (e.g., Magura, Kang, Nwakeze, & Demsky, 1998). Comparing current substance use rates in MMT and to those in the general population can be complex. That is, some studies with MMT clients assess substance use based on urine screen results (e.g., Brands et al., 2008), whereas other studies use self-report (e.g., Gollnisch, 1997). When similar measures are compared between MMT clients and the general population, MMT clients appear to have similar (e.g., alcohol, hallucinogens) or higher prevalence rates for current use of all substances (e.g., cocaine, cannabis). For example, Gollnisch (1997) found in the 30 days prior to the study interview, 44% of MMT clients used alcohol, 0% used hallucinogens (e.g., LSD), 25% used cannabis, and 35% used cocaine/crack. Based on the most recent USA national substance use statistics where the relevant data was available, 39.7-67.4%[4] of the general population aged 26 and older used alcohol, 0.1% used hallucinogens, 4.2% used cannabis, and 0.7% used cocaine (SAMSHA, 2009b) in the previous 30 days.

[4] SAMSHA, 2009b reports prevalence for past month alcohol use by distinct age groups (e.g., 26-29, 30-34 years) thus a range is given to encompass prevalence rates for all age groups 26 years and older. Past month illicit substance use is reported for the entire group of participants aged 26 or older.

Continued use of substances while enrolled in MMT is a predictor of poorer treatment outcome (e.g., abstinence from opioids, treatment retention; Brands et al., 2008; Condelli et al., 1991; Craig & Olson, 2004; Davstad et al., 2007; Magura, Nwakeze, & Demsky, 1998; Maremmani et al., 2007; Morral, Belding, & Iguchi, 1999; Peles, Schreiber, & Adelson, 2006) and represents an ongoing challenge to current MMT providers and clinicians (Darke, 1998a; Kleber, 2008; Marion, 2005). For example, clients who continue to use cocaine in MMT may not have the same reductions in crime, opioid use, or intravenous administration of drugs (and thus reduction of risk for contracting HIV) as those not using cocaine in MMT (Condelli et al., 1991; Bux, Lam, & Iguchi, 1995; Hartel et al., 1995).

It is important to note that the side effects related to taking methadone on a regular basis could possibly be contributing to ongoing use, or possibly even increasing use or contributing to use initiation into, use, of some substances while individuals are enrolled in MMT. As noted above (see Section 1.8.1.1), methadone has some unpleasant side effects, such as drowsiness (e.g.., Brown et al., 1975). Some researchers have suggested that previous studies investigating ongoing substance use in MMT may have had biased methodology such that patterns of increasing use of stimulant substances (notably cocaine) are minimized or misrepresented (see Fischer, et al., 2005 for review). That is, participants enrolled in many MMT programs are expelled from treatment due to ongoing substance use, thus. Thus, they are not included in treatment statistics reflecting how MMT may influence other, non-opioid, substance use behaviors. It

is possible that individuals may be using cocaine to self-medicate (Khantzian, 1985) the depression-like side effects of methadone. Consequently, investigations of ongoing substance use in low-threshold MMT programs where individuals are not expelled for ongoing substance use is particularly important.

1.8.1.3 Interrelationship of Psychiatric Symptoms, Substance Use, and Substance Related Problems in MMT Clients

Current psychiatric symptoms, current substance use, and substance related problems have been found to be interrelated among MMT clients. Clients enrolled in MMT who have a non-substance related psychiatric disorder have been found to have a significantly greater number of lifetime substance use disorder diagnoses (Strain, Brooner, & Bigelow, 1991), have more severe substance use problems (Brooner, King, Kidorf, Schmidt, & Bigelow, 1997) and be currently using more substances in MMT (Batki et al., 1996; Gelkopf et al., 2006) than those without any psychiatric comorbidity. Additionally, the number of psychiatric diagnoses a client has while enrolled in MMT has been found to be significantly correlated with higher Drug Problems Severity Index scores on the Addiction Severity Index (Mason et al., 1998).

In turn, ongoing substance use in MMT appears to be associated with psychiatric symptoms. For example, cocaine users in MMT are more likely to report depressive symptoms (Magura, Siffiq, Freeman, & Lipton, 1991). Benzodiazepine users in MMT have been found to have higher levels of

depression, anxiety, suicidal ideation, and suicide attempts than non-users (Brands et al., 2008).

1.8.2 Limitations of the Literature on MMT, Psychiatric Symptoms and Substance Use: Rationale for Study Two - Part 1.

Most research to date on both psychiatric symptoms and substance use by methadone patients has focused on general level of psychiatric distress/severity, presence/absence of *any* psychiatric comorbidity, a limited number of psychiatric disorders (e.g., depression), and/or one or two substances (e.g., benzodiazepines, cocaine). Little research to date has focused on how *specific* types of current psychiatric symptoms may vary by *specific* types of substances currently used in MMT. Existing theories (e.g., Khantzian, 1985; 1997) and previous research in non-MMT samples (e.g., Conrod, Pihl, Stewart, & Dongier, 2000) suggest that specific psychiatric symptoms may be associated with use of specific substances (e.g., anxiety-type symptoms and substances with anxiolytic properties, such as benzodiazepines).

Increased knowledge regarding not only prevalence of these two issues, but also the intricacies of these interrelationships (i.e., specific relationships between certain substances and certain psychiatric symptoms) is particularly relevant to those who work within, and those who are enrolled in, MMT programs. Recent research reviews have suggested that integrated treatment of both substance use and psychiatric symptoms is the most favourable treatment

approach (e.g., Stewart & O'Connor, 2009). However, integrated treatments are not always available to individuals accessing mental health or substance use services. For example, in many jurisdictions these two interrelated mental health issues are treated by separate services and professionals. In the Halifax Regional Municipality, for example, Addiction Prevention Treatment Services are a separate service entity, with separate referral processes and counsellors, from Community Mental Health Services, which provides mental health services for psychiatric disorders outside of substance abuse and dependence. Knowing the scope of these issues and the nature of these interrelationships enables treatment providers to advocate for improved funding for effective, empirically supported treatment services, as well as to better develop, tailor, and evaluate such services. This should assist in better meeting clients' needs and may, in turn, improve outcomes and decrease social costs of both substance use and psychiatric illness.

1.8.3 Limitations of the Literature on MMT with Prescription Opioid Users: Rationale for Study Two - Part 2.

While MMT has been extensively researched, much research has focused on heroin-using clients (e.g., Peles et al., 2006; Schreiber et al., 2008), or the types of opioids used by participants have not been specified (e.g., McCowan et al., 2009). Consequently, little research to date has investigated the efficacy of MMT with prescription opioid users. Brands, Blake, Sproule, Gourlay, and Busto

(2004) indicated that some barriers may exist in preventing prescription opioid users from obtaining MMT, such as treatment being restricted to individuals with serious medical or psychiatric issues who also inject heroin. Additionally, when comparing MMT clients dependent on prescription opioids to those dependent on heroin, they found significant differences between the two groups. Clients dependent on prescription opioids were less likely to use illicit substances, less likely use substances via injection, more likely to report pain difficulties, and more likely to be currently receiving psychiatric treatment. As such, one would hypothesize prescription opioid-using clients enrolled in MMT may have different treatment needs and objectives than heroin-using clients. However, this study was limited to only individuals entering a specific MMT program in 1997-1999 in Toronto. The extent to which these results are generalizable or representative of other prescription opioid-dependent individuals entering or enrolled in MMT in the present day, a decade later, is unclear. This is particularly noteworthy given that prescription opioid use and misuse, and related treatment admissions, have increased greatly since 1999 (see Section 1.5).

1.8.4 Summary of Rational for Study Two.

Previous research indicates high prevalence of both current substance use and psychiatric symptoms in MMT clients. These issues have been found to be interrelated and both negatively affect clients' health and outcomes in MMT. Little research has comprehensively evaluated how specific types of current

substance use and types of psychiatric symptoms may be related. Further, no research to date has examined such issues among clients enrolled in MMT primarily related to prescription opioid use. Given the changing characteristics of opioid use in North America (i.e., that opioid use is increasingly comprised of non-medical prescription opioid and misuse; Fischer et al., 2006; Fischer & Rehm, 2007; Fischer, Rehm et al., 2008), further research of this population in treatment is warranted.

1.9 Overarching Goals of the Current Research

The first overarching goal of the current research was to examine specific prescription opioid use characteristics, particularly for the opioid hydromorphone. That is, given the increasing prevalence and problems associated with non-medical prescription opioid use and misuse, how do individuals initiate into use of hydromorphone, a prescription opioid of particular interest, and what is their hydromorphone use like later in life? Are there any factors that affect how a person might use the prescription opioid hydromorphone, or why they might use this substance?

The second overarching goal of the current research was to gain insight into issues faced by prescription opioid users in treatment. That is, what kinds of psychiatric symptoms might they be experiencing? What kinds of substances might they be using? Are these two variables related? How might the results

obtained with prescription opioid users compare to previous MMT investigations where clients were predominantly heroin users?

CHAPTER 2 INTEGRATED, DETAILED METHODS OF DISSERTATION STUDIES AND RELIABILITY OF MEASURES USED

2.1 Participants

All participants were recruited from a low-threshold MMT clinic in Halifax, Nova Scotia. The target populations served by the low-threshold MMT clinic are injection drug users who also have significant comorbid mental health issues; are dependent on a variety substances; are HIV- , Hepatitis B- and/or C-infected, or at risk of such an infection; have been, or are currently, involved with the criminal justice system; are homeless and/or street-involved; and/or have been unsuccessful in higher-threshold or abstinence-based treatment programs (Marshall, 2004).

Approximately 190 clients are enrolled at this MMT clinic at all times. The majority of clients enrolled in the low-threshold MMT program are self referred (approximately 85%, approximately *n*=162/190) with the remainder being referred by other service providers (e.g., family doctor, infection specialists). No clients are mandated to treatment and participation in the treatment program is voluntary. Clinic information for all clients enrolled reveals that clients are, on average, 36 years of age, 98% (*n*=186/190) Caucasian, and 60% (*n*=114/190)

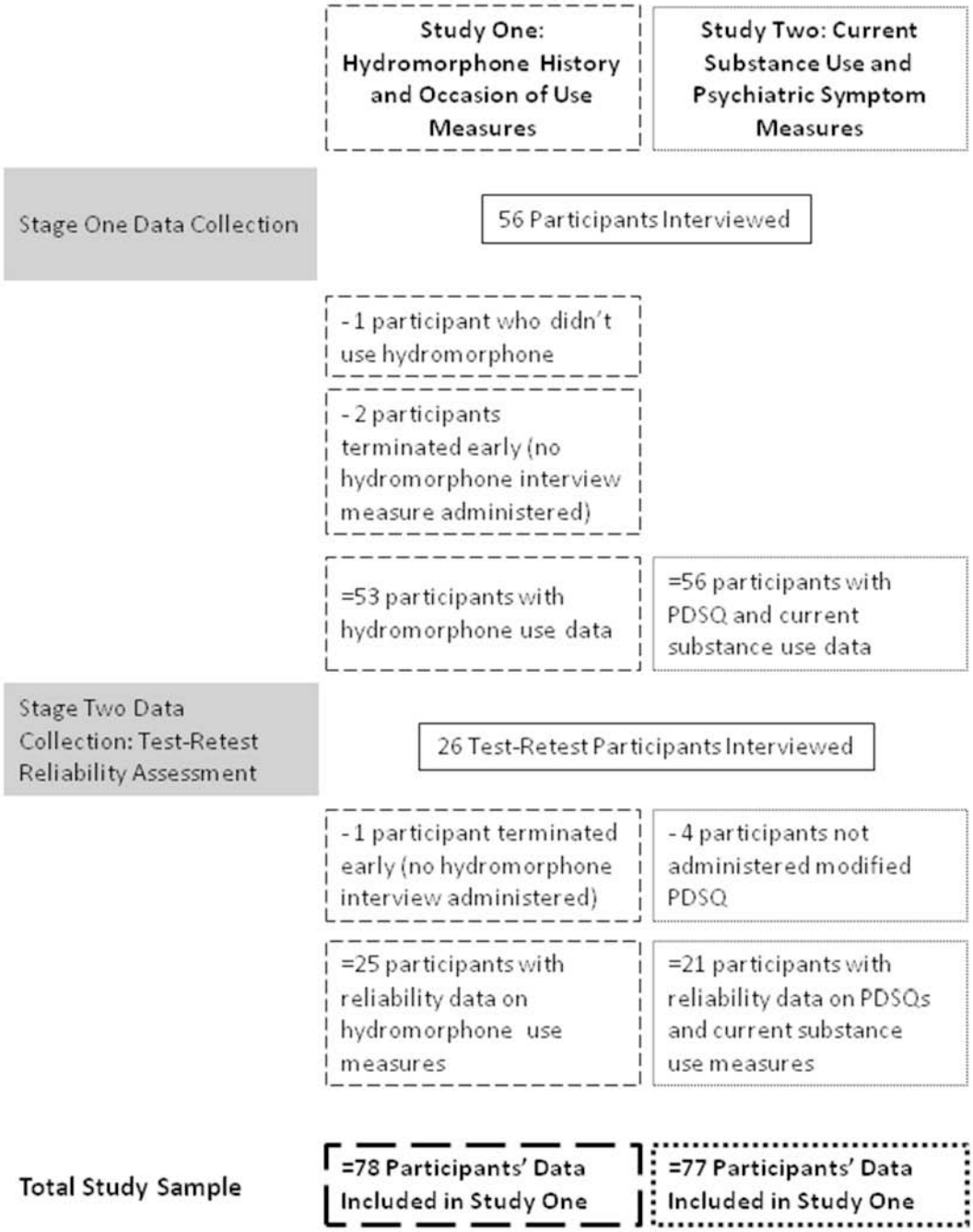
male. At any time, approximately 37% (*n*=70/190) of clients enrolled at the clinic take their methadone via daily witnessed ingestion by staff at the clinic, 50% (*n*=95/190) have privileges to take their methadone at a community pharmacy or to receive "carry"/take-home doses, and 13% (*n*=25/190) of clients are incarcerated (C. MacIsaac, personal communication, June 13, 2011).

2.1.1 Entire Sample

Ninety-three individuals from the clinic were approached, and 82 individuals chose to participate in the present thesis studies. There were no exclusion criteria to participate in the studies beyond the requirement of being a current client at the MMT program clinic.

Not all participants completed all measures (e.g., the interview was terminated early). In such cases the participant was excluded from data analysis in the study. This resulted in 78 participants being included in analyses for Study One and 77 participants being included in analysis for Study Two (see Figure 2.1). Demographics regarding participants for each thesis study are given in the relevant manuscript-based chapter (Chapters 4 and 6).

Figure 2.1. Data collection and participant data inclusion for Studies One and Two (see Chapters 4 and 6, respectively, for each manuscript-style publication).



2.1.2 Subsample of Test-Retest Participants

The last 25 and 21 participants interviewed in Studies One and Two respectively (see Figure 2.1), were interviewed a second time, one day later to assess stability (also known as test-retest reliability) of participants' self report on measures included in each study. Participants who were part of the initial sample and participants who were part of the test-retest sample did not significantly differ on demographic variables previously found to be associated with substance use and/or psychiatric symptoms (e.g., methadone dose, gender, Ward et al., 1998a; King & Brooner, 1999; see Tables 2.1, 2.2).

Table 2.1

Demographic characteristics of Study One (examining hydromorphone history and occasions of use) participants interviewed during initial data collection period, and those who comprised the second phase of data collection where they were interviewed twice to assess test-retest reliability.

Demographic variable	Initial sample (*n*=53) % sample(*n*) or *M*[*SD*]	Test-retest sample (*n*=25) % sample(*n*) or *M*[*SD*]
Age (years)	40.36[8.61]	39.08[9.69]
Gender		
Male	62.3% (33)	68.0% (17)
Female	37.7% (20)	32.0 (8)
Ethnicity		
Caucasian	83.0% (44)	84.0% (21)
Other	17.0% (9)	16.0% (4)
Duration enrolled in current MMT program (years)	3.15[2.65]	3.66[3.25]
Daily Methadone dose (mg)	112.96[45.38]	105.20[41.55]
Total number of substances used in life[1]	11.94[3.66]	12.80[3.71]

[1]*Note: Tobacco included, crack cocaine and power cocaine are considered separate substances, prescription opioids and benzodiazepines are counted as one substance each*

Table 2.2

Demographic characteristics of Study Two (examining current substance use and psychiatric symptoms) participants interviewed during initial data collection period, and those who comprised the second phase of data collection where they were interviewed twice to assess test-retest reliability.

Demographic variable	Initial sample (*n*=56) % sample(*n*) or (*M*[*SD*])	Test-retest sample (*n*=21) % sample(*n*) or (*M*[*SD*])
Age (years)	39.95[8.64]	38.90[9.33]
Gender		
Male	60.7% (34)	66.7% (14)
Female	39.3% (22)	33.3% (7)
Ethnicity		
Caucasian	80.4% (45)	81.0% (17)
Other	19.6% (11)	19.0% (4)
Duration enrolled in current MMT program (years)	3.16[2.58]	4.04[4.02]
Daily Methadone dose (mg)	113.25[44.76]	108.81[42.69]
Total number of substances used in life[1]	12.20[3.67]	12.48[3.76]

[1]*Note: Tobacco included, crack cocaine and power cocaine are considered separate substances, prescription opioids and benzodiazepines are counted as one substance each*

2.2 Measures

All measures in Studies One and Two were administered as part of a larger research project examining substance use behaviours (e.g., cocaine use; Barrett, 2007; Barrett, 2009) Each interview was approximately 2 to 2.5 hours in duration. All study measures included in the present thesis studies are described below.

2.2.1 Demographics and Methadone Use

Participants were asked about demographic variables (e.g., age, ethnicity; See Appendix A) and methadone usage variables (e.g., duration in current MMT program, current daily MMT dose; See Appendix A).

2.2.2 Substance Use History

A measure adapted by Gross, Barrett, Shetowsky, and Pihl (2002) from the Addiction Severity Index (McLellan et al., 1985), the Drug History Chart, was used to assess current and lifetime substance use. For 18 different licit and illicit substances (i.e., tobacco, alcohol, cannabis, powder cocaine, crack cocaine, amphetamine/methamphetamine, heroin, opium, LSD [lysergic acid diethylamide], magic mushrooms/psilocybin, MDMA[3,4-methylenedioxymethamphetamine]/MDA[3,4-methylenedioxyamphetamine]/ecstasy, GHB [gamma-hydroxybutyric acid], PCP [phencyclidine], inhalants, mescaline, ketamine, salvia, peyote), participants were asked to report if they ever used, age of first use, and the number of days they used the substance out of the past 30 days (See Appendix B, Drug History Chart).

2.2.3 Prescription Drug Use History

A slightly different method was used to assess prescription drug use history. To assist with recall, participants were shown cards depicting photos and names of different opioid and benzodiazepine medications. These cards were adapted from the National Survey on Drug Use and Health (NSDUH; SAMHSA, 2009b) to include Canadian forms of medications from the Compendium of Pharmaceuticals (e-CPS, 2007; see Appendix C). Participants were asked to indicate which opioids and benzodiazepines they had ever used in their lives with and without a prescription.

The first 20 participants interviewed were asked the same questions on the Drug History Chart (see Section 2.2.2 above) as other licit and illicit substances for every prescription medication they had ever used with and/or without a prescription. They were also asked if they were prescribed the medication during their initial use. However, due to the observation that participants had used a much greater number of different prescription medications than researchers' expected, participants' feedback that they could not remember exact details about every prescription medication they had ever used (e.g., for medications they had tried only once because their opioid of choice was not available), and the relatively long period of time that was required to ask and record the use histories of all the prescription medications used by each participant, the interview was modified for all subsequent participants to only ask about the general classes of prescription opioids (exclusive of

methadone) and benzodiazepines (see Appendix D. Drug History Chart). Additional questions were asked to determine which medication from each class of opioids and benzodiazepines was used first, and if the participant had been prescribed that medication during their initial use.

Although much of the data from the first 20 participants could be derived to determine participant values for the general classes of prescription opioids and benzodiazepines, some data are missing for these participants (e.g., number of days/past 30 days substance was used). When two different medications from the same class were used by a participant in the past 30 days, the value for total number of days/30 that the medication class was used was uncertain (e.g., if a participant used both clonazepam and diazepam in the past 30days, it could not be determined if clonazepam and diazepam were used on separate days or the same days, thus the total number of days/30 that benzodiazepines were used was unclear). In such cases this variable was left missing. All *n*s and percents are used in relevant tables and table notes are also given where relevant to explain any missing data. The earliest ages of use for the prescription medication classes for the first 20 participants were derived by using the youngest age of use reported from all the medications used by the participant in that class.

All participants were asked to indicate their primary opioid of choice (including heroin and opium) that they ever used or use in their life (See Appendix D).

2.2.4 Hydromorphone Use History

If a participant endorsed using medications containing hydromorphone in their lifetime, then a detailed semi-structured polysubstance interview was conducted (see Appendix E: Hydromorphone Use Interview). Participants reported whether they ever used hydromorphone with and/or without a prescription. If they had received a prescription, they were asked to freely recall the reason(s) and responses were written onto the study measures by the interviewer. Participants then reported the age of their first use of hydromorphone and if they had been prescribed hydromorphone during their initial use. They were also asked to indicate the age of their last, or most recent, use of hydromorphone.

Each participant was asked specific details about the earliest and most recent occasions of hydromorphone use that they could recall. For each occasion, the participant was asked to report their age during the recalled occasion, if the participants was with at least one other person during the occasion, if other individual(s) was(were) also using hydromorphone, if the participant had used other substances with hydromorphone and, if so, what substances. Participants were asked to list the order, amount, and route of administration for each substance used. That is, participants were asked, “which substance did you use first? How much of [the first substance] did you consume at this point in time? How did you use [the first substance] at this point in time? What substance did you use next? How much of [the second substance] did you

consume at this point in time?" etc., (see Appendix E). Similar methods for detailing patterns of multiple substance use have been used in other drug using populations and have been found to produce reliable results (e.g., Barrett, Gross, Garand, & Pihl, 2005).

Participants were also asked to identify their primary reason for using hydromorphone during each use occasion. Participants were provided with a list of possible reasons for use of hydromorphone (i.e., out of curiosity, to get high/stoned/drunk/ buzzed, to fit in with peers, to increase the effects of another drug, to decrease the effects of another drug, to study/concentrate, to stay awake, to give you more energy, to reduce appetite/manage weight, to help with sleep, to reduce anxiety, to reduce pain, to avoid withdrawal, because it was safer than street drugs; See Appendix E) and given the opportunity to specify other reasons. If other reasons were specified, the reasons were written down verbatim by the interviewer.

2.2.5 Psychiatric Symptoms

To assess current psychiatric symptoms, a modified Psychiatric Diagnostic Screening Questionnaire (PDSQ, [Zimmerman, 2002]; see Appendix F) was used. This measure contained 125 yes/no questions regarding experiencing symptoms of 13 *DSM-IV* (APA, 1994) Axis I disorders (i.e., Psychosis, Hypochondriasis, Somatization Disorder, Depression, Post Traumatic Stress Disorder [PTSD], Obsessive Compulsive Disorder [OCD], Panic Disorder,

Agoraphobia, Social Phobia, Generalized Anxiety Disorder [GAD], Alcohol Dependence, Drug Dependence, and Eating Disorder), in the past two weeks or past 30 days. The original version of the PDSQ (see Appendix G) assessed symptoms in the past two weeks to past six months (as is relevant based on *DSM-IV* [APA, 1994] criteria for the different disorders). The modification enabled the period of reported psychiatric symptoms to be consistent with the substance use interview's assessment of use in the preceding 30 days. The disorders assessed on the PDSQ are the most prevalent mental health disorders encountered in adult out-patient mental health clinics (Zimmerman, 2002). An individual screens "positive" for a disorder on the PDSQ if s/he endorses the predetermined minimal number of symptoms for that diagnostic category (see Table 3.5 for number of symptoms required to be endorsed for each disorder assessed on the PDSQ). Screening positive for a disorder on the PDSQ suggests that symptoms experienced are at a level such that an individual would be significantly more likely to qualify for a diagnosis of that disorder than an individual who did not screen positive (Zimmerman, 2002). Questions relating to drug and alcohol dependence were excluded from analysis given Study Two's objective of evaluating the relationship between substance use and non-substance dependent psychiatric symptoms.

The original version of the PDSQ has been found to be reliable and valid (see Zimmerman, 2002 for review), and has shown good sensitivity and negative predictive values in a sample of individuals with substance use disorders (Zimmerman, Sheeran, Chelminski, & Young, 2004).

2.3 Procedure

2.3.1 Participants 1-56 (Stage One Data Collection)

Recruitment for Stage One Data collection took place January 2008-April 2009. All clients enrolled in the MMT program were informed of their eligibility to participate in the present study during client group meetings and through conversations with study personnel. Study personnel were independent from clinic staff (i.e., had not previously/were not currently employed by the clinic), were students completing either their Bachelors or PhD in Psychology, and were trained and supervised by a registered, PhD-level psychologist. Study personnel identified themselves to potential participants as university students conducting a confidential research study on substance use. Clients were informed that study information would be kept confidential; participation was voluntary and their decision to participate (or not) would not affect their treatment. Willing participants gave verbal and written informed consent and were compensated $20 at the completion of the study interview, or if the interview was not fully completed, $10/hour spent with the interviewer to a maximum of $20. All interviews were conducted in a private room at the MMT clinic. Sampling, procedures, and materials were reviewed and approved by the Dalhousie University Research Ethics Board.

2.3.2 Participants 57-82 (Stage Two Data Collection)

The procedure for the last 26 participants interviewed varied somewhat from the earlier participants in order to determine reliability of participants' self-report on the study measures used in the present thesis. For the last 26 participants interviewed, the substance use history questions (see Appendix D, Drug History Chart), and details regarding the earliest and most recent occasions of hydromorphone use (see Appendix E) were administered a second time by a different interviewer the following day. The original version of the PDSQ (see Appendix G) was also administered to the last 21 participants by a different interviewer on a separate day to determine reliability between the modified and original versions. A one day interval between the first and second interviews was chosen so that the periods of recall for substance use behaviours (e.g., number of days out of the past 30 that alcohol was used) and psychiatric symptoms (e.g., two weeks prior to the study interview when a participant may have felt sad and depressed most of the day, nearly every day) had as much overlap as possible. If a longer period of time had elapsed between the two interviews (e.g., one week), additional error not related to reliability of participants recall would be introduced. That is, participants' responses between the first and second interviews could be different because their behaviour or experiences were different between the two assessed periods of time (e.g., s/he used alcohol more frequently, s/he felt more depressed) - not because they were recalling the same events differently.

Participants were not informed during the initial interview that they would be invited to participate in a study the following day with another interviewer who would ask identical questions. The initial interview was administered to participants in the same fashion as the previous 56 participants (see Section 2.3.1). After the initial interview was completed and the participant was compensated for their time, the interviewer informed them of the possibility to participate in "a different study" with a different interviewer the following day. All participants agreed to participate in the second interview. The study purpose of assessing reliability of participants' self-report was partially masked through administration of other measures (e.g., Substance Use Risk Profile Scale; Woicik, Conrod, Stewart & Pihl, 2009) during this second interview. Interviewers were counterbalanced across the two days of the test-retest portion of the study so that no interviewer gave a greater proportion of interviews on the first or second day.

As with the initial interview (see Section 2.3.1), at the start of the second interview, clients were informed that all study information would be kept confidential; participation was voluntary and would not affect their treatment at the MMT clinic in any way. At the end of the second interview, after the participant had been compensated for their time, participants were asked, "did you know that I would be asking you some of the same questions today that the researcher asked you yesterday?". If a participant said yes, then further details were asked regarding how they knew this and what questions specifically they thought prior to the interview were going to be asked again. Participants'

responses were written down and summarized by the interviewer. It had previously been observed by interviewers that study participants would often discuss the study with each other. Consequently, the aim of this question was to serve as a rough manipulation check in order to assess whether participants knew the reliability of their recall was being assessed (i.e., from discussing the study with other participants), and thus if their behaviour on the first or second interview may have been affected by this prior knowledge.

All interviews with participants took place in a private room at the MMT clinic. Participants gave verbal and written informed consent and were compensated $20 at the completion of the study interview, or if the interview was not fully completed, $10/hour spent with the interviewer to a maximum of $20. All sampling, procedures, and materials were reviewed and approved by the Capital Health Research Ethics Board.

2.4 Statistical Analyses

All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 15.0. In a small percentage of cases, data were missing for some variables (e.g., participant responded “I don’t know”). Proportions of missing data and reasons for missingness are detailed in the relevant manuscript chapters. Specific analytic techniques are also explained in the relevant manuscript chapters; however a general overview is presented below.

2.4.1 Quantitative Data Analysis- Descriptive and Inferential Statistics

Descriptive univariate statistics were used to summarize data. Chi-square (χ^2) and McNemar tests were used to evaluate differences for between- and within-participant categorical variables, respectively. Fisher's exact tests were run in place of χ^2 if any expected cell counts were less than 5 to minimize the chance of Type 1 error (Field, 2009). Student *t*-tests were used to compare any continuous between-participant variables, and paired-sample *t*-tests were used to compare any continuous within-participant variables. Multiple linear regressions and logistic regressions were used to evaluate the ability of quantitative variables to predict outcome variables of interest (see Chapter 6). Effect sizes (e.g., Odds Ratios [OR], Phi [ϕ]) are given for significant findings where relevant.

2.4.2 Reliability Analyses of Thesis Study Measures

Reliabilities (stabilities) of the present measures were assessed using Cohen's Kappa (κ), Partial and Bias Adjusted Kappas (PABAK; Byrt, Bishop & Carlin, 1993), and percent agreements. Cohen's Kappa (κ) is a frequently used test-retest reliability measure. However, this measure can be greatly influenced by the prevalence of the outcome of interest (e.g., κs of outcomes where prevalence is close to 50%:50% are less influenced by disagreement between each test than outcomes where prevalence is more skewed [e.g., 5%:95%]). The

presence of bias in the agreement between test-retest occasions can also affect κ. An example of bias would be if most participants said they used a substance during the first interview, but on the second interview participants are equally likely to say they used or did not use the substance. In such a case, bias exists for participants to say they used a substance on the first interview compared to the second interview. Some statisticians (e.g., Hoehler; 2000) believe that estimates with skewed prevalence and/or bias issues are informative in assessing agreement and κ should still be used instead of prevalence- and/or bias-adjusted estimates. In general it is recommended (e.g., Chen, Garis, Hemmelgarn, Walker, & Quan, 2009; Sim & Wright, 2005) that researchers report κ, PABAK, and levels of agreement (i.e., percentages).

Values for κ and PABAK < 0.40 are considered to be indicative of "unsatisfactory agreement", 0.41 - 0.60 as "acceptable" or "moderate" agreement, 0.61 - 0.80 as "good/satisfactory" or "substantial" agreement, and values 0.81-1.00 as "very satisfactory" or "almost perfect" agreement (Landis & Koch, 1977; Sim & Wright, 2005). Positive and negative agreement statistics reported in Tables 3.1 and 3.2 represent positive percent agreement (i.e., [number of observations where variable present during Interview 1 and Interview 2]/number of all observations * 100%) and negative percent agreement (i.e., [number of observations where variable absent during Interview 1 and Interview 2]/number of all observations * 100%) between the two interviews for each categorical variable. Positive percent agreement and negative percent agreement are similar to the measures of sensitivity (i.e., percent of true positives

that were correctly classified as positives) and specificity (i.e., percent of true negatives that were correctly classified as negative; Tabachnick & Fidell, 2001), respectively. Sensitivity and specificity, however, are used in assessing the performance of a binary classification test (e.g., ability of a diagnostic measure to determine if a patient has cancer), whereas positive and negative agreement statistics assess whether the same results are obtained at two different time points. Total observed agreement reflects the percent agreement of the two interviews, regardless of whether the agreements were positive or negative (Landis & Koch, 1977; Sim & Wright, 2005).

Other statistical tests used to assess reliability were McNemar tests, paired *t*-tests, and Pearson's correlations (*r*). McNemar tests were used to assess if there were significant differences within-participants regarding endorsement of categorical variables between the first and second interview. Paired t-tests were used to assess if there were significant differences within-participants regarding continuous variables between the first and second interview. Pearson's correlation coefficient's (*r*) were also used to assess reliability for continuous variable measures.

2.4.3 Free-Response Data Analysis

Free-response reasons for receiving a hydromorphone prescription were coded using an inductive (i.e., codes/themes emerging from the data) classical content analysis (i.e., each code/theme from the data is subjected to a frequency

count; Leech & Onwuegbuzie, 2007). Based on observed frequencies, free-response reasons for receiving a hydromorphone prescription were categorized into two codes/themes: 1-Pain Management, 2-Other (e.g., to “maintain” the individual on hydromorphone while on the waitlist to join the MMT program). Six of the 68 participants with histories of prescriptions (8.8%) reported receiving prescriptions for both reasons. In such cases, both reason categories were counted as endorsed.

Free-response and listed reasons for using hydromorphone on earliest and most recent recalled use occasions were reduced to a smaller number of categorical reason categories using the same inductive classical content analysis explained above. Based on observed frequencies, reasons for hydromorphone use were categorized into the following codes/themes: 1-To get high, 2-Curiosity, 3-To decrease/manage pain, 4-To avoid/cope with withdrawal, 5-Other (e.g., to fit in with peers). Eight of the 78 participants (10.3%) reported using hydromorphone for two reason categories (e.g., to get high and avoid withdrawal) for the earliest and most recent recalled use occasions. In such cases both reason categories were counted as endorsed.

2.4.4 Data Analysis: Power

Power analyses were conducted to ensure there was sufficient power to detect effects in the inferential statistical analyses as well as test-retest reliability analyses.

For inferential statistics, power analyses were conducted using Cohen's (1992) guidelines. For Study One, effect size estimates for χ^2 were expected to be medium to large based on Fulmer and Lapidus' (1980) findings for motives for initiating and continuing to use heroin and Strang, Griffiths, Powis, Abbey, and Gossop's (1997) findings regarding changes of heroin administration routes. With α=.05, the guidelines suggested an *n*=26-87 participants to detect large to medium effects, respectively (note: fewer participants are needed to detect larger effects). Consequently the Study One sample of *n*=78 could be considered close to adequately powered for detecting medium effects and adequately powered to detect large effects. Study Two logistic regressions were conducted using guidelines outlined in Field (2009) for sufficient power. The number of predictors entered into regression analyses did not exceed the recommended 1:5 (predictor variables: participants) ratio.

For test-retest reliability power analyses, a variety of techniques outlined by Cohen (1992) and Sim and Wright (2005)[5] were used to determine the necessary sample for assessing the reliability of participants' recall on the drug use history measure (i.e., ever used [substance], age of first use, number of days/past 30 [substance] used; Drug History Chart, See Appendix D). For power analyses, all expected effects were based upon κs and *r*s previously obtained in a study with a large sample of injection drug users who were not enrolled in substance use treatment (i.e., Dowling-Guyer et al., 1994; Napper, Fisher, Johnson, & Wood, 2010). This study was chosen as the basis for the present

[5]Cohen's (1992) guidelines were used for correlational analyses, t-tests, and χ^2 tests. Sim and Wright's (2005) guidelines were used for κ and PABAK analyses.

power calculations because the researchers used very similar drug history questions (e.g., ever used [substance]; age of first use, number of days [substance] used/past 30) in a population of substance users that were likely to share similar characteristics to the present sample (i.e., mostly male [73.9%[6]], participants in mid to late thirties [M{SD} age=5.3{8.2} years], the majority had used crack cocaine [87.2%], powder cocaine [88.7%], and/or heroin [59.0%]). Additionally, similar to the present study, the researchers conducted both test-retest assessment interviews within 48 hours. While the test-retest reliability for all variables, and for every substance were not reported (Dowling-Gueyer et al., 1994; Napper et al., 2010), the test-retest reliability of lifetime amphetamine use was κ=0.79. The correlation for the age of first using amphetamine between the two interviews was *r*=.64. The correlations for number of days a substance was used/past 30 between the two interviews ranged from *r*=.80 to .88 for crack cocaine, powder cocaine, and heroin.

The necessary sample size for assessing the reliability of recall (i.e., κ and PABAK) for lifetime use of a substance was determined using the guidelines outlined by Sim and Wright (2005). A desired power level of 0.8 was set for test-retest reliability analyses. Based on the findings above for lifetime amphetamine use (i.e., κ=0.79), it was assumed that the present study would find at least an "acceptable" level of agreement (i.e., κ≥0.70) with the null hypothesis as no agreement between interviews (κ=0.00). Any proportion of positive ratings was

[6] Note: % male reflects test-retest specific subsample of 218 clients given in Dowling-Gueyer et al., 1994; other demographic variables of interest are only given for the entire sample of 4027 individuals in the Napper et al. (2010) study.

permitted (i.e., .1-.9 using a substances) given the diversity of substances being assessed for reliability (e.g., use of alcohol, peyote, heroin). An *n* of 17 participants was recommended; thus the test-retest samples for lifetime substance use variables for Studies One and Two could be considered to be sufficient.

The necessary sample for test-retest reliability comparisons for ages of first use and number of days/past 30 days a substance was used were determined using Cohen's (1992) recommendations. The previously obtained test-retest correlations noted above (i.e., *r*s=.64; .80-.88) could considered to be high (i.e., greater than .5; Cohen, 1992). Thus, 28 participants were recommended to detect a significant relationship between reports on the two interview days for the present studies. Consequently the Study One test-retest sample of *n*=25 and Study Two test-retest sample of *n*=21 participants could be could be considered to be close to being adequately powered to assess these relationships.

The test-retest reliability power analyses to assess the Study One hydromorphone occasions of use measure were conducted using recommendations from Sim and Wright (2005). A desired power level of 0.8 was used, and it was assumed that the present study would find at least an "acceptable" level of agreement (i.e., $\kappa \geq 0.60$), with the null hypothesis of no agreement between interviews ($\kappa = 0.00$). This expected level of agreement assumption was made based on previous literature using similar methodologies; these authors found levels of agreement ranging between 0.65 and 1.00 for κ

(Barrett et al., 2005). Any proportion of positive ratings was permitted (i.e., 0.1-0.9) given the diversity of items being assessed for reliability (e.g., likelihood to be in presence of others, likelihood to co-use substances with hydromorphone, likelihood to use orally). This resulted in a necessary sample size of at least 22 participants for test-retest reliability analyses. Consequently the Study One test-retest sample of *n*=25 could be could be considered to be adequately powered to assess these relationships.

The necessary sample needed for comparisons between the modified and original versions of the PDSQ were based upon κs obtained by Zimmerman (2002) in assessing the reliability of the original PDSQ items (κs were not given for the reliability of screening positive on the scales). Researchers administered the original PDSQ to 63 psychiatric outpatients twice, with approximately one week in between assessments. In this replication study, all items were found to have κs=0.65 or greater (later test-retest studies found similar item test-retest reliability values). Using the above sample estimation procedure in Sim and Wright (2005), and assuming the present study would obtain a κ=0.60, the null hypothesis was no agreement (κ=0.00), desired power was 0.8, α=.05, and any proportions of positive endorsements was permitted (i.e., proportion of individuals screening positive for a particular disorder on the PDSQ). The test-retest sample for Study Two was found to be very close to being adequately powered (22 participants were recommended) with the data of 21 participants being used for that portion of the reliability study.

Zimmerman (2002) also reported correlations of the number of items endorsed on subscales for the test-retest assessments of the original PDSQ. Given similar comparisons would be made between the one-month modified and original versions of the PDSQ, sample size requirement analyses were conducted to determine if analyses would have adequate power. All correlations for subscales in the Zimmerman's (2002) test-retest reliability studies were high (i.e., greater than 0.5; Cohen, 1992). Using Cohen's (1992) recommendations for power, 28 participants were required to assess a significant correlation (i.e., assess if there is a significant relationship between number of symptoms reported on the subscales of original PDSQ and modified PDSQ measures). The sample of 21 participants thus could be considered close to adequately powered to assess this relationship.

Despite being slightly underpowered for a small number of the inferential and test-retest reliability analyses outlined above, these analyses were still conducted and reported in the manuscripts of the relevant studies (see Chapters 4 and 6) When a study is underpowered, Type II error is more likely than Type I (Field, 2009). It was hypothesized that if significant results were obtained for inferential statistical analyses and/or acceptable levels agreement observed between the two interview days for the test-retest reliability analyses, then the relationships would likely be indicative of large effect sizes and could likely be considered to be robust.

CHAPTER 3 TEST-RETEST RELIABILITY OF THESIS STUDY MEASURES AND RELATED DISCUSSION

3.1 Participant Awareness of Self-Report Reliability Assessment

One participant out of the 26 who participated in the test-retest reliability assessment responded yes to the question, “Did you know that I would be asking you some of the same questions today that the researcher asked you yesterday?” with the explanation that s/he “had done these studies [i.e., participated in other researchers’ studies] before” and so s/he “had a feeling” that the second interview would consist of similar or identical questions to the first interview. All other participants indicated that they did not know they would be asked identical questions on the second interview. That is, 25/26 of the test-retest participants were unaware of the study’s objective of assessing the reliability of their self-report.

Results did not change substantially if the one participant who suspected reliability was being assessed was included or excluded from analyses. Consequently this individual was included in subsequent statistical analyses.

3.2 Substance Use History: Study One and Two Participant Use Data

Acceptable levels of reliability were obtained for participants' endorsement of the use of different substances over their lifetimes (see Table 3.1) and in the past 30 days (see Table 3.2). Lowest reliabilities for lifetime use were obtained for substances that were used by a minority of the sample (e.g., GHB, ketamine; see Table 4.1), whereas more commonly used substances (e.g., alcohol, cannabis, benzodiazepines, see Table 4.1) had excellent levels of reliability (see Tables 3.1, 3.2). Similarly, ages of first use for different substances had high correlations between the values reported during the first and second interview, with the exception of infrequently used substances (see Table 3.1). There were also no differences between the two interviews in the total number of different substances reportedly used in the past 30 days - when tobacco was included($M[SD]_{\text{First interview}}$=3.38[1.69] substances, $M[SD]_{\text{Second interview}}$=3.54[1.96] substances, paired t[23]=-1.16, p=.257), or excluded from the total substance count ($M[SD]_{\text{First interview}}$=2.38[1.69] substances, $M[SD]_{\text{Second interview}}$=2.54[1.96] substances, paired t[23]=-1.16, p=.257).

It is important to note that 25 participants from Study One took part in the test-retest reliability assessment; while only 21 of these 25 participants from Study Two were included in Study Two analyses (see Figure 2.1). Data from 25 participants was analysed above in order to maximize completeness of data and

power. Reliability estimates did not significantly change if data from only 21 participants were used.

Table 3.1

*Test-retest reliability of participants' (*n=*25) self-reported lifetime substance use history using Drug History Chart (see Appendix D).*

	Reliability Measure of Drug History Chart Variable					
	Ever used substance					*r* for
Substance	κ	PABAK	% Positive Agreement	% Negative Agreement	%Total Observed Agreement	Age of first use (*n*)
Alcohol	0.00	0.92	98.0	0.0[1]	96.0	.84(24)
Cannabis	1.00	1.00	100.0	100.0	100.0	.90(24)
Powder Cocaine	1.00	1.00	100.0	100.0	100.0	.97(22)
Crack Cocaine	1.00	1.00	100.0	100.0	100.0	.97(24)
Amphetamine	0.73	0.76	90.9	82.4	88.0	.80(15)
MDMA	0.90	0.92	97.9	92.3	95.8	.87(17)
Heroin	1.00	1.00	100.0	100.0	100.0	.89(16)
GHB	0.70	0.84	75.0	95.2	86.7	.94(3)
Ketamine	0.69	0.76	76.9	91.9	88.0	.84(5)
Magic Mushrooms	1.00	1.00	100.0	100.0	100.0	.92(18)
LSD	0.83	0.92	97.7	85.7	96.0	.81(21)
Mescaline	0.92	0.92	96.3	95.7	96.0	.66(13)
PCP	0.84	0.84	90.9	92.9	92.0	.49(10)
Salvia	1.00	1.00	100.0	100.0	100.0	1.00(3)
Inhalants	0.82	0.84	87.5	94.1	92.0	.63(7)
Peyote	1.00	1.00	100.0	100.0	100.0	.02(5)
Opium	0.68	0.68	83.3	84.6	84.0	.95(10)
Benzodiaze-pines	1.00	1.00	100.0	100.0	100.0	.83(22)
Prescription opioids	--[2]	--	--	100.0	100.0	.84(25)

[1]*Statistic is 0.0% due to empty cells (e.g., 0 participants reported no lifetime use of alcohol on both interview days; this results in 0 in the numerator for calculating % agreement)*

[2]*-- indicates that the statistic could not be calculated due to empty cells (e.g., every participant reported using substance on both the first and second interviews; this resulted in 0 in the denominator for calculating % agreement and other statistics).*

Table 3.2

*Test-retest reliability of participants' (*n=*25) self-reported current substance use using Drug History Chart (see Appendix D).*

	Reliability Measure of Drug History Chart Variable					
	Used substance in past 30 days					*r* for # days used/ past 30 (*n*)
Substance	κ	PABAK	% Positive Agreement	% Negative Agreement	% Total Observed Agreement	
Alcohol	0.80	0.84	85.7	94.4	92.0	.76(24)
Cannabis	0.92	0.92	96.8	94.7	96.0	.98(24)
Powder Cocaine	0.71	0.84	75.0	95.2	92.0	.49(22)
Crack Cocaine	0.76	0.76	88.0	88.0	88.0	.96(24)
Amphetamine	0.0	0.83	0.0[1]	95.7	91.7	--[2]
MDMA	--	--	--	100.0	100.0	--
Heroin	--	--	--	100.0	100.0	--
GHB	--	--	--	100.0	100.0	--
Ketamine	--	--	--	100.0	100.0	--
Magic Mushrooms	0.00	0.92	0.0	98.0	96.0	--
LSD	--	--	--	100.0	100.0	--
Mescaline	--	--	--	100.0	100.0	--
PCP	--	--	--	100.0	100.0	--
Salvia	--	--	--	100.0	100.0	--
Inhalants	--	--	--	100.0	100.0	--
Peyote	--	--	--	100.0	100.0	--
Opium	--	--	--	100.0	100.0	--
Benzodiaze-pines	0.83	0.83	91.7	91.7	91.7	.85(19)
Prescription opioids	0.80	0.84	85.7	94.4	92.0	.95(25)

[1] *Statistic is 0.0% due to empty cells (e.g., 0 participants reported using amphetamine on both interview days; this results in 0 in the numerator for calculating % agreement)*

[2] *-- indicates that the statistic could not be calculated due to empty cells (e.g., 0 participants reported using substance on both the first and second interviews; this results in 0 in the denominator for calculating % agreement and other statistics).*

3.3 Discussion of Substance Use History Test-Retest Reliability Results

High levels of reliability between the two interview days for self-reported substance use were obtained. While some have questioned the use of self-report measures (see Darke, 1998b for review), the results suggest that the method used in the present studies is quite reliable in assessing lifetime and current substance use. However, some caution is warranted in interpreting these findings, and in turn, the related findings based on this method in Study One and Study Two. Firstly, while reliability is a necessary pre-condition for validity (Nunnaly, 1967), they are not the same. Reliability, in this case test-retest reliability, refers to the consistency of results. That is, if the study is conducted again, using the same measures and procedures, will the same results be obtained? Validity, however, refers to the accuracy of results. That is, does the measure assess what it is intended to assess? In order to confirm validity of self-reported substance use (i.e., did the participant actually use the substance that they reported using?) in the present study, biological measures such as urine screens or hair screens and/or collateral informant data would be necessary. Such measures were not used in the present study for a variety of reasons. Biological measures are not 100% valid or reliable and have limitations themselves. Namely, biological measures have small windows of detection and are costly (Carroll, 1995). Additionally, unknown diluents in substances can result in inconsistencies between self-report and biological measures even

though the diluent may not have been intentionally or knowingly used by the participant (Andreasen, Lindholst, & Kaa, 2009). Similarly, reliable and valid collateral information to confirm substance use behaviour is not always possible given participants may use substances when alone, they may hide or minimize their substance use from the collateral informant, or the collateral informant witnessing the substance use may not be abstinent during the substance use occasion and their recall could also be impaired (Carroll, 1995). Further, obtaining consent for such collateral information would likely have been difficult in the present study given the sensitive nature of substance use (i.e., a collateral informant may not have been willing to participate in the study due to fear that prosecution may result), and asking for such information could have been harmful to the researchers' reputations and rapport with clients at the clinic (i.e., because the message of distrusting clients' reports at the clinic would be implied by asking for such information).

A second caution in interpreting the test-retest reliability assessment findings is that the test-retest reliability sample was relatively small and the period between each assessment was relatively short. Further research is needed to determine if low threshold MMT clients can reliably recall their lifetime and current substance use histories over longer periods of time.

Third, it should also be noted that reliability was somewhat low for infrequently used substances (e.g., peyote) - particularly the continuous variables representing such substance use. The low test-retest reliability obtained for these variables may reflect the low number of participants reporting associated

ages of use and past 30 day use. That is, although the *n* of 25 participants was above the recommendation of 22 participants for sufficient power, when only 5 of the 25 participants have used a substance, only 5 participants' data are used in analyses for continuous variables (e.g., age of first use). Thus, those analyses are underpowered. As a result, interpreting the analytic results for such substances should be tentative; at present there is not sufficient data to suggest that the recall of the use of such infrequently used substances is or is not reliable among MMT clients.

3.4 Hydromorphone Occasions of Use: Test-Retest Reliability Results for Study One Data

Two participants (10.0%, *n*=2/25) could not recall their earliest hydromorphone use occasion on the first or second interview. Consequently statistical reliability analyses were conducted using data from the 23 participants who could remember an occasion of earliest use on both interview days. Results are presented in Table 3.3.

One (5.0%, *n*=1/25) participant could not recall his/her most recent use occasion on the second interview. Consequently statistical reliability analyses were conducted using data from the 24 participants who could remember an occasion of most recent use on both interview days. Results are presented in Table 3.4.

Table 3.3

*Reliability of self-reported characteristics for earliest recalled hydromorphone use occasion (*n=*23). In order to make reliability comparisons between the two interview days, participants were excluded from analyses if they could not remember an occasion of use on both interview days.*

		Reliability Measure of Earliest Recalled Hydromorphone Use Characteristic				
Characteristic of Use Occasion		κ(*r*)	PABAK	% Positive Agree-ment	% Negative Agree-ment	% Total Observed Agree-ment
Other substances were used with hydromorphone[1]		0.35	0.39	58.8	75.9	69.6
Number of substances used with hydromorphone[1]		(0.28)				
Were others present during this occasion of use		-0.15	0.48	85.0	0.0[2]	73.9
Were others also using hydromorphone during this occasion of use		0.13	0.22	40.0	71.0	60.9
Route of Administration	Oral	0.88	0.91	90.9	97.1	95.7
	Intranasal	0.47	0.57	84.9	61.5	78.3
	Inject	0.57	0.57	78.3	78.3	78.3
Reason for use	To get high	0.55	0.65	66.7	88.2	82.6
	Out of Curiosity	0.59	0.65	71.4	87.5	82.6
	To decrease pain	0.42	0.57	54.6	85.7	78.3
	To avoid withdrawal	0.47	0.83	50.0	95.2	91.3
	Other reasons	0.25	0.65	33.3	90.0	82.6

[1]Not including tobacco; tobacco was excluded from analyses given 91.0% (n=68/76) participants used tobacco during the earliest recalled occasion of use. When the variable of Any Use of Tobacco was analysed separately, κ and PABAK could not be calculated due to empty cells, %Positive agreement=97.7%, %Negative agreement=0.0%[2], Total agreement was 95.5%.
[2]Statistic is 0.0% due to empty cells (e.g., 0 participants reported being alone on both interview days; this results in 0 in the numerator for calculating % agreement)

Table 3.4

*Reliability of self-reported characteristics for most recent hydromorphone use occasion (*n=*24). In order to make reliability comparisons between the two interviews, participants were excluded from analyses if they could not remember an occasion of use on both interview days.*

		Reliability Measure of Most Recent Recalled Hydromorphone Use Characteristic				
Characteristic of Use Occasion		κ (*r*)	PABAK	% Positive Agree-ment	% Negative Agree--ment	% Total Observed Agree-ment
Other substances were used with hydromorphone[1]		0.42	0.42	72.0	70.0	70.8
Number of substances used with hydromorphone[1]		(0.28)				
Were others present during this occasion of use		0.25	0.25	69.0	52.6	62.5
Were others also using hydromorphone during this occasion of use		0.13	0.00	57.1	40.0	50.0
Route of Administration	Oral	-0.06	0.75	0.0[2]	93.3	87.5
	Intranasal	--[3]	--	--	100.0	100.0
	Inject	0.00	0.83	95.6	0.0[2]	91.7
Reason for use	To get high	0.50	0.67	60.0	89.5	83.3
	Out of Curiosity	--	--	--	100.0	100.0
	To decrease pain	0.41	0.67	50.0	90.0	83.3
	To avoid withdrawal	0.32	0.33	60.0	71.4	66.7
	Other reasons	0.50	0.67	60.0	89.5	83.3

[1]Not including tobacco; tobacco was excluded from analyses given 96.1% (n=73/76) participants in Study One used tobacco during the most recent recalled occasion of use. When the variable of Any Use of Tobacco was analysed separately, κ=-.05, PABAK=.82, %Positive Agreement=95.2%, %Negative Agreement=0.0%[2], % Total Agreement=90.0%.

[2]Statistic is 0.0% due to empty cells (e.g., 0 participants reported using orally on both interview days; this results in 0 in the numerator for calculating % agreement).

[3]*-- indicates that the statistic could not be calculated due to empty cells (e.g., 0 participants reported using the particular route of administration on this use occasion during the first and second interviews; this results in a 0 in the denominator).*

3.5 Discussion of Hydromorphone Occasions of Use Test-Retest Reliability Results

Reliability was good for most recent occasion of use data regarding routes of administration and reasons for use. However, levels of agreement and reliability were poor regarding co-use of substances, and presence of others during the use occasion. Additionally, a small number of the sampled participants were not able to recall an earliest (*n*=2/25) or most recent (*n*=1/25) occasion of hydromorphone use. While these reliability findings are mostly supportive of the methodology used to assess occasions of use in Study One, some caution is warranted in interpretation of the results given the limitations of the present test-retest reliability assessment.

The first limitation is the extensive substance use histories of the participants in the thesis studies. Sobell and Sobell (2003) identify a long history of substance use as a characteristic associated with less accurate substance use reporting. Almost all clients in Studies One and Two had used a variety of substances for many years – particularly opioids. The neurological effects of substance use may have influenced recall for participants given that substance users, including individuals enrolled in MMT, have been found to be more impaired on memory (e.g., working, semantic, autobiographical) and attention

tests than non-substance users (Eber & Schmitt, 1997; Mintzer & Stitzer, 2002; Oliveira, Scheuer, & Scivoletto, 2007).

A second limitation of the present findings is that it is possible that poor recall reliability for some variables was due to the first and last occasions of hydromorphone use not being sufficiently salient occasions. That is, these occasions of use may not have been easily remembered by this population because so many different prescription opioids have been tried and repeatedly used during different periods in their lifetimes. However, hydromorphone was the most commonly identified primary opioid of choice by participants (see Table 4.2). Thus, it is possible that initiation and cessation of this favoured substance may be more salient than other opioid use occasions.

Third, the effects of an opioid can last several hours. Thus, the context in which one uses a substance may change over the course of the use occasion. That is, a participant may have administered hydromorphone when s/he was alone, but later other people were present while the participant was still experiencing the effects of the opioid. Thus, it is possible that even though the questions were designed to be clear and objective, some participants may have found the questions to be ambiguous and error may have been introduced based on how they interpreted the question during the two different interviews.

Fourth, the one-day interval between the first and second interviews (i.e., test and retest interviews) was relatively short. Barrett and colleagues (2005) assessed reliability using a one week inter-interview interval. It is possible that participants in the present study may have been able to recall their responses on

the interview from the previous day and thus reliability between the two interviews was overestimated. However, given the participants did not know their reliability of their recall was being assessed, separate interviewers conducted each interview, and each interview was described to participants as a separate study, there was no obvious motivation for participants to try to remember their first interview responses and repeat them on the second interview.

Similar to the fourth limitation outlined above, a fifth limitation of the test-retest reliability findings for hydromorphone occasions of use is that the procedure used to assess reliability was somewhat different compared to previous research investigating occasions of substance use (i.e., Barrett et al., 2005). Participants in Barrett and colleagues' (2005) study were young rave attendees who were asked to recall substance use occasions that had happened recently (i.e., most occasions of use occurred within the 30 days prior to the assessment) and during the second interview, they were anchored to the occasion of use that they recalled during the first interview (e.g., details regarding the location and date were given by the interviewer to the participant to facilitate recall). Participants in the present study were middle-aged opioid users enrolled in low-threshold MMT. It could be argued that middle-aged opioid-users enrolled in a low-threshold MMT program likely have much more extensive substance use histories which, in turn, could be related to poorer recall due to neurological effects of prior substance use (Eber & Schmitt, 1997; Mintzer & Stitzer, 2002; Oliveira, Scheuer & Scivoletto, 2007) and/or difficulties in accurately recalling memories of distinct substance use occasions. Additionally, participants in the

present study were asked to recall occasions of use that may have occurred several years or decades prior to the assessment interview (e.g., the first use of hydromorphone in their teens). Participants in the present study were also not anchored to the occasions of hydromorphone use that they recalled on the previous day with the previous interviewer. Consequently, using the study by Barrett and colleagues (2005) to estimate the necessary sample size for sufficient power in evaluating test-retest reliability in the present study may have led to an underestimate of the *n* required. That is, while Barrett and colleagues (2005) obtained κ's $\geq$ 0.65, it would be expected the present study would likely find less agreement due to participants' recalling more distal occasions of use, no anchoring to the occasions recalled during the first interview, and their extensive use histories. If expected κs=0.50 or 0.40 are used in the Sim and Wright (2005) sample estimation procedure instead of κ=0.60, samples of 32 or 52 participants, respectively, are recommended. Thus, the present reliability analyses may be underpowered for testing the stability of reports of hydromorphone use occasions.

Despite the above noted limitations to the present methodology, there were also some strengths to the approach used. Much of substance use research relies on self report and the accuracy of self-report data has been found to be greatly influenced by contextual factors in an interview (e.g., consequences of admitting substance use, confidentiality of information disclosed; Sobell & Sobell, 2003). The present data were collected using recommendations to encourage honest reporting and accuracy (Sobell & Sobell, 2003). Namely,

participants were assured confidentiality, they were interviewed in a private room, they were asked clearly worded, specific questions, and memory aids were used (i.e., participants were oriented to the specific use occasion by asking them to recall when the occasion occurred, who they were with, etc.).

In summary, the test-retest reliability results for recall of specific occasions of hydromorphone use are adequate for most, but not all (e.g., reporting of co-use of substances), questions. The low reliability for the small number of items may reflect issues with the method used to assess reliability, that occasions of hydromorphone use were not sufficiently salient or recent enough to be reliably recalled, or possibly there was insufficient power to adequately assess reliability in the present subsample of participants. Regardless, many findings appear to be robust and further research is recommended to better evaluate factors influencing reliability of recall of specific substance use occasions, as well as if the present results will be replicated over a longer test-retest interval.

3.6 Psychiatric Symptom Measure: Study Two Data

Good reliability between the two versions of the PDSQ in terms of the number of symptoms endorsed and number of positive screens of disorders was found when separated over one day (*r*s=.87 and .81, respectively). Reliability for the individual disorders and symptoms between the original version of the PDSQ and the modified version are presented in Table 3.5.

Table 3.5

*Reliability of test-retest participants' (*n=*21) psychiatric symptom reporting, and categorization on both modified and original forms of the PDSQ assessed one day apart.*

Disorder assessed on PDSQ (# of symptom items on PDSQ; # of symptoms required to be endorsed for positive screen)	Reliability between Original and Modified PDSQ					
	Positive Screen for Disorder on PDSQ					Correlation (*r*) of Number of Symptoms Endorsed
	κ	PABAK	% Positive Agreement	% Negative Agreement	% Total Observed Agreement	
Depression (21;9)	0.57	0.62	71.4	85.7	81.0	0.85
PTSD (15;5)	0.42	0.43	75.0	66.7	71.4	0.80
Eating disorder (10;7)	-0.05	0.81	0.0[1]	95.0	90.5	0.72
OCD (7;1)	0.53	0.52	73.7	78.3	76.2	0.83
Panic disorder (8;4)	0.49	0.52	66.7	81.5	76.2	0.73
Psychosis (6;1)	0.39	0.43	62.5	76.9	71.4	0.74
Agoraphobia (12;4)	0.80	0.81	87.5	92.3	90.5	0.82
Social phobia (15;4)	0.71	0.71	84.2	87.0	85.7	0.72
GAD (10;7)	0.58	0.62	71.4	85.7	81.0	0.86
Somatization (5;1)	0.29	0.24	60.0	63.6	61.9	0.54
Hypochondriasis (5;1)	0.53	0.52	76.2	76.2	76.2	0.17
Screening positive for at least one disorder on PDSQ[2]	0.61	0.81	94.4	66.7	90.5	
Number of positive screens on PDSQ[2]						0.81
Number of symptoms endorsed on PDSQ[2]						0.87

[1]Statistic is 0.0% due to empty cells (e.g., 0 participants screened positive for an eating disorder on both interview days; this results in 0 in the numerator for calculating % agreement).
[2]Positive screens for drug or alcohol dependence, and associated symptoms, were excluded to be consistent with Study Two purpose and analyses.

3.7 Discussion of Psychiatric Symptom Measure Reliability Results

High correlations were obtained on the original and modified PDSQ measures for the number of symptom items endorsed, and number of positive screens for disorders. Additionally, while many of the subscales also had high correlations between the two versions, some subscales had low correlations (i.e., low levels of reliability) between the two PDSQ versions. It was not surprising, based on psychometric theory (Nunnaly, 1967; Raykov & Marcoulides, 2010), that, overall, the subscales of the PDSQ were found to have lower levels of reliability than the full scale measures (i.e., total number of symptoms endorsed, positive screens) because the subscales, by definition, have a smaller number of items. Similarly, subscales that were composed of relatively few items (i.e., somatization, hypochondriasis) had the lowest correlations between the two versions for the number of symptoms endorsed on the subscales.

It is possible that low levels of agreement between some subscales may be due to the different symptom window reporting between the modified (i.e., one month) and original (i.e., 6 month) versions of the PDSQ. That is, a symptom window of one month on the modified PDSQ maybe more restrictive and result in an underestimation of the presence of psychiatric symptoms relative to the original version which has already been demonstrated to be reliable and valid (Zimmerman, 2002). A second possible reason for low agreement is that the two versions of the PDSQ were administered verbally to participants by two different

interviewers (see Section 2.3.2). Although the PDSQ questions were read verbatim by interviewers, it is possible that interviewer characteristics (e.g., level of rapport established with client) may have introduced some additional variability into the study and thereby influenced findings regarding reliability between the two versions. A third possible reason for some scales having low reliability may be a lack of power. As described in Section 2.2.4, the sample sizes suggested for kappa analyses (suggested *n*=22) and correlations (suggested *n*=28) was somewhat greater than the sample size obtained (*n*=21). It is possible that the findings of relatively low κs, PABAKs, and correlations reflect this low level of power. However, many of the other correlation coefficients obtained for subscales between the modified and original PDSQ versions were very similar to test-retest correlation coefficients for different items obtained by Zimmerman (2002) in his test-retest reliability studies of the original version of the PDSQ.

Consequently, although some caution is warranted in interpreting the findings of Study Two given that a small number of subscales have low levels of agreement between the modified and original PDSQ, the small test-retest interview interval, and that the psychometric properties and validity of the modified version have yet to be assessed, the modified version likely measures some level of specific psychiatric symptomatology, and overall agreement between the two versions appears to be quite high and similar to that obtained for stability with the original version.

CHAPTER 4 PRESCRIPTION OPIOID MISUSE: CHARACTERISTICS OF EARLIEST AND MOST RECENT MEMORY OF HYDROMORPHONE USE

4.1 Overarching Goals of and Specific Hypotheses of Study One

As outlined in Section 1.9, the main overarching goal of the first thesis study was to examine characteristics of prescription opioid use, namely hydromorphone. Given the documented increases in both prevalence (e.g., Manchikanti & Singh, 2008) and problems associated with non-medical prescription opioid use and misuse (e.g., Dhalla et al., 2009; SAMHSA, 2010b; 2010c; Warner et al., 2009) and the particular similarities between heroin and hydromorphone (Brands et al., 1979; Brands, Marsh et al., 2004; Daglish et al., 2008; Oviedo-Joekes et al., 2010), four main study questions were developed: 1) How do individuals initiate into hydromorphone use (i.e., do they have a prescription)? 2) Are initially prescribed individuals different from those who initially used without a prescription? 3) What are the characteristics associated with the initial use occasion, and do these characteristics differ between those who are initially prescribed or not prescribed? 4) What are the characteristics associated with later use, and are people who were initially prescribed or not prescribed different in terms of any of these more recent use variables?

A population of individuals receiving methadone treatment for opioid dependence was sampled to answer these questions. Previous research (Marshall, 2004) indicated that histories of prescription opioid use were highly prevalent in this population. Consequently, sampling this population would likely provide information not only on prescription opioid use in general, but information on prescription opioid use from people who developed problems with opioids.

As summarized in Chapter 1, previous research has found that hydromorphone is a frequently used substance by regular illicit opioid users (Leri et al., 2005) and opioid dependent populations (e.g., Marshall, 2004) in Canada. Consequently, it was predicted that, with respect to the first main study question, hydromorphone would also be found to be a commonly used substance in the Study One sample of MMT clients in Halifax, Nova Scotia, Canada. Given that hydromorphone is available as a licit, prescription medication (e-CPS, 2007), as well as available through street-level drug dealers and/or from other individuals (e.g., friends or relatives) with prescriptions (Canfield et al., 2010), it was predicted that some individuals would first be introduced to hydromorphone through a medical prescription while others would first use hydromorphone illicitly (i.e., without a prescription).

In terms of the second study question, it was predicted that individuals who first used hydromorphone with a prescription would differ demographically from individuals who first used hydromorphone without a prescription. Previous research (Smith et al., 2007) found that the majority of non-medical users and misusers of hydromorphone sampled through 2003 USA National Survey of Drug

Use and Health were male and Caucasian. Women have been found to be more likely to be prescribed opioid medications (Simoni-Wastila et al., 2004). Consequently, it was predicted that initially non-prescribed hydromorphone users would be more likely to be male than initially prescribed hydromorphone users. It was also predicted that participants who first used hydromorphone without a prescription (i.e., used illicitly) would be more likely than prescribed participants to have used other illicit substances (e.g., cocaine, hallucinogens).

In terms of the third main study question, it was predicted that individuals who first used hydromorphone with a prescription would report using it during their first recalled use occasion as prescribed (i.e., orally; to reduce pain; be equally likely to be using it in the presence of others or by themselves, and be unlikely to co-use other substances when using hydromorphone; e-CPS, 2007). Individuals who initially used hydromorphone without a prescription were predicted to report initially using hydromorphone in a manner that closely resembled previously documented recreational opioid use. That is, heroin is typically administered intranasally or intravenously, used with other individuals present, used to get high or out of curiosity, and co-used with other substances (Epstein et al., 2005; Fulmer & Lapidus, 1980).

In terms of the fourth main study question, it was predicted, based on opponent-process theory[7] (Koob & LeMoal, 1997; 2008), that the majority of participants (regardless of whether they were initially prescribed or non-prescribed) would report using hydromorphone more recently in ways to overcome physical tolerance (i.e., using methods such as injection which maximize the bioavailability of a substance relative to oral methods; Stevens & Ghazi, 2000), and for reasons related to alleviating aversive withdrawal symptoms. It was predicted that initially prescribed and non-prescribed participants would not significantly differ in terms of their most recent recalled use occasion because it was assumed that all participants would be physically, and likely psychologically, dependent on opioids at the time of their most recent recalled use occasion. This was hypothesized because all study participants later entered treatment for opioid dependence (i.e., the current MMT program). Although reasons, methods, and microenvironment upon initiation may have differed, all participants developed dependence on opioids, and consequently would be using in similar ways and for similar reasons more recently.

[7] Briefly, opponent process theory is a motivational theory posited to explain the development of substance dependence. Individuals initially use a substance and typically experience a short, positive, intense emotional reaction (e.g., euphoria). This is followed by a compensatory response by the body which is typically the opposite of the initial reaction. This secondary response is slower and longer lasting than the initial response (e.g., chills, runny nose, nausea, low mood). As a person continues to use a substance, the initial response becomes shorter and less intense (i.e., tolerance) and the secondary response occurs sooner after using the substance, becomes more intense and lasts longer.

4.2 Study One Manuscript

PRESCRIPTION OPIOID MISUSE: CHARACTERISTICS OF EARLIEST AND MOST RECENT MEMORY OF HYDROMORPHONE USE[8]

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Fulton, H. G., Stewart, S. H., MacIsaac, C. & Barrett, S. P. (in press). *Journal of Addiction Medicine.*

Please note that Figures 4.1-4.4 in this dissertation refer to Figures 1-4 in this journal article. Similarly, Tables 4.1-4.3 in this dissertation refer to Tables 1-3 in this journal article.

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[8] *Adapted from Journal of Addiction Medicine, Fulton, Stewart, MacIsaac & Barrettt, "Prescription Opioid Misuse: Characteristics of Earliest and Most Recent Memory of Hydromorphone Use", (in press), Copyright with permission from Publisher (see Appendix H). As first author of this manuscript I assisted with the planning and logistics of the study, collected data, conducted data analysis, collaborated on interpreting the findings with my co-authors, and wrote the manuscript. I also revised the manuscript based on suggested changes from my co-authors, peer-reviewers, and journal editor.*

4.3 Epilogue to Study One: Supplementary Results

Due to word restrictions not all data were analysed and included in the published manuscript for Study One (see Section 4.2). Relevant data, analyses, and discussion relating to main study questions (see Section 4.1) not presented in the published manuscript are presented below.

4.3.1 Details Regarding Initiation into Hydromorphone Use: Demographics of Initially Prescribed Versus Non-Prescribed Users

Initially prescribed participants and non-prescribed participants were compared on a variety of demographic and substance use history variables in order to further evaluate the second main study question (i.e., are people who initially used hydromorphone with a prescription different from those who initially used without a prescription?). No significant differences were found between participants who were initially prescribed and not prescribed hydromorphone (see Table 4.4), although there was a trend (p=.096) toward initially non-prescribed users to be Caucasian, and, consistent with prediction, (p=.083) toward a greater proportion of women in the initially prescribed users group.

Table 4.4

*Comparison of demographics and substance use history variables between participants who were initially prescribed (*n=*24) and not prescribed (*n=*54) hydromorphone.*

Demographic variable	Initially prescribed M(SD) [%, *n*]	Initially non-prescribed M(SD) [%, *n*]	*t*-test, *df*=74 (χ^2 square, *df*=1)	*p*
Age (years) at time of interview	40.08(9.16)	39.89(8.91)	0.09	.930
Gender (% female)	[50.0, *n*=12/24]	[29.6, *n*=16/54]	(3.00)	.083
Ethnicity (% Caucasian)	[70.6, *n*=17/24]	[88.9, *n*=48/54]	(--[1])	.096
Current methadone dose (mg)	114.58(45.37)	108.65(43.78)	0.55	.586
Duration (years) enrolled in current MMT program	3.22(3.55)	3.36(2.52)	-0.19	.850
Substance, opioid and hydromorphone use history variable				
Number of substances used in lifetime[2]	11.48(4.05)	12.49(3.44)	-1.12	.268
Number of substances used before trying hydromorphone[2]	8.91(4.13)	9.42(3.92)	-0.51	.613
Age (years) during first prescription opioid use	22.37(7.08)	20.46(8.32)	0.55	.586
Age (years) during earliest recalled hydromorphone use	27.05(7.88)	27.45(9.12)	-0.18	.857
Age (years) during most recent recalled hydromorphone use	38.21(7.61)	37.33(8.74)	0.43	.672

[1]*Fisher's exact test was used as 1 cell had expected frequencies < 5.*
[2]*Tobacco excluded, crack cocaine and powder cocaine considered separate substances, prescription opioids and benzodiazepines each count as one substance*

4.3.2 Hydromorphone Occasions of Use Supplementary Data

As outlined in Sections 2.2.4 and 3.3, participants were also asked about the presence of others and others' usage of hydromorphone during their earliest and most recent recalled use occasions. Two participants could not recall an occasion of early hydromorphone use; thus the occasions of use data was based on 76 of the 78 participants.

4.3.2.1 Earliest versus Most Recent Recalled Occasion of Use Comparisons

In comparing earliest versus most recent occasions of use within participants, participants were significantly more likely to report being in the presence of others during their earliest (78.9% of sample, *n*=60/76, in the presence of others) compared to their most recent (53.9% of sample, *n*=41/76, in presence of others) hydromorphone use occasion (McNemar χ^2 test=12.00, *p*<.001). Additionally, participants were unlikely to be the only person using hydromorphone during these occasions. That is, participants were not just more likely to be in the presence of others during these recalled use occasions, participants were significant more likely to be using hydromorphone with others *who were also using hydromorphone* during their earliest recalled use occasion (67.1% of sample, *n*=51/76) compared to their most recent use occasion (34.2% of sample, *n*=26/76; McNemar χ^2 test=17.45, *p*<.001).

4.3.2.2. Earliest Occasion of Use Comparisons: Initially Prescribed versus Non-Prescribed Users

Likelihood to be in the presence of others during the earliest recalled hydromorphone use occasion significantly differed between those who were and were not initially prescribed hydromorphone; initially non-prescribed participants were more likely to be in the presence of others than initially prescribed participants (see Figure 4.5). Similarly, likelihood to be using hydromorphone *with other hydromorphone users* significantly differed between those who were and were not initially prescribed hydromorphone during the earliest use occasion; initially non-prescribed participants were more likely to be in the presence of others *who were also using hydromorphone* than initially prescribed participants (see Figure 4.6).

4.3.2.3 Most Recent Occasion of Use Comparisons: Initially Prescribed versus Non-Prescribed Users

There was no significant difference between initially prescribed and non-prescribed groups during the most recent recalled use occasion in terms of the likelihood to be in the presence of others during the most recent use recalled use occasion (see Figure 4.5), or to be in the presence of others *who were also using hydromorphone* during the most recent use occasion (see Figure 4.6).

Figure 4.5. Reported presence of others with participant during earliest and most recent recalled use occasions of hydromorphone use. Data are separated according to prescription status of hydromorphone at initiation. Values of *p* are given for all significant chi-square findings (*df*s=1, *p*<.05) between initially prescribed and non-prescribed participants; phi (ϕ) indicates effect size of significant findings.

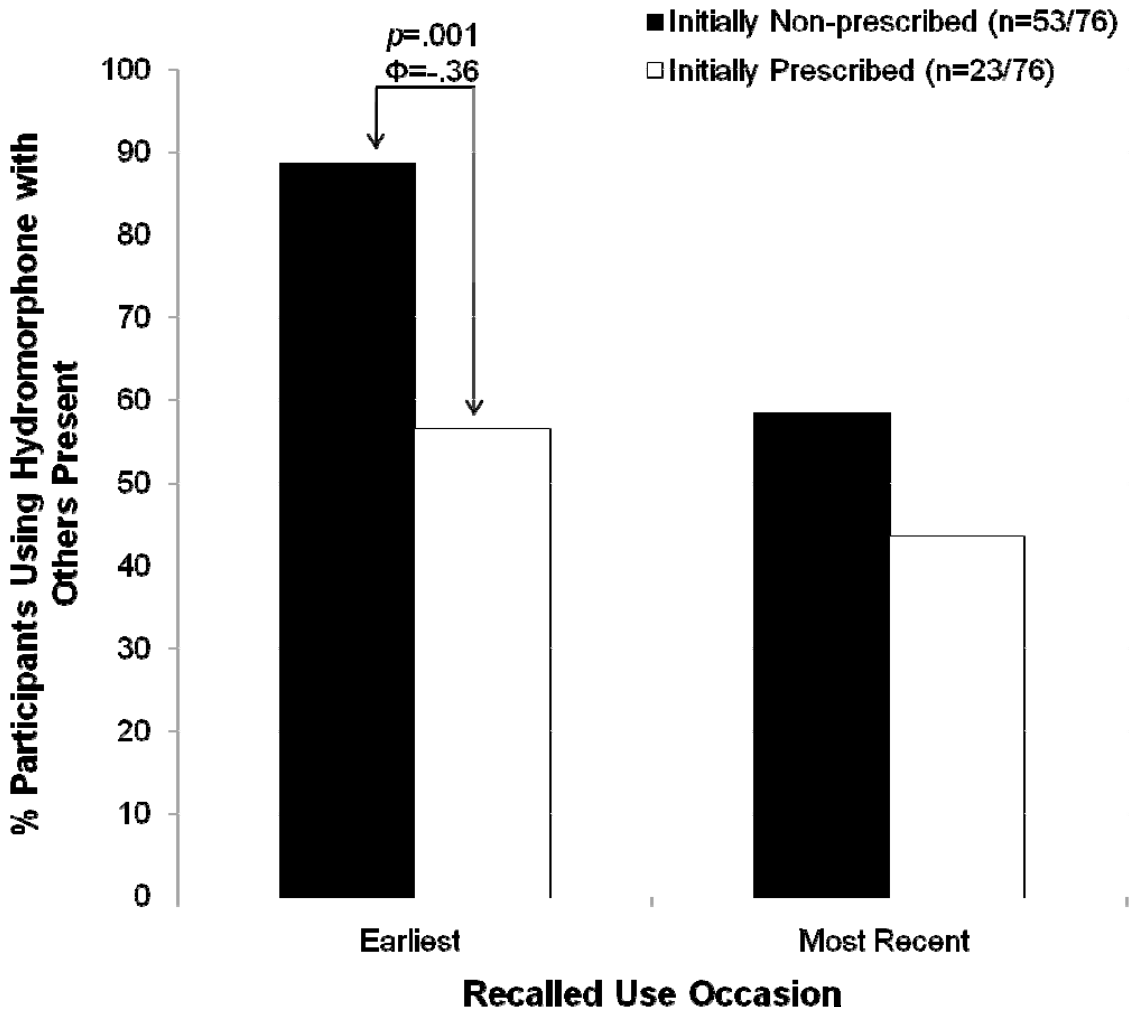
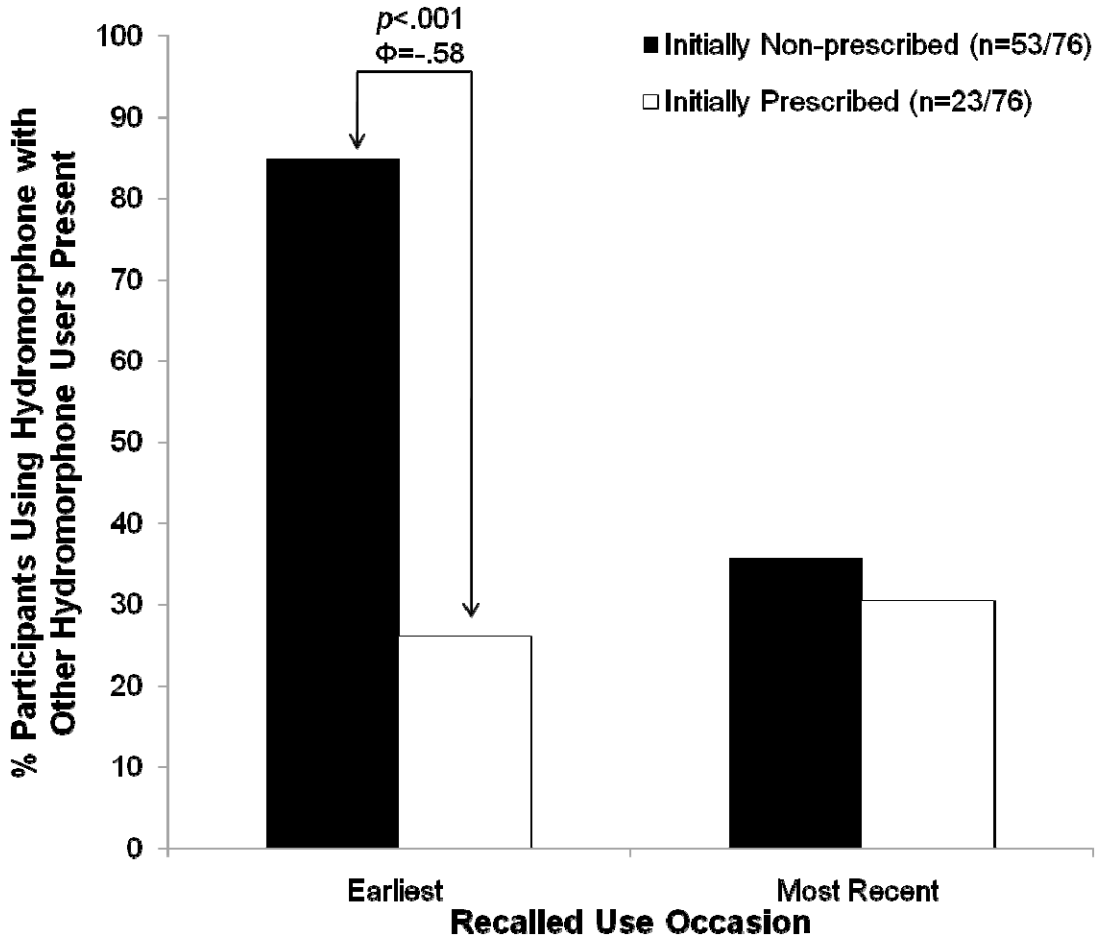


Figure 4.6. Reported presence of others who were also using hydromorphone with participant during recalled earliest and most recent recalled hydromorphone use occasions. Data are separated according to prescription status of hydromorphone at initiation. Values of *p* are given for all significant chi-square findings (*df*s=1, *p*<.05) between initially prescribed and non-prescribed participants; phi (ϕ) indicates effect size of significant findings



4.4 Discussion of Supplementary Results

4.4.1 Demographic Variable and Substance Use History Comparisons Between Participants Initially Prescribed and Not Prescribed Hydromorphone

As outlined in Section 4.1, it was predicted that, based on previous research, participants who had been initially prescribed hydromorphone would differ from individuals who were not initially prescribed hydromorphone. Specifically, it was predicted that initially non-prescribed participants would be more likely to be male, and have used a greater number of substances before trying hydromorphone than participants who initially used hydromorphone with a prescription. These hypotheses were not completely supported by the present results. No significant differences were found between the two groups; however there was a trend for non-prescribed participants to be male. Additionally, although Smith and colleagues (2007) found non-medical users and misusers of prescription opioids to be more likely to be Caucasian, no hypothesis was made a priori regarding ethnicity and prescription status in the present study. This was due to an anticipated lack of ethnic diversity in a Nova Scotia MMT program sample. However, a trend was observed for initially non-prescribed participants to be Caucasian compared to initially prescribed participants in the present study. Given the small sample size of the present sample (*n*=78) relative to Smith and colleagues' (2007) and Simoni-Wastila and colleagues' (2004), both of which

consisted of thousands of participants, it is possible the present study was underpowered to detect these differences in demographics.

The hypothesis that initially non-prescribed participants would use a greater number of other illicit substances compared to participants who did not initially use hydromorphone illicitly (i.e., were prescribed) was not supported in the present study. It is possible that this result differed from existing literature due to the difference in samples. The NSDUH/National Household Survey on Drug Abuse[10] studies, upon which the Smith and colleagues' (2007) and Simoni-Wastila and colleagues' (2004) studies are based, are population-based studies. Consequently a very small minority of the sample are opioid dependent individuals, heavy substance users, or receiving treatment for such problems (SAMSHA, 2009a; 2009b). The present study was conducted using opioid users receiving treatment and all clients had extensive substance use histories (inclusive and exclusive of opioids). Low threshold MMT programs are designed to treat individuals that are not typically engaged in treatment programs (Marlatt & Tapert, 1993; Ryrie, Dickson, Robbins, MacLean & Climpson, 1997). That is, low-threshold clients are likely to be heavy substance users, involved with the criminal justice system, and have many physical and mental health comorbidities (Marlatt & Tapert, 1993; Ryrie et al., 1997). Indeed, these are the characteristics of the target population served by the present MMT low-threshold clinic (Marshall, 2004). Thus, there may not be as much variability in terms of demographic and substance use history (prescribed or non-prescribed use)

[10] National Household Survey on Drug Abuse is the previous title for the NSDUH studies.

among those who are enrolled in low-threshold treatment programs in comparison to the large number of individuals who use prescription opioids (with or without prescriptions), or enrol in traditional (high threshold) MMT programs; the specialized nature of the current MMT program results in a fairly homogenous population of clients (i.e., heavy substance users with extensive use histories) relative to other clinics or services which likely serve a wider variety of clientele.

4.4.2 Presence of Others

The supplementary results regarding the presence of others during the use occasion are consistent with the pattern of results in the Study One manuscript (see Section 4.2). That is, participants who were initially prescribed or not prescribed hydromorphone differed in characteristics of the earliest recalled use occasion yet were very similar in terms of the characteristics of their most recent recalled use occasion. The usage characteristics associated with non-prescribed hydromorphone use were also very similar to previous reports of recreational opioid use, namely heroin. That is, previous studies have noted that individuals tend to initiate into heroin use in the presence of others (Chitwood, Comerford, & Whitby; 1998).

Additionally, the observed pattern of participants tending to initiate into the use of a new substance in the presence of others is consistent with previous literature with regards to initiation of other substances (Dupre, Miller, Gold, &

Rospenda, 1995; Urberg, Degirmenciolglu, & Pilgrim, 1997), new routes of administration (Roy et al., 2003), and existing theories of substance use initiation (e.g., peer cluster theory[11]; Oetting & Beauvais, 1986).

Previous research has found substances such as alcohol, marijuana, and cocaine are typically initiated when peers are present (Dupre et al., 1995; Urberg et al.,1997) and the first time a person injects a drug often takes place in the presence of a more experienced user (Roy et al., 2003). One of the most robust indicators for trying a substance is knowing others who engage in that behaviour (Beman, 1995; Swadi, 1999). Presence of peers/others is thought to increase the likelihood of using a substance non-medically in a number of different ways. First, peers familiar with the substance/behaviour provide information regarding how to use the substance/engage in the behaviour (Roy et al., 2003). Peers/others present during a use occasion may also provide rationalizations and justifications for trying a new substance (Beman, 1995) or route of administration, thereby resulting in the individual using the substance. Similarly, it is also possible that the presence of others, particularly those who are also using hydromorphone, during initiation reflects the importance of peer pressure in initiating into use. Peer pressure may influence a person to use a substance because s/he wants to develop and/or maintain their relationships with others, or s/he may fear rejection or loss of the relationships if s/he does not use (Swadi,

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[11] Briefly, peer cluster theory posits that when, where and how adolescents' initiate into and continue to use substances is directly influenced by the attitudes and behaviours of their peers. The relative influence of peers on adolescents (and thus, indirectly, their substance use) is influenced by other psychosocial factors (e.g., ethnicity) and relationships in an adolescent's life (e.g., parents).

1999). While all of these explanations may be able to account for the increased likelihood of hydromorphone-using others to be present during the earliest recalled use occasion, it is important to note that very few participants reported explicitly that peer pressure was their primary reason for using hydromorphone during their earliest recalled occasion of use (see Figure 4.1). It is possible that peer pressure may have been a secondary reason for use relative to the desire to get high, satisfy curiosity, etc. Presence of others, particularly other users of a substance, is likely less essential to those who are prescribed a substance because such individuals are provided with written instructions regarding how to administer a substance from a pharmacist when a prescription is filled.

During more recent use occasions it is probable that hydromorphone had been used extensively by both groups, and problematic opioid use behaviour patterns established (e.g., injecting, using to overcome withdrawal symptoms). Consequently, the present results reflect that peers may be less important to later substance use for both initially prescribed and non-prescribed participants (i.e., the individuals knows how to use the substance, is familiar with the directions for using; the individual has already chosen to repeatedly administer the substance and thus encouragement to use is likely no longer needed).

4.4.3 Extended Commentary Regarding Study One Limitations

The main limitations of Study One were explicitly discussed in the published manuscript (see Section 4.2.4), but an elaboration and discussion of

additional possible limitations appears below. First, the specific hydromorphone occasions of use examined in this study may not have represented the first ever, or most recent use of any opioid. While this limitation was carefully considered prior to collecting data, it was determined that, if data for any prescription opioid use were collected, the variation in the pharmacokinetic properties of different prescription opioids (e.g., Tylenol 3 pill vs. Fentanyl transdermal patch) would complicate any comparisons between the different use occasions. Pharmacokinetic properties of substances of abuse are important to how and why a substance is used/misused (Epstein et al., 2005; Oldendorf, 1992). Consequently, it was hoped that restricting the interviews to evaluation of one specific prescription opioid would minimize possible confounds and complexities in interpretation of results.

Second, as discussed in Section 3.3, it is possible that participants may not be able to reliably recall all details for earliest and most recent hydromorphone use occasions. Current evidence from the Study One sample (see Section 3.2) suggests that the participants in the present sample were adequately reliable for much of the information provided. However, reliability for some information was poor. It could be argued that the test-retest reliability results/percent agreement was not as high as would be expected given that participants are asked identical questions only one day apart. Therefore, some participants may not have been truthful in their recall of use occasions, or they could not remember (or may have misremembered) use occasions. It seems unlikely that participants would fabricate use occasions because there was no

positive reinforcement motivation to do so (or penalty for not remembering the occasion) in the present study. In the case of not remembering all details of a use occasion, interviewers emphasized the importance of responding "I don't know" when appropriate.

A third possible limitation is that it is possible that the process of administering the first interview may have affected recall on the second interview (see Section 3.5 for additional discussion of this issue). That is, after engaging in an interview about their substance use, a participant may have ruminated and thought about their history of substance use after the first interview was completed. This may have lead them to recall an earlier, or more recent occasion of hydromorphone use than what was recalled during the initial interview. This participant may have then discussed this newly recalled memory during the second interview as it represented a more accurate report of their initial or most recent use. Participants were not anchored to their previous report during their first interview by the second interviewer (e.g., "yesterday you recalled an early occasion of use that happened when you were xx years old and at a party in the city of xx; tell me about that occasion again, were you with other people? Were they also using hydromorphone?" etc.).

Fourth, no direct comparison was made in the present study regarding characteristics of use occasions between heroin and hydromorphone. Previous studies have collected heroin use information but the methods were slightly different from those used in the present study. Consequently, similarities and contrasts of the Study One findings to the existing literature of heroin use are

somewhat tentative. For example, Fulmer and Lapidus (1980) investigated reasons for beginning and continuing to use heroin. However, they only sampled male participants, and specific use occasions were not recalled. Instead, participants were asked if they "ever used heroin for xxxx reason". If a reason was endorsed, participants were asked if this reason was a reason for using heroin at the beginning of their heroin use, and if it was a reason for continuing to use heroin after they had developed an addiction to the substance. Strang and colleagues (1997) collected information regarding initial route of administration for heroin, and later methods of use. However, information regarding presence of others, reasons for use, or extent of co-use of other substances was not collected. In summary, there is no data on specific heroin use occasions with which to compare the present hydromorphone use occasion data. However, given the marked similarities of the findings of early non-prescribed use and later prescribed and non-prescribed use of hydromorphone to existing general knowledge of heroin use, it is likely that the present findings would be robust if direct comparisons with similarly collected data were obtained.

Fifth, due to the small sample size, discriminations between receiving a hydromorphone prescription for different pain-related reasons (e.g., short-term acute pain resulting from injury versus long-term chronic pain) or with different prescription schedules (e.g., on an as-needed basis versus regularly scheduled method) were not able to be made due to low power (i.e., 24 participants were initially prescribed hydromorphone and 23 of the 24 participants could recall specific occasions of hydromorphone use; there was insufficient *n* to further

divide this subgroup to conduct between-participant comparisons based on recommendations outlined in Cohen [1992]). A description of and comparisons between different prescription characteristics could be helpful with future research in identifying possible factors associated with risk for hydromorphone misuse.

Another limitation of Study One was that a measure of chronic pain and/or chronic pain history was not included, nor was an assessment or medical record check regarding pain status at the time of prescription for hydromorphone conducted. The effects of prescription opioids have been found to vary according to whether an individual has pain or not: individuals experiencing pain (who were not physically or psychologically dependent on opioids) reported feeling less “high”, “sleepy”, “light-headed” and “spaced out” after being administered morphine than individuals who were not in pain during morphine administration (Conley, Toledano, Apfelbaum, & Zacny, 1997). Thus, knowing an individual’s pain status during these specific occasions of hydromorphone use could have been important in determining whether pain status (e.g., acute versus chronic versus malingered) affected any of the present findings.

4.4.4 Extended Implications for Future Research

Previous research has demonstrated some pharmacokinetic,Previous research has demonstrated some pharmacokinetic and pharmacodynamic (including subjective) similarities of hydromorphone to heroin (Brands et al.,

1979; Wallenstein et al., 1990; Brands, Marsh et al., 2004; Oveido-Joekes et al., 2010). The current research suggests that, under some circumstances (namely early non-prescribed and later use), hydromorphone may also be used in a similar manner to heroin by this unique sample of opioid users in treatment. Further research is needed to establish whether hydromorphone could be used as a more socially-acceptable, less-stigmatized replacement/maintenance substance than heroin for individuals dependent on opioids.

The present study findings also support the need to conduct investigations into individual prescription medications - not just the general class of prescription opioids. Pharmacological (and pharmacokinetic) properties of a substance are important for how and why a substance is used (Epstein et al., 2005; Oldendorf, 1992). For example, solubility of a substance determines its ability to be absorbed in nasal mucosa [Pires, Fortuna, Alves, & Flacão, 2009]; thus, a drug with low solubility, like crack cocaine, is rarely used intranasally, or it is mixed with an acid (e.g., lemon juice) to increase solubility in order for it to be injected (Waninger, Gotsche, Watts, & Thuanai., 2008). Similarly, substances with short onsets of action are considered to be more likely to be abused (Epstein et al., 2005). Given the wide range of pharmacological actions, subjective effects, and formulations across the class of opioid medications, greater attention and research to how different medications may be misused, the contexts associated with different use patterns, and their risk for misuse is warranted.

4.4.5 Extended Implications for Future Practice

As described in the Study One manuscript (see Section 4.2.4), it could not be determined from the present study whether individuals receiving prescriptions for hydromorphone were appropriately prescribed the medication and received appropriate interventions and services to prevent dependence on the substance. Nor is it known whether the prescription for the medication was a key factor in the development of their opioid dependence. However, it is clear from the results that all individuals who were prescribed during their first use of hydromorphone had extensive substance use histories prior to receiving the prescription. Individuals with previous substance abuse problems are more likely to be prescribed both short (e.g., Dilaudid®) and long-acting (e.g., Hydromorph Contin®) opioids, be prescribed opioids for long periods of time, and at higher doses than those without histories of substance abuse problems (Weisner et al., 2009). Individuals with previous substance use problems are also more likely to misuse opioids (Ives et al., 2007) and to receive a diagnosis of opioid abuse/dependence (Edlund et al., 2007) when treated with opioids for chronic non-cancer pain. Individuals with prior and/or current problematic substance use histories can be effectively treated for their acute and/or chronic pain with prescription opioids (Sinatra & Mitra, 2008; Simopoulos, 2008) and numerous investigators have suggested that under-treatment of these individuals' pain could actually increase the risk of relapse and drug seeking behaviour (see Gardner, 2008 for review). However, precautions in order to prevent

development of any problems are essential. Current recommendations indicate that a general medical practitioner treating an individual for pain complaints should consistently screen patients for opioid addiction risk by openly asking them about substance use histories. If a practitioner has a patient who admits to an extensive or problematic substance use history, the practitioner should consult with or refer the patient to a specialist in pain and addiction so that relevant safeguards against that individual developing an addiction can be put in place (e.g., frequent urine tests, utilization of MMT for pain; daily medication dispensed by pharmacist; American Medical Association, 2010; National Opioid Use Guideline Group, 2010). Again, it is not known to what extent improper opioid prescribing practices were associated with hydromorphone use in the present sample. However, given that the majority of the sample (87.2%, *n*=68/78) received a prescription for opioid medications at some point in their lifetimes, it is worthy of note.

It was somewhat surprising that the majority of the sample in the present study did not initially receive hydromorphone via a prescription. Initially non-prescribed participants were also more likely to co-use other substances such as alcohol or benzodiazepines with hydromorphone during their initial use, and a similar proportion of participants were still co-using with such substances on more recent use occasions. Many opioid overdoses (Dhalla et al., 2009; not necessarily only prescription opioid) occur when opioids are co-administered with sedative substances - such as benzodiazepines or alcohol. Thus, it is possible that significant harms relating to opioid use could be reduced if users are

educated about such overdose risks. Services such as pain clinics, needle exchanges, or other health clinics could provide such educational interventions to the wide variety of individuals who use, misuse, and are prescribed prescription opioids. Additionally, informal peer to peer networks of substance users have been identified as a potential way to share educational information regarding substance use and harm reduction strategies (Treloar & Abelson, 2005). Such interventions could also be helpful in MMT clinics given the majority (75.0%; *n*=57/76) of most recent use occasions occurred after entry into the current MMT program.

4.5 Summary of Study One Findings

The objective of Study One was to examine the use characteristics of prescription opioids, specifically hydromorphone. The following study questions were asked: 1) How do individuals initiate into use (i.e., do they have a prescription)? 2) Are people who initially used an opioid with a prescription different from those who initially used hydromorphone without a prescription? 3) What are the characteristics associated with the initial use occasion, and do these characteristics differ between those who are initially prescribed or not prescribed hydromorphone? 4) What are the characteristics associated with later use, and are people who were initially prescribed or not prescribed different in terms of any of these more recent use variables?

In terms of the first study question, the majority of participants in a low-threshold MMT program in Halifax, Nova Scotia were found to have first used hydromorphone without a prescription, although approximately one third of the sample had initially had a prescription for hydromorphone when they first used it. This finding was consistent with the original hypothesis that there would be variability in terms of whether individuals were first exposed to this medication through medical means versus illicitly (see Section 4.1).

In terms of the second study question, the present study found some evidence for differences in the demographics, but no difference in substance use histories, of individuals who initially used hydromorphone with or without a prescription. That is, there was a trend towards significance for the hypothesis that initially non-prescribed participants would be more likely to be male than initially prescribed participants. However, the data was not supportive of the hypothesis that participants with and without initial prescriptions would be different in terms of substance use histories.

In terms of the third study question, it was found that the earliest recalled use of hydromorphone typically occurred in the presence of others; participants reported using it to reduce pain, to get high, and/or out of curiosity. The majority of participants used hydromorphone via injection, although a substantial minority reported initially using it orally or intranasally during this occasion. These use characteristics for the earliest recalled use occasion were found to differ between those who were initially prescribed or were not prescribed hydromorphone. Initially prescribed individuals were significantly less likely to be in the presence

of others, were more likely to report using hydromorphone to reduce pain, were more likely to report using orally and less likely to report co-using other substances during this use occasion than initially non-prescribed participants. Initially non-prescribed participants were significantly more likely to be in the presence of others- including in the presence of others who were also using hydromorphone, were more likely to report using to get high and out of curiosity, and to use via injection that initially non-prescribed participants during the earliest recalled use occasion. The hypotheses that initially prescribed participants would use hydromorphone in a medically indicated manner (i.e., to reduce pain, orally, little co-use of other substances), and initially non-prescribed participants would use hydromorphone similar to how other illicit opioids are used (i.e., with others present, to get high or out of curiosity, to snort or inject, and to co-use other substances) were supported.

In terms of the fourth study question, hydromorphone was typically used to avoid withdrawal and via injection during the most recent recalled occasion of use. Initially prescribed and non-prescribed participants were approximately equally likely to be in the presence of others or alone, and to be co-using other substances or using hydromorphone in isolation. Initially prescribed and non-prescribed participants had very few differences in their characteristics of use during this recalled use occasion. Initially prescribed participants were slightly more likely to report using hydromorphone to reduce pain during the most recent use occasion. The hypothesis that initially prescribed and non-prescribed participants would have very similar characteristics of use during the most recent

recalled use occasion was largely supported.

CHAPTER 5 EXPLANATION OF HOW STUDY ONE EXTENDS TO STUDY TWO

Study One established how individuals, who go on to enter treatment for opioid use, initiate and later use a prevalent and popular prescription opioid: hydromorphone. The following study will examine current issues faced by this population in treatment- specifically the issues of ongoing substance use and psychiatric symptoms. As discussed in Chapter 1, understanding prescription opioid users in treatment is important because prescription opioids appear to be replacing heroin as the predominant illicit opioid used in Canada (Fischer et al., 2006). The non-medical use and misuse of prescription opioids is more prevalent than such frequently researched substances as cocaine or hallucinogens (SAMHSA, 2005; 2009a). Very little specialized treatment exists for this under-researched population of prescription opioid users (Brands, Blake et al., 2004). It is unclear whether previous findings and issues identified in the treatment of heroin users are applicable to prescription opioid misusing populations. In fact, some previous research suggests prescription opioid users presenting to treatment may be quite different from those presenting for heroin use (McBride, 1980; Brands, Blake et al., 2004).

Additionally, no research to date has broadly examined how different, current psychiatric symptoms and different, current use of substances may be interrelated in MMT clients. Both issues are major concerns of MMT

professionals and affect treatment success (see Sections 1.8.1.1 and 1.8.1.2 for a more detailed review), yet only a limited number of different disorders (e.g., depression; Schreiber et al., 2008) or substances (e.g., benzodiazepines; Brands et al., 2008) have been examined in this context. A greater knowledge base of these issues, particularly with the current, changing population of individuals presenting for treatment related to their prescription opioid use, is warranted.

CHAPTER 6 STUDY TWO: THE RELATIONSHIP OF SELF-REPORTED SUBSTANCE USE AND PSYCHIATRIC SYMPTOMS IN LOW-THRESHOLD METHADONE MAINTENANCE TREATMENT CLIENTS

6.1 Overarching Goals and Specific Hypotheses of Study Two

As detailed in Section 1.9, the overarching goal of the second thesis study was to gain insight into current psychiatric and substance use issues faced by prescription opioid users in treatment. The following four study questions were developed: 1) What kinds of psychiatric symptoms might prescription opioid users enrolled in treatment be experiencing? 2) What kinds of substances might they be using? 3) Are these two variables related? 4) How might the results obtained with prescription opioid users compare to previous MMT investigations where clients were predominantly heroin users?

In terms of the first study question, previous research with MMT populations, largely consisting of heroin users[12], estimated that approximately 28-76% of MMT clients have comorbid psychiatric diagnoses (see Section 1.7.1.1 for review). Across many different studies of MMT clients and opioid-dependent individuals presenting for treatment, the disorders of major

[12]Not all studies specifically identified the type of opioids participants used; however heroin was referred to throughout the introduction and/or discussion sections (e.g., McCowan et al., 2009)

depression, PTSD, and GAD have been found to be among the most common psychiatric disorders; non-mood and non-anxiety disorders (e.g., psychotic disorders), conversely, have been found to be relatively rare (see King, Pierce & Brooner, 2006 for review). It was hypothesized that similar psychiatric prevalence findings would be obtained in the present study. That is, depression, GAD, and PTSD symptoms would be prevalent while psychotic disorder symptoms would be rare.

In terms of the second study question, across prior MMT studies with largely heroin using clients, cocaine and benzodiazepines appear to be particularly common substances that continue to be used by clients while enrolled in MMT (Condelli et al., 1991, Darke, Swift, Hall & Ross, 1993). No study to the knowledge of the author, has found high rates of continued use of hallucinogens (excluding cannabis), or inhalants. Based on these previous research findings with predominantly heroin-users in MMT[13], it was hypothesized that similar current substance use findings to would be obtained in Study Two. That is, use of alcohol, cocaine, cannabis, and benzodiazepines would be relatively more common, whereas current use of other substances (e.g., PCP) would be comparatively less prevalent than the aforementioned substances.

In terms of the third study question, it was predicted that current types of substance use would be related current types of psychiatric symptoms. Specifically it was predicted that anxiety-related symptoms (e.g., symptoms of

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[13] As mentioned earlier, not all studies identify the type of opioids used by participants, although heroin is frequently referred to throughout the introduction and discussion sections of most studies.

Generalized Anxiety Disorder [GAD], Post-Traumatic Stress Disorder [PTSD]) would be related to current anxiolytic (e.g., benzodiazepines, alcohol) use. Similarly, it was predicted that impulsive-type psychiatric symptoms (e.g., symptoms related to binge eating) would be related to current stimulant use (e.g., cocaine). These predictions were made based on previous research findings with MMT clients and theory. Benzodiazepine users in MMT have been found to have higher levels of depression and anxiety than non-users (Brands et al., 2008) and a previous study has found a relationship between cocaine-positive urine screen test results and problem gambling (Ledgerwood & Downey, 2002)- an impulsive-type psychiatric issue. Research conducted by Conrod and colleagues (2000) with other substance-using individuals (not MMT clients) has also found patterns of associations between types of substances used and types of psychiatric symptoms experienced (e.g., relationships between anxiolytics and anxiety-related symptoms; stimulant use and impulsive-related symptoms). Additionally, theories, such as the self-medication hypothesis[14] (Khantzian, 1985; 1997), would also predict that types of psychiatric symptoms are related to types of substances used. It was predicted such findings and theories would extend to the present sample of MMT clients.

Lastly, in terms of the fourth study question regarding the prevalence of psychiatric symptoms in the present sample versus previously-tested samples of MMT clients who were largely heroin users, Millson and colleagues (2006) found

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[14] While the self-medication hypothesis has evolved over time, essentially it posits that individuals use substances to alleviate psychiatric distress; different substances have different subjective effects and thus they are used to counteract different, aversive emotional states (e.g., use of sedatives to self-medicate anxiety).

that 60% of individuals entering low-threshold MMT reported experiencing current mental health difficulties. Brands, Blake and colleagues (2004) found prescription opioid-dependent participants presenting for MMT were more likely to report being involved in psychiatric treatment than individuals dependent on heroin. Consequently, it was predicted that psychiatric symptom reporting in the present sample would also be found to be elevated compared to existing research with individuals enrolled in MMT, including low-threshold MMT, related to heroin use.

In terms of the fourth study question regarding current substance use in the present sample versus previously-tested samples of MMT clients who are largely heroin dependent, it was expected that there would be similar types of current substance use observed in the present sample compared to previous research with MMT populations, although greater proportions of participants currently using such substances would be observed. While previous research found prescription opioid users presenting to MMT were less likely to have used illicit substances (Brands, Blake et al., 2004), individuals who use and present to treatment for problems relating to their use of prescription opioids may have changed since the 1997-1999 period when the Brands, Blake and colleagues (2004) study was conducted. For example, hydromorphone use increased 319% in the USA between 1997 and 2007 (Manchikanti et al., 2010). If more people are prescribed prescription opioids, then there is likely greater variability in terms of those who are exposed to these substances due to the increased population of users. Consequently it is possible that the characteristics of individuals who go

on to develop problems with prescription opioids, and in turn present to treatment, may also have changed (e.g., more females, a greater proportion of individuals with extensive substance use histories). Additionally, the MMT program from which the present sample was recruited had a low-threshold treatment philosophy. This means that clients are not expelled from treatment for ongoing substance use (see Section 1.8.1). Thus, because individuals who continue to use substances in other MMT programs are expelled, and individuals who continue to use substances in the present MMT program are not, it was anticipated that similar, or even elevated, levels of substance use would be observed relative to substance use rates reported in previous studies. Additionally, research on clients enrolled a low-threshold MMT clinic in the United Kingdom found that 76% of clients reported continuing to inject drugs (the type of drug was not specified) after four months enrolled in the program (Finch, Groves, Feinmann, & Farmer, 1995). Another study with low-threshold MMT clients in Amsterdam found that 90% of current clients reported using “hard drugs” (i.e., opioids, amphetamine, cocaine, LSD, or inhalants) in the past 30 days. This estimate excluded current use of substances such as cannabis and alcohol (Reijneveld & Plomp, 1993). Given that the present study sample consisted of low-threshold MMT clients, it was expected that the present study would find similar levels of substance use to previous investigations of low-threshold MMT clients - even though the present population was expected to largely consist of prescription opioid users rather than heroin users.

6.2 Study Two Manuscript

THE RELATIONSHIP OF SELF-REPORTED SUBSTANCE USE AND PSYCHIATRIC SYMPTOMS IN LOW-THRESHOLD METHADONE MAINTENANCE TREATMENT CLIENTS[15]

6.2.1 Abstract

Background: Ongoing psychiatric symptoms and substance use are common difficulties experienced by clients enrolled in methadone maintenance treatment (MMT). However, little research to date has evaluated if specific types of current substance use are related to specific types of current psychiatric symptoms. The present study investigated these relationships with a sample of clients enrolled in a low-threshold MMT program (i.e., clients are not expelled if they continue to use substances). Some clients enrolled in low-threshold programs may never achieve complete abstinence from all substances. Thus, understanding the possibly perpetuating relationships between concurrent substance use and psychiatric symptoms is important. Understanding such relationships may aid in developing possible target areas of treatment to reduce substance use and/or

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[15] *Adapted from Harm Reduction Journal, Fulton, Barrett, MacIsaac, & Stewart, "The relationship of self-reported substance use and psychiatric symptoms in low-threshold methadone maintenance treatment clients", 18, Copyright (2011), with permission from Publisher (see Appendix I). As first author of this manuscript, I assisted with the planning and logistics of the study, collected data, conducted data analysis, collaborated on interpreting the findings with my co-authors, and wrote the manuscript. I also revised the manuscript based on suggested changes from my co-authors, peer-reviewers, and journal editor.*

related harms in this population. **Methods:** Seventy-seven individuals were interviewed regarding methadone usage and current and past substance use. Current psychiatric symptoms were assessed using a modified version of the Psychiatric Diagnostic Screening Questionnaire (PDSQ). Relationships between types of substances used in the past 30 days and the types and number of psychiatric symptoms experienced in the same timeframe were examined. **Results**: The majority of participants (87.0%) reported using alcohol, illicit substances, non-prescribed prescription opioids, or non-prescribed benzodiazepines in the past 30 days and 77.9% of participants reported currently experiencing psychiatric symptoms at levels that would likely warrant diagnosis. Current non-prescribed benzodiazepine use was a predictor for increased severity (i.e., symptom count) of almost all anxiety and mood disorders assessed. Conversely, number and presence of generalized anxiety symptoms and presence of social phobia symptoms predicted current non-prescribed benzodiazepine and alcohol use, respectively. **Conclusions:** Individuals enrolled in the present low-threshold MMT program experience a wide variety of psychiatric symptoms and continue to use a variety of substances, including opioids. There was a particularly consistent pattern of associations between non-prescribed benzodiazepine use and a variety of psychiatric symptoms (particularly anxiety) suggesting that addressing concurrent illicit benzodiazepine use and anxiety symptoms in MMT clients warrants further clinical attention and research.

Key words: methadone, psychiatric symptoms, psychopathology, low-threshold, substance use, benzodiazepine

6.2.2 Background

Individuals enrolled in Methadone Maintenance Treatment (MMT) programs often continue to misuse substances (Darke, 1998a; Stitzer & Chutuape, 1999). Continued use of substances while in MMT is a predictor of poorer MMT treatment outcome (e.g., Magura et al., 1998; Morral et al., 1999), and represents an ongoing challenge to treatment providers (Darke, 1998a; Kleber, 2008). Another important factor related to MMT success is clients' mental health (McLellan et al., 1983; McLellan et al., 1984). While figures greatly vary, it has been estimated that between 28-76% of MMT clients have at least one co-morbid psychiatric disorder (Astals et al., 2009; Callaly et al., 2001; Gelkopf et al., 2006). Current psychiatric co-morbidity in MMT clients is associated with poorer psychosocial (Brooner et al., 1997) and medical (Cacciola et al., 2001) status as well as decreased quality of life (Carpentier et al., 2009). Similarly, psychiatric distress/severity is generally predictive of poorer MMT outcome (Darke, 1998a) although this finding has not always been consistent (Gelkopf et al., 2006; Pani et al., 1997). Current psychiatric symptoms also appear to be associated with ongoing substance use and substance-related problems during MMT. Individuals in MMT with a co-morbid psychiatric disorder have a significantly greater number of lifetime substance use disorders (Strain, Brooner,

& Bigelow, 1991), more severe substance use problems (Brooner et al., 1997), and use more substances during MMT (Batki et al., 1996; Gelkopf et al., 2006).

While some studies have examined relations between psychiatric symptoms and substance use by MMT clients, most research has focused on presence/absence of any psychiatric co-morbidity (i.e., presence/absence of *any* psychiatric disorder, not presence/absence of *specific* psychiatric disorders), general level of psychiatric distress/severity, or only a limited number of disorders (e.g., depression only). Little research has focused on how different types of psychiatric symptoms may vary by types of substances used. Theory (e.g., Khantzian, 1985) and previous research in non-MMT substance-using samples suggest that specific forms of co-morbidity may be associated with use of specific substances. For example, individuals who fear anxiety-related sensations are more likely to use anxiolytics and to suffer from anxiety-related disorders. Conversely, individuals who tend to act impulsively are more likely to use substances such as cocaine and to suffer psychiatric symptoms in the impulsive domain (Conrod et al., 2000).

The relationships of specific types of self-reported, current substance use to specific types of current psychiatric symptoms were examined in the present study. While evaluating concurrent substance use and psychiatric symptoms in the present study does not permit an analysis of which disorder came first (i.e., a determination of temporality as it may relate to causality), the present evaluation is important to understanding possible perpetuating factors that may maintain both substance use and psychiatric distress in MMT clients. For example, if illicit

benzodiazepine use is associated with only one type of psychiatric symptoms (e.g., panic symptoms but not depression), tailoring interventions specific to helping clients cope with panic symptoms could potentially assist in reducing benzodiazepine use and associated overdose risks (Longo & Johnson, 2000; Wolff, 2002). Further, evaluating concurrent substance use and psychiatric symptom relationships in low-threshold MMT programs (i.e., clients are not expelled if they continue to use substances) is of particular importance given some clients in these programs may never achieve complete abstinence from all substances. Whether clients' psychiatric symptoms are the pathogenic result of substance use or reflect an independent psychiatric disorder may be relatively unimportant if the substance use never ceases. Instead, reducing harms associated with their use (e.g., overdose risk), including reducing distress (e.g., through decreasing anxiety), are important and relevant treatment goals.

In the present study, individuals enrolled in a low-threshold MMT program, who were predominantly receiving treatment for prescription opioid misuse, underwent confidential face-to-face interviews as part of a larger study examining substance use behaviours. It was predicted that current types of substance use would be related to current types of psychiatric symptoms. Specifically it was predicted that anxiety-related symptoms (e.g., symptoms of Generalized Anxiety Disorder [GAD], Post-Traumatic Stress Disorder [PTSD]) would be related to current anxiolytic (e.g., benzodiazepines, alcohol) use. Similarly, it was predicted that impulsive-type psychiatric symptoms (e.g., symptoms related to binge eating) would be related to current stimulant use (e.g., cocaine).

6.2.3 Methods

6.2.3.1 Participants

Seventy-seven participants recruited from a low-threshold MMT program in Halifax, Nova Scotia, Canada took part in the present study. In comparison to more traditional, or "high-threshold", MMT clinics, "low-threshold" clinics do not require clients to be abstinent from all substances in order to remain in treatment (Royal College of Psychiatrists, 2000). Instead a harm-reduction approach is taken whereby clients obtain privileges, such as the ability to receive their methadone at a community pharmacy, for remaining abstinent from substances. The target population of the clinic are injection drug users who have significant comorbid mental health issues; are dependent on a variety substances; are HIV-, Hepatitis B- and/or C-infected, are homeless and/or street-involved, and/or have been unsuccessful in higher-threshold or abstinence-based treatment programs. All clients enrolled in the MMT program were eligible to participate; there were no exclusion criteria. Demographic data are displayed in Table 6.1.

6.2.3.2 Measures

All measures were administered verbally to participants so that no participant was excluded due to low literacy. Using a semi-structured interview,

participants were interviewed regarding demographics, methadone treatment (see Table 6.1), and current and lifetime substance use (Gross et al., 2002). For 19 different substances (see Table 6.2), participants were asked whether they ever used the substance, age of first use, and number of days in the past 30 they used the substance. Participants were also asked whether they used medications from the classes of prescription opioids (excluding methadone) and benzodiazepines with and without a prescription in their lifetime and in the previous 30 days. Participants who had used *any* benzodiazepines or prescription opioids without a prescription in the past 30 days were defined as "any non-prescribed users". Participants who had *only* used benzodiazepines or prescription opioids with a prescription were defined as "only prescribed users".

For the last 21 participants tested, the above substance use questions were administered a second time by a different interviewer the following day to determine reliability. Substantial reliability for presence of past 30 day use was obtained (Cohen's *κ*s=0.82-1.00; 95.0-100.0% agreement[16]).

To assess current psychiatric symptoms, a modified Psychiatric Diagnostic Screening Questionnaire (PDSQ; Zimmerman, 2002) was used. This measure contained 125 yes/no questions regarding experiencing symptoms of 13 *DSM-IV* (APA, 1994) Axis I disorders in the past two weeks or past 30 days (past two weeks and past six months are used in the original version). This modification enabled the period of reported psychiatric symptoms to be within the

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[16] κ and agreement values given here slightly differ from those reported in Table 3.2. This is because Table 3.2 displays data based on a sample of *n*=25. Only data from participants who also completed the PDSQ portion of the reliability assessment (*n*=21) are reported in this publication. See Section 3.2 for additional information and rationale.

substance use interview's assessment of use in the preceding 30 days. An individual screened positive for a disorder on the PDSQ if s/he endorsed the predetermined minimal number of symptoms for that diagnostic category (see Table 6.3). Screening positive for a disorder on the PDSQ suggests that an individual would be significantly more likely to qualify for a diagnosis of that disorder than someone who did not screen positive (Zimmerman, 2002). In previous studies the PDSQ has been found to have good sensitivity (90% of cases screening positive warranted a diagnosis), negative predictive values (97% of cases that did not screen positive did not warrant a diagnosis), and to be reliable and valid (see Zimmerman, 2002 for review) - even in a sample of individuals with substance use disorders (Zimmerman et al., 2004).

The modified and original versions of the PDSQ were administered to the last 21 participants in the present study by separate interviewers one day apart. Good reliability between the two versions in terms of the number of symptoms endorsed and number of positive screens of disorders was found (*r*s=.87,.81, respectively).

PDSQ questions relating to drug and alcohol dependence were excluded from analysis given the present study's objective of evaluating the relationship between substance use and symptoms of psychiatric disorders other than substance use disorders.

6.2.3.3 Procedure

All clients enrolled in the MMT program were informed of their eligibility to participate in the present study. Clients were informed that all study information would be kept confidential, participation (or lack thereof) would not affect their treatment, and participation was voluntary. All interviews were conducted by personnel separate from clinic staff in a private room at the clinic. Participants gave verbal and written informed consent and were compensated $20 at the completion of the study. All sampling, procedures, and materials were reviewed and approved by the Dalhousie and Capital Health Research Ethics Boards.

6.2.3.4 Analyses

In order to ensure adequate variability for statistical analyses, if at least 10% of the sample, but not more than 90%, had used a substance in the past 30 days or screened positive for a psychiatric disorder, the variable was included in further analyses examining the relationships between current substance use and psychiatric symptoms. Dichotomous variables were analyzed using chi-square (χ^2) tests; two-sided Fisher's exact tests were used whenever expected counts were less than 5 to minimize chances of Type 1 error (Field, 2009). Continuous variables were analyzed using independent sample *t*-tests and bivariate correlations (*r*).

Because substances are often used in a polysubstance context (Barrett, Darredeau & Pihl, 2006), multiple regressions were conducted to evaluate whether current use of specific substance(s) was(were) better predictor(s) of the number of psychiatric symptoms endorsed for each type of disorder assessed by the PDSQ. Logistic regressions were also conducted to evaluate whether current use of specific substance(s) was(were) better predictor(s) of screening positive on the PDSQ for different types of psychiatric symptoms.

Because psychiatric symptoms also often co-occur (Brown & Barlow, 1992), and due the possible bidirectional relationship of psychiatric symptoms and substance use (Conrod & Stewart, 2005), logistic regressions were conducted to evaluate if the number of specific types of psychiatric symptoms were better predictors of the likelihood to be currently using different substances. Additional logistic regressions were conducted to evaluate whether screening positive for certain types of psychiatric symptoms on the PDSQ would also predict the likelihood of currently using different substances.

6.2.4 Results

6.2.4.1 Substance use

The majority of participants (87.0%, *n*=67/77) reported using alcohol, illicit substances, non-prescribed prescription opioids, and/or non-prescribed benzodiazepines at least once in the past 30 days (see Table 6.2). Participants

used, on average, 2.04(*SD*=1.67) different substances, excluding tobacco, in the past 30 days; or 3.01(*SD*=1.68) different substances if tobacco is included. Prescription opioids and benzodiazepines were each counted as one substance, regardless of whether the type of medication was used with and/or without a prescription. Participants reported that all current benzodiazepine and opioid prescriptions were from doctors not affiliated with the present MMT program; prescriptions were obtained from family or emergency room doctors.

6.2.4.2 Psychiatric Symptoms

Sixty participants (77.9%, *n*=60/77) screened positive for at least one psychiatric disorder on the modified PDSQ. Participants, on average, screened positive for 3.52(*SD*=3.16) different psychiatric disorders (see Table 6.3).

Because reporting of psychiatric symptoms has been found to decrease with time enrolled in MMT in some studies (Conrod & Stewart, 2005; King & Brooner, 1999), relationships between psychiatric symptoms and current methadone treatment variables were examined. There were no significant differences in current methadone dose or duration enrolled in the current MMT program between those who did and did not screen positive for any psychiatric disorders (*p*s>0.05).

6.2.4.3 Current Substance Use and Psychiatric Symptoms

Results of the multiple regression analyses of current substance use predicting the number of symptoms of different types of psychiatric disorders are displayed in Table 6.4. Non-prescribed benzodiazepine use significantly predicted the number of symptoms endorsed for almost all mood and anxiety symptoms assessed as well as the total number of symptoms endorsed on the PDSQ. Similar results were also obtained when logistic regressions were run with current substance use predicting the likelihood to screen positive on the PDSQ for different disorders (see Table 6.5). Non-prescribed benzodiazepine use significantly predicted the likelihood to screen positive for depression, PTSD, GAD, social phobia, as well as the likelihood to screen positive for at least one disorder on the PDSQ (Any disorder assessed on the PDSQ). Current alcohol use was also a significant univariate predictor for likelihood to screen positive for social phobia.

For the logistic regressions of psychiatric symptoms predicting the likelihood to use different substances, non-prescribed benzodiazepine use was significantly predicted by the number of different types of psychiatric symptoms ($\chi^2(10)=36.27$, $p<.001$); number of GAD symptoms was the only univariate predictor ($p=.024$, OR=1.48, 95% CI=1.05-2.08). When screening positive for different psychiatric disorders were used as predictors in the logistic regression analyses instead of the number of psychiatric symptoms endorsed, current non-prescribed benzodiazepine use was significantly predicted ($\chi^2(10)=35.24$,

p<.001) by screening positive for GAD (*p*=.033, OR=17.52, 95% CI=1.26-246.10) and agoraphobia (*p*=.040, OR=0.07, 95% CI=0.01-0.88). That is, screening positive for GAD was associated with an *increased* likelihood of currently using non-prescribed benzodiazepines while screening positive for agoraphobia was associated with a *decreased* likelihood of currently using non-prescribed benzodiazepines. However, the relationship of screening positive for agoraphobia and past 30 day non-prescribed benzodiazepine use was examined further for possible suppressor effects. There was no significant correlation between screening positive for agoraphobia and past 30 day non-prescribed benzodiazepine use (point biserial *r*=.13, *p*=.277) but screening positive for GAD and agoraphobia were highly correlated (point biserial *r*=.57, *p*<.001). Thus, it is likely that the relationship between agoraphobia and non-prescribed benzodiazepine use reflects a suppressor effect [31][a]. Lastly, past 30 day alcohol use was found to be significantly predicted ($\chi^2(10)=18.97$, *p*=.041) by screening positive for social phobia (*p*=.025, OR=15.28, 95% CI=1.40-166.56).

6.2.5 Discussion

The present study found high rates of current use of a variety of substances as reported by clients enrolled in a low-threshold MMT program. Similar to previous studies of substance use by MMT clients (Darke, 1998a; Stitzer & Chutuape, 1999), alcohol, cannabis, cocaine, prescription opioids, and benzodiazepines were commonly-used substances; current use of hallucinogens

or inhalants was rare. Consistent with previous research in higher-threshold MMT programs (e.g., Callaly et al., 2001; Gelkopf et al., 1999; Cacciola et al., 2001), the present study also found high rates of psychiatric symptom reporting by low-threshold MMT clients. For many clients, these reports revealed levels of psychiatric symptoms that may warrant clinical diagnosis (Zimmerman, 2002).

As expected, we found support for relations between current substance use and current psychiatric symptom reporting. In particular, current non-prescribed benzodiazepine use predicted the number of psychiatric symptoms endorsed for most mood- and anxiety-related psychiatric disorders as well as predicting the likelihood of screening positive for most mood- and anxiety-related disorders assessed on the PDSQ. That is, current non-prescribed benzodiazepine use was associated with an increased number of psychiatric symptoms, and was associated with an increased likelihood of experiencing different psychiatric symptoms at levels that may warrant diagnosis. Current alcohol use (in addition to non-prescribed benzodiazepine use) was also found to be associated with an increased likelihood to screen positive for social phobia (see Table 6.5).

Conversely, current psychiatric symptoms were found to predict the likelihood of different types of current substance use. Number of GAD symptoms, as well as screening positive for this disorder on the PDSQ, made a unique contribution in predicting current non-prescribed benzodiazepine use. Screening positive for social phobia (but not the number of these types of symptoms) was associated with an increased likelihood of current alcohol use.

The findings that any current non-prescribed benzodiazepine use uniquely predicted number and the likelihood of experiencing psychiatric symptoms - namely anxiety and depression, and that GAD symptoms appear to be a unique predictor among psychiatric symptoms of current non-prescribed benzodiazepine use, are consistent with previous literature. While little research has indicated whether benzodiazepine use was prescribed or non-prescribed, benzodiazepine users in MMT programs have been found to have higher levels of anxiety symptoms (Brands et al., 2008; Darke et al., 1993), suicidal ideation, more suicide attempts (Brands et al., 2008), and lower psychosocial functioning (Darke et al., 1993) than non-users.

It is possible that non-prescribed benzodiazepines are being used to self medicate distressing psychiatric symptoms such as generalized anxiety symptoms (Khantzian, 1985). It is also possible anxiety-related withdrawal symptoms from benzodiazepines may be causing or exacerbating any existing anxiety symptoms (Longo & Johnson, 2000; Ciraulo et al., 2005; Posternak & Mueller, 2001; Westra & Stewart, 2002). Alternatively, these individuals could have a common underlying vulnerability to both benzodiazepine use and psychiatric symptoms (King & Brooner, 1999; Martins et al., 2009). Regardless of the basis for the relationship, these findings, in combination with existing literature (Brands et al., 2008; Darke et al., 1993), suggest that non-prescribed benzodiazepine use may be indicative of higher levels of psychopathology and related problems in MMT clients. Multiple systemic barriers (e.g., organization of services, finances; Ridgely, Goldman & Willenbring, 1990) often prevent

individuals with concurrent psychiatric and substance use issues from accessing appropriate treatment. Thus, further investigations and treatment development in this area are likely to be fruitful.

Of note is the finding that screening positive for agoraphobia was a significant predictor of *decreased* likelihood to use non-prescribed benzodiazepines and this relationship was likely indicative of a suppressor effect (Tzelgov & Henik, 1991). In this case, while screening positive for GAD may capture much of the variance in predicting non-prescribed benzodiazepine use, it is likely that screening positive for agoraphobia improves prediction of non-prescribed benzodiazepine use (despite the lack of an independent relationship with between these two variables) by accounting for avoidance related to anxiety. That is, agoraphobia may be protective of non-prescribed benzodiazepine use because individuals who often avoid anxiety-inducing situations may not feel they need to use benzodiazepines to manage their anxiety. They may be able to avoid anxiety through avoiding certain situations, whereas people with GAD symptoms may avoid anxiety through non-prescribed benzodiazepine use. Further investigations are needed to determine if this hypothesis is correct.

The finding that social phobia and alcohol use were related is also consistent with previous literature. Many studies have found high rates of comorbidity between social anxiety and alcohol problems (see Morris, Stewart & Ham, 2005 for review). Alcohol use while enrolled in MMT is also associated with increased overdose risk (Wolff, 2002). Thus, programming to address this association could also be beneficial to decreasing mortality and other harms.

There are a number of limitations to the present study. First, the present study consisted of a relatively small sample. Thus, there could be concerns regarding reliability of the findings. However, Type II error, not Type I, is more likely with small sample sizes, and the present sample size exceeds the 5:1 (participants: predictor variable) regression guidelines, as well as those suggested by Miles and Shevlin (2001; Field, 2009). Second, the PDSQ is weighted for emphasis on anxiety disorders. Although it assesses eating disorder symptoms, the PDSQ does not assess other disorders that theoretically would be related to stimulant use rather than benzodiazepine use (e.g., ADHD). More complex relationships between types of current psychiatric symptoms and types of current substance use may be revealed with more comprehensive psychiatric assessments. Third, the PDSQ does not assess Axis II symptomatology. Personality disorders, particularly antisocial and borderline, have been found to be highly prevalent in opioid-dependent individuals (see Ward, et al., 1998a for review; prevalence rates can vary between 15-73% for presence of any personality disorder compared to 10% in the general population). Opioid-dependent individuals with personality disorders have been found to have increased severity of depression, anxiety, and substance use problems (i.e., alcohol dependence; Kosten, Kosten, & Rounsaville, 1989). Further investigations into what extent such personality pathology may be accounting for the observed psychiatric symptoms and substance use relationships are warranted. Fourth, it is possible that the positive screens on the PDSQ may be over inclusive for some disorders regarding likelihood to receive a diagnosis. It

seems somewhat unlikely that almost 50% of the sample would receive a legitimate diagnosis of OCD or somatization disorder if further assessed. Instead, endorsing items such as repeated checking of locks on doors may better reflect the sometimes unstable and unsafe circumstances of participants' housing, and endorsement of somatization disorder symptoms such as "stomach and intestinal problems" may reflect side effects of MMT. Despite these possibilities, the rates of psychiatric symptom reporting in the present study were comparable to previous research with methadone clients (e.g., Callaly et al., 2001; Cacciola et al., 2001; Gelkopf et al., 2006) and the PDSQ clearly measured some level of specific psychiatric symptomatology in the present study given the large effect sizes and consistency of relationships with non-prescribed benzodiazepine use. Another limitation of the present study was that substance use behaviour was based on self-report. While there are some criticisms of this method (Darke, 1998b), it has been found to produce accurate results, particularly under circumstances enhancing accurate reporting like those used in the present study (Darke, 1998b; Ward, Mattick, & Hall, 1998b). Because of assurances of confidentiality, participation not influencing treatment, and compensation for participation not being contingent upon reporting (or not reporting) substance use, there was no motivation to minimize or exaggerate any substance use. Indeed, when assessed, the test-retest reliability of the present study measures was excellent.

The present research has a number of implications for both further practice and research. In terms of practice, it was somewhat surprising to have

found a relatively large (20.8%, *n*=16/77) percentage of clients having current prescriptions for benzodiazepines and/or opioids from health professionals outside of the current MMT program. It is possible some clients' family or emergency room doctors may not be aware their clients are on methadone, and/or MMT programs may not be aware a client is obtaining benzodiazepines or opioids via other medical professionals. This suggests that access to updated health records - for both MMT programs and other physicians (e.g., through electronic health records) could be beneficial given prescription drug monitoring programs may not always flag occurrences such as those in the present study. While prescribed benzodiazepine use did not have the same associations as non-prescribed use, there is still substantial overdose risk by concurrently using benzodiazepines with methadone (Caplehorn & Drummer, 2002; Wolff, 2002). In terms of research implications, given that there is remaining uncertainty if individuals enrolled in MMT may be using non-prescribed benzodiazepines to manage distressing mood states (such as anxiety), or if the reverse or another reason may be accounting for the observed relationships, research examining longitudinal patterns of substance use and psychiatric symptoms in MMT clients, or specific occasions of use should be conducted to further examine these competing hypotheses. The present study findings also suggest that future research and practice could focus on further developing, tailoring, and evaluating interventions to address benzodiazepine use by MMT clients. Possible therapeutic targets could include tailored interventions focusing on managing generalized anxiety symptoms and psychoeducation (e.g., Ahmed, Westra, &

Stewart) regarding the biological and psychological effects (both long- and short-term) of using benzodiazepines. It is possible such interventions could help this population to reduce benzodiazepine use, its related negative effects, as well as associated psychiatric symptom severity. Similar tailored programming may also be beneficial if focused on alcohol use and social anxiety symptoms. Previous research suggests that addressing both psychiatric symptoms and substance use concurrently in treatment, in an integrated fashion, is likely to be the most favourable treatment approach (Stewart & O'Connor, 2009).

6.2.6 Conclusions

Low-threshold MMT clients report high rates of both current substance use and current psychiatric symptoms. Non-prescribed benzodiazepine use appears to be a unique predictor of experiencing psychiatric symptoms - particularly various types of anxiety. Conversely, GAD symptoms appear to be a unique predictor amongst psychiatric symptoms in identifying current non-prescribed benzodiazepine use. Further investigations regarding the temporal nature of benzodiazepine use and psychiatric symptoms, as well as possible development of interventions tailored specifically to addressing this relationship, could be beneficial to our understanding of psychopathology and substance use. Further, additional research and clinical work in this area may assist in reducing the serious risk of overdose and harm posed by using substances, particularly benzodiazepines, while enrolled in MMT

6.2.7 Endnotes

[a]Briefly, a classic suppressor effect occurs when the addition of a predictor to the regression results in another predictor (or group of predictors) increasing in predictive validity, even though the newly added predictor may be unrelated to the dependent variable. See Tzelgov and Henik (1991) for further explanation.

6.2.8 List of abbreviations

CI - Confidence Interval

F – F ratio for overall regression model

GAD - Generalized Anxiety Disorder

GHB - Gamma-hydroxybutyrate

LSD - Lysergic acid diethylamide

M - Mean

MDMA - 3,4-Methylenedioxymethamphetamine

MMT - Methadone Maintenance Treatment

n – Number of participants in subsample

OCD - Obsessive Compulsive Disorder

OR - Odds Ratio

p – Probability of Type 1 error

PCP - Phencyclidine

PDSQ - Psychiatric Diagnostic Screening Questionnaire

PTSD - Post-Traumatic Stress Disorder

r - Correlation coefficient

R^2 - Coefficient of determination

SD - Standard Deviation

χ^2 - Chi square

6.2.9 Competing interests

The authors declare that they have no competing interests.

6.2.10 Authors' contributions

All authors have contributed significantly to this research report and are in agreement with its content. HGF assisted with the planning of the study, conducted data collection, contributed to data analysis, interpretation, write-up, and funding of the study. SPB and SHS assisted with planning of the study, data analysis, interpretation of results, writing of the manuscript, and funding of the study. CM assisted with planning of the study, data collection, practice implications, as well as reviewed and revised the drafts of the manuscript.

6.2.11 Acknowledgements

The authors would like to acknowledge those who assisted with the present study: Jessica Meisner, Cathy Hilchey, Haley Gray, Desiree MacDonald, Sergiu Mocanu, Lindsay Peters, Lyndsay Bozec, and Direction 180 staff and clientele. The authors would also like to thank the funders of this study and the authors' work: a Canadian Institutes of Health Research grant to SPB & SHS, a Canadian Institutes of Health Research Doctoral Research Award and research stipend to HGF, a Killam Doctoral Scholarship to HGF, and a Killam Research Professorship to SHS.

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Table 6.1

*Demographic information reported by sample participants (*n=*77).*

Characteristic		% (*n)* of Sample or [*M{SD}*]
Age	Years	[39.66{8.79}]
Gender	Male	62.3 (48)
	Female	37.7 (29)
Psychiatric Medication	Prescribed antidepressant (e.g., citalopram)	33.8 (26)
	Prescribed antipsychotic (e.g., quetiapine)	22.1 (17)
	Prescribed any psychiatric medication	63.6 (49)
Education	Less than high school/equivalent	50.6 (39)
	Completed high school/equivalent	49.4 (38)
Ethnicity	Caucasian	80.5 (62)
	Non-Caucasian/multiple ethnicities	19.5 (15)
Income	$10 000 or less per year	67.5 (52)
	More than $10 000 per year	32.5 (25)
Living Status	Renting	87.0 (67)
	Community Shelter	10.4 (8)
	Other	2.6 (2)
Current MMT program use	Years enrolled in current program prior to study interview	[3.00][1]
	Daily methadone dose (mg)	[112.04{43.97}]
	Days/past 30 methadone used	[28.36{4.48}]
	Proportion enrolled in previous MMT programs	46.8 (36)

[1]Median is reported due to the large standard deviation for this variable: *M*(*SD*)=3.40(3.05)

Table 6.2

*Substance use by sample participants (*n=*77) attending a low-threshold MMT program.*

Drug	% (*n*) Sample Ever Used	Mean Age (*SD*) of First Use for Lifetime Users	% (*n*) Sample Using in Preceding 30 days	Of Lifetime Users, Number of Days of Use in Preceding 30 Days *M*(*SD*)
Tobacco	100.0 (77)	11.5(4.0)	97.4 (75)	29.68(1.95)
Alcohol	98.7 (76)	13.0(4.5)	21.1 (16)	1.72(5.23)
Crack Cocaine	93.5 (72)	26.1(9.1)	44.2 (34)	4.92(9.39)
Powder Cocaine	89.6 (69)	19.2(5.8)	9.1 (7)	0.59(3.65)
Amphetamine/ Methamphetamine	57.1 (44)	20.4(7.0)	0 (0)	0(0)
MDMA[1]	66.2 (51)	26.5(9.9)	3.9 (3)	0.12(0.52)
Cannabis	94.8 (73)	13.2(3.4)	48.1 (37)	6.47(10.70)
LSD[2]	84.4 (65)	16.2(3.7)	1.3 (1)	0.14(1.13)
Psilocybin	71.4 (55)	17.0(4.4)	0 (0)	0(0)
Mescaline	59.7 (46)	19.1(4.7)	0 (0)	0(0)
Peyote	14.3 (11)	18.5(2.8)	0 (0)	0(0)
Salvia	14.3 (11)	32.2(11.3)	1.3 (1)	0.90(0.30)
GHB[3]	9.1 (7)	20.4(6.3)	0 (0)	0(0)
Peyote	14.3 (11)	18.5(2.8)	0 (0)	0(0)
PCP[4]	44.2 (34)	20.8(7.4)	1.3 (1)	0.47(2.65)
Ketamine	23.4 (18)	26.1(7.3)	2.6 (2)	1.06(4.24)
Inhalants	40.3 (31)	16.6(7.0)	1.3 (1)	0.32(0.18)
Opium	22.1 (17)	22.4(6.7)	0 (0)	0(0)
Heroin	49.4 (38)	24.3(6.1)	0 (0)	0(0)
Only Prescribed Prescription Opioids	88.3(68)	--[5]	9.1(7)	--
Any Non-prescribed Prescription Opioids	98.7 (76)	--	24.7 (19)	--
Only Prescribed Benzodiazepines	76.6 (59)	--	20.8 (16)	--
Any Non-prescribed Benzodiazepines	89.6 (69)	--	40.3 (31)	--

[1] *3,4-Methylenedioxymethamphetamine*
[2] *Lysergic acid diethylamide*
[3] *Gamma-hydroxybutyrate*
[4] *Phencyclidine*

[5]*Data for the general categories of Only Prescription Opioids, Any Non-Prescribed Prescription Opioids, Only Prescribed Benzodiazepines, and Any Non-Prescribed Benzodiazepines were not collected for age of ever use and number days of use/past 30. See Section 2.2.3.*

Table 6.3

*Psychiatric symptoms of sample (*n=*77) as assessed by the modified PDSQ.*

Disorder (# of symptoms assessed on PDSQ; # of symptoms required for a positive screen)	Mean(*SD*) number of symptoms endorsed by sample	% Sample Screening Positive for Disorder(*n*)
Eating Disorder (10;7)	1.64 (2.55)	7.8 (6)
Psychosis (6;1)	0.68 (1.24)	32.5 (25)
Hypochondriasis (5;1)	0.75 (1.31)	33.8 (26)
Somatization Disorder (5;1)	1.36 (1.38)	42.9 (33)
Depression (21;9)	6.45 (5.20)	31.2 (24)
Post Traumatic Stress Disorder ([PTSD] 15;5)	5.78 (5.26)	48.1 (37)
Obsessive Compulsive Disorder ([OCD] 7;1)	1.58 (2.10)	49.4 (38)
Panic Disorder (8;4)	2.05 (2.49)	27.3 (21)
Agoraphobia (12;4)	2.08 (2.83)	24.7 (19)
Social Phobia (15;4)	2.65 (3.80)	29.9 (23)
Generalized Anxiety Disorder ([GAD] 10;7)	3.81 (3.77)	28.6 (22)
Total number of symptoms endorsed (114)	28.83 (24.00)	

Table 6.4

Multiple regressions of past 30 day substance-use predicting psychiatric symptoms.

Dependent Variable (# of symptoms endorsed on PDSQ)	Model $F(6,67)$ =	p	Adjusted R^2	Significant predictors (p)	Beta
Psychosis	1.44	.212	.04		
Hypochondriasis	1.71	.133	.06		
Somatization disorder	1.83	.107	.06		
Depression	6.16	<.001	.27	-Any non-prescribed benzodiazepine use (<.001)	.58
PTSD	3.60	.004	.18	-Any non-prescribed benzodiazepine use (<.001)	.46
OCD	3.99	.002	.20	-Any non-prescribed benzodiazepine use (<.001)	.44
Panic disorder	2.42	.035	.11	-Any non-prescribed benzodiazepine use (.001)	.41
Agoraphobia	1.40	.226	.03		
Social phobia	2.73	.020	.12	-Any non-prescribed benzodiazepine use (.004)	.37
GAD	6.06	<.001	.29	-Any non-prescribed benzodiazepine use (<.001)	.60
Total number of all symptoms assessed	3.08	.010	.15	-Any non-prescribed benzodiazepine use (<.001)	.49

*Predictors entered in all regressions: Any non-prescribed benzodiazepine use, Only prescribed benzodiazepine use, Any non-prescribed prescription opioid use, Any alcohol use, Any cannabis use, and Any crack use in the past 30 days.

**Significant univariate predictors are presented only in the case of a significant multivariate model.

Table 6.5

Logistic regressions of past 30 day substance use predicting screening positive for types of psychiatric symptoms.

Dependent Variable (screening positive for disorder on PDSQ)	Model $X^2(p)$	Significant predictors (p)	Odds ratio (OR)	95% confidence interval for OR
Psychosis	8.01(.238)			
Hypochondriasis	10.08(.121)			
Somatization disorder	10.50(.105)			
Depression	22.08(.001)	-Any non-prescribed benzodiazepine use (.001)	9.63	2.67-34.68
PTSD	22.40(.001)	-Any non-prescribed benzodiazepine use (.001)	7.56	2.26-25.31
OCD	11.91(.064)			
Panic disorder	10.43(.108)			
Agoraphobia	10.82(.091)			
Social phobia	23.37(.001)	-Any non-prescribed benzodiazepine use (.003)	7.70	2.00-29.58
		-Alcohol use (.018)	6.59	1.28-31.33
GAD	21.06(.002)	-Any non-prescribed benzodiazepine use (<.001)	12.30	3.17-47.72
Any disorder assessed on PDSQ	18.25(.006)	-Any non-prescribed benzodiazepine use (.006)	22.14	2.42-203.00

*Predictors entered in all regressions: Any non-prescribed benzodiazepine use, Only prescribed benzodiazepine use, Any non-prescribed prescription opioid use, Any alcohol use, Any cannabis use, and Any crack use in the past 30 days.
**Significant univariate predictors are presented only in the case of a significant multivariate model.

6.3 Epilogue to Study Two: Additional Discussion of Findings

6.3.1 Supplementary Regression Tables for Study Two

Due to manuscript space limitations, regression results of psychiatric symptoms predicting current substance use were summarized in text instead of presented in table format in the Study Two manuscript (see Section 6.2.4). Consequently, tables of these regression results are given below for ease of comparison to regression tables of current substance use predicting psychiatric symptoms.

Table 6.6

Logistic regressions of number of psychiatric symptoms (as measured by the modified PDSQ) predicting past 30 day substance use

Dependent Variable (presence of past 30 day use)	Model X^2 (*p*)	Significant predictors (*p*)	Odds ratio (OR)	95% CI for OR
Any non-prescribed benzodiazepines	36.27 (<.001)	-GAD symptoms (.024)	1.48	1.05-2.08
Only prescribed benzodiazepines	17.35 (.067)			
Any non-prescribed prescription opioids	10.26 (.418)			
Any alcohol	12.33 (.264)			
Any cannabis	11.12 (.349)			
Any crack	7.36 (.691)			

*Predictors entered in all regressions: number of symptoms endorsed in the disorder categories of Psychosis, Hypochondriasis, Somatization disorder, Depression, PTSD, OCD, Panic disorder, Agoraphobia, Social Phobia, and GAD.
**Only significant univariate predictors are presented in the case of a significant overall model.

Table 6.7

Logistic regressions of screening positive for different psychiatric symptoms (as measured by the modified PDSQ) predicting past 30 day substance use

Dependent Variable (presence of past 30 day use)	Model X^2 (*p*)	Significant predictors (*p*)	Odds ratio (OR)	95% CI for OR
Any non-prescribed benzodiazepines	35.24 (<.001)	-GAD (.033) -Agoraphobia (.040)	17.52 0.07	1.26-246.10 0.01-0.88
Only prescribed benzodiazepines	17.87 (.057)			
Any non-prescribed prescription opioids	9.19 (.514)			
Any alcohol	18.97 (.041)	-Social Phobia (.025)	15.28	1.40-166.56
Any cannabis	11.76 (.302)			
Any crack	9.29 (.505)			

*Predictors entered in all regressions: screening positive for the PDSQ disorder categories of Psychosis, Hypochondriasis, Somatization disorder, Depression, PTSD, OCD, Panic disorder, Agoraphobia, Social Phobia, and GAD.
**Only significant univariate predictors are presented in the case of a significant overall model.

6.3.2 Supplementary analyses of substance use and MMT variables

Because some researchers have posited that ongoing substance use (particularly stimulant use) in MMT may be reflective of an effort by participants to self-medicate side-effects (e.g.., lethargy/ drowsiness) of methadone (Fischer et al., 2005), the relationships of current substance use and methadone treatment variables with current substance use were investigated further. Individuals who used any non-prescribed prescription opioids (*M*[*SD*]=80.32[49.86]mL) had a lower methadone dose than those who had not

used any non-prescribed (*M*[*SD*]=121.25[35.89]mL) prescription opioids (*t*(74)=-3.89, *p*<.001). Also, those who had used any non-prescribed prescription opioids were enrolled in the current methadone program for less time (*M*[*SD*]=2.04[2.09]years), and used methadone on fewer days out of the past 30 (*M*[*SD*]=25.21[7.66]days), than those who did not use any non-prescribed prescription opioids (*M*[*SD*]=3.87[3.20]years; 29.39[1.96]days), *t*(73)=-2.32, *p*=.023; *t*(18.79)=-3.80, *p*=.030, respectively. Individuals who used alcohol tended to have lower methadone doses (*M*[*SD*]=91.00[41.60]mL) than those who had not used alcohol in the past 30 days (*M*[*SD*]=117.56[43.21]mL), *t*(75)=-2.20, *p*=.031.

Supplementary regressions where MMT variables were added as predictors for either current substance use (i.e., past 30 day use) or psychiatric symptoms (i.e., number of symptoms endorsed, screening positive) were not able to be conducted due to low sample size. That is, the number of predictors would have exceeded the 1 to 5, number of predictor variables to number of participants, guidelines outlined in Field, 2009 (see Section 2.4.4),

6.3.3 Summary of Study Two Findings in Relation to Main Study Questions

The objective of Study Two was to gain insight into current psychiatric and substance use issues faced by prescription opioid users in low-threshold MMT. Four specific research questions were asked: 1) What kinds of psychiatric

symptoms might these participants be experiencing? 2) What kinds of substances might they be using? 3) Are these two variables related? 4) How might the results obtained with prescription opioid users compare to previous MMT investigations where clients were predominantly heroin users?

To answer the first study question, the majority of participants (77.9%, *n*=60/77) reported currently experiencing psychiatric symptoms and, on average, participants reported experiencing a number of different types of psychiatric symptoms (*M* [*SD*] = 3.52 [3.16]). In order, symptoms of OCD, PTSD, and somatization disorder were the three most prevalent types of symptoms reported. However, almost one third of the sample also reported experiencing symptoms of hypochondriasis, psychosis, and depression, respectively. Prevalence rates of symptom reporting of all other disorders, with the exception of eating disorder, on the PDSQ were between is 25-50%. The hypothesis that PTSD symptoms would be more prevalently reported by participants relative to other psychiatric symptoms was supported. However, the hypothesis that GAD and depression symptoms would also be among the most prevalent psychiatric symptoms was not completely supported. A variety of other anxiety (e.g., OCD, 49.4%, *n*=38/77) and psychiatric symptoms (e.g., hypochondriasis, 33.8%, *n*=26/77) were also similarly prevalent. However, it is of note that hypochondriasis is a disorder that is frequently debated as to whether it is better classified as an anxiety disorder (i.e., health anxiety) rather than a somatic disorder (e.g., Noyes, 1999; Olatunji, Deacon, & Abramowitz, 2009). If hypochondriasis is considered as an anxiety disorder, the high prevalence observed is consistent with the overall trend of high

rates of anxiety in the present sample. However, even if hypochondriasis is included as an anxiety disorder rather than a somatic disorder, the hypothesis that reporting of non-mood, non-anxiety symptoms (e.g., psychosis) would be rare was not supported. Almost one third of the sample reported psychosis-related symptoms and/or over 40% reported somatization disorder symptoms. However, as discussed in the full manuscript, it should be noted that somatization symptoms may also be reflective of MMT side-effects.

To answer the second study question, the majority of participants reported using substances in the past 30 days- even if tobacco use was excluded from consideration. As hypothesized, the most common currently used substances were (in order, after tobacco) cannabis, crack cocaine, non-prescribed benzodiazepines, non-prescribed prescription opioids, and alcohol. The hypothesis that few clients would report current use of hallucinogens and inhalants was also supported; less than 5% of the sample reported current use of such substances. Another finding of particular note in Study Two was that approximately 1 out every 5 study participants reported having current prescriptions for benzodiazepines. Medical staff members at the methadone clinic do not prescribe this medication to any of the clients due to overdose risks with methadone and letters are sent to the family doctors of all clients asking them to not prescribe such substances to their clients while enrolled in MMT (C. MacIsaac, personal communication, February, 2011).

To answer the third study question, there was evidence for relationships between substance use and psychiatric symptoms, but the relationships

observed were not completely consistent with the a priori hypotheses. Current non-prescribed benzodiazepine use predicted the likelihood to screen positive for depression and most anxiety disorders assessed on the PDSQ, as well as the number of symptoms endorsed for each of these disorders. In turn, generalized anxiety symptoms predicted current non-prescribed benzodiazepine use. While these results were consistent with the a priori hypotheses, there failed to be support for the hypothesis that current stimulant (e.g., cocaine) use and impulsive-type symptoms (e.g., eating disorder) would be related. Also, while it was not specifically predicted that a relationship between current alcohol and social anxiety symptoms would be observed, this finding was consistent with the hypothesis that different types of current substance use would be related to different types of current psychiatric symptoms, and that anxiolytic substance use specifically would be related to anxiety symptoms (and vice versa). Further, the relationship between alcohol use and social anxiety is consistent with previous research findings in non-MMT populations (Conrod et al., 2000), previous findings regarding high comorbidity between alcohol abuse and social phobia (see Morris, Stewart & Ham, 2005 for review), and is consistent with theories such as the self-medication hypothesis (Khantzian, 1985; 1997).

To answer the fourth study question, the Study Two findings were largely consistent with previous MMT findings of current psychiatric symptom and substance use in the literature – both with heroin-dependent (as opposed to prescription opioid), low threshold and higher threshold MMT programs. As mentioned previously (see Section 1.8.3), not all of the previous studies

investigating psychiatric symptoms and substance use by MMT clients described the types of opioids used by participants prior to entering MMT. Similarly, many publications with MMT clients do not specifically outline their treatment philosophy or programming guidelines (i.e., whether clients are expelled after positive urine drug screen results, is it a low-threshold treatment program).

In terms of psychiatric symptoms, previous studies of MMT clients found that 28-76% met diagnostic criteria for a psychiatric disorder (Callaly et al., 2001; Gelkopf et al., 2006; Astals et al., 2009). Previous research with prescription opioid users entering MMT found that 18-40%[17] reported currently receiving psychiatric treatment (Brands, Blake et al., 2004). Other research with low-threshold MMT clients found that 60%-76% of participants reported mental health problems or difficulties in the past 30 days (Millson et al, 2006; Reijneveld & Plomp, 1993). The Study Two finding that almost 80% of participants reported notable levels of psychiatric symptoms in the past 30 days was quite consistent with, although slightly elevated relative to, previous findings. Thus, the hypothesis relating to the psychiatric symptom component of the fourth main study question was supported. Additionally, if the findings of psychiatric symptom prevalence are compared to estimates for psychiatric outpatients, the levels of psychiatric symptom endorsement are elevated across the different disorders assessed- with the exception of major depression (where psychiatric outpatients have a higher prevalence estimate at 55% compared to the present sample where 31.2%, *n*=24/77, of the sample screened positive [see Table 6.3]).

[17] A range is given because the study sample was subdivided depending on whether prescription opioids or heroin were first used, or if heroin was never used.

The Study Two findings of psychiatric symptom prevalence are also elevated when compared to a non-clinical sample of individuals from the general population (see Zimmerman, 2002).

In terms of substance use, previous studies with heroin-dependent MMT clients have found 81% of participants had used a substance other than methadone, in the past 30 days, and the most popular substances were alcohol, cocaine/crack, and cannabis (Gollnisch, 1997). Although not all MMT studies have such high rates of ongoing use (e.g., Maremanni et al., 2007), most studies have found substantial proportions (approximately 30-70%) of MMT clients to report ongoing substance use (Ball & Ross, 1991; Kamal et al., 2007). There is no published research to date, to the knowledge of the author, examining ongoing substance use by prescription opioid users specifically in MMT. However, previous research examining substance use histories of individuals who had used prescription opioids exclusively (i.e., no lifetime heroin use) upon entry to MMT found decreased likelihood to have used cannabis or cocaine relative to participants who had also used heroin, or used heroin exclusively, in their lives (Brands, Blake et al., 2004).

The current substance use results of Study Two were comparable to previous research of ongoing substance use in low-threshold MMT populations. Previous research found 76% of clients reported continuing to inject drugs in treatment (Ryrie et al., 1997), and 90% of current clients report using “hard drugs” (i.e., opioids, amphetamine, cocaine, LSD or inhalants; alcohol, tobacco, and cannabis are not included) in the past 30 days (Reijneveld & Plomp, 1993).

Thus, the hypothesis relating to the current substance use component of the fourth main study question was supported as almost 90% of the Study Two sample reported current substance use (excluding tobacco) in the past 30 days. Additionally, if the current substance use rates by the present sample (i.e., percent of participants reporting past 30day use of various substances) are compared to the general population, the present sample was found to have higher rates of current use than results obtained for current use for the general population in the USA - except for current alcohol use. That is, 27.7% of the population aged 12 or older in the USA used tobacco, and 8.7% used any illicit substance, in the past month whereas 97.4% (*n*=75/77) of the study sample used tobacco, and over 40% of the sample used illicit substances such as crack cocaine (44.2%, *n*=34/77) or cannabis (48.1%, *n*=37/77) in the past month. In terms of current alcohol use, the results obtained with the present study sample indicated a lower past-month use prevalence compared to the general population; 51.6% of the general population USA used alcohol in the past month (SAMSHA, 2009b), whereas 21.1% (*n*=16/77) of the study sample reported past month alcohol use. Past month reported substance use statistics are not available for the Canadian general population for comparison with the present study sample; instead population-based substance use statistics are based on the interval of past 12 month use. Despite this difference in substance use reporting windows, it can be inferred that current substance use rates for tobacco and illicit substances for the Study Two sample were greater than that in the general Canadian population; the past month use rates reported by the study

sample for these substances are greater than the past 12 month use rates reported for the general Canadian population (e.g., 14.1% of Canadians report past 12 month use of cannabis (Adlaf, Begin & Sawka, 2005), 48.1% (n=37/77) of the study sample reported past month use of cannabis).

6.3.4 Extended Commentary Regarding Study Two Limitations

Not all of the main limitations of Study Two were able to be discussed in the Study Two manuscript due to the need for brevity in journal article publications. However there are a number of additional possible limitations that should be highlighted. First, a current pain assessment measure was not administered to Study Two participants. Previous research indicates that 37% to 60% of MMT clients have some level of chronic pain (the range in estimates reflects severe intensity versus chronic pain of any intensity; Rosenblum et al., 2003; Jamison, Kaufman, & Katz, 2000). Chronic pain and psychiatric symptoms, particularly anxiety and depression, have been found to be positively associated although the directionality of this association is not clear. That is, the presence of pain is considered to be a stressor that increases emotional distress. In turn, individuals with pain, who also have comorbid symptoms of anxiety and/or depression, have greater impairment in function, increased levels of pain, and/or poorer prognosis (Eisendrath, 1995; Tunks, Crook & Weir, 2008). Barry and colleagues (2009) found that MMT clients with severe pain or chronic severe pain had significantly higher levels of anxiety and somatization than MMT clients

with less severe or no pain. It is possible that pain symptoms may have been an important factor in the types or level of psychiatric symptoms experienced in Study Two if it had been evaluated. Conversely, individuals with somatization disorder and hypochondriasis frequently have chronic pain complaints (Eisendrath, 1995) and thus are often prescribed opioids after presenting to a family doctor or other medical setting. It is possible that some of these individuals may have developed problems with their use of prescription opioids. Consequently the relatively high level rates of screening positive for somatization disorder and hypochondriasis in the Study Two sample may reflect the increased prevalence of these two disorders in a prescription opioid using methadone population as opposed to heroin-using populations. It was not possible to evaluate this possibility given the lack of pain assessment or medical file review in the present study but is another possible avenue for future research.

While Barry and colleagues (2009) did not find any differences between MMT clients with chronic or severe pain compared to those with no pain in terms of substance use, other researchers have suggested that under-treatment of pain can lead to increased risk of addiction, substance use and/or risk of relapse to substance misuse (Scimeca, Savage, Portenoy & Lowinson, 2000; Gardner, 2008). Additionally, 40-60% of chronic pain patients have received a prescription for a benzodiazepine even though there is not a strong evidence base supporting benzodiazepine effectiveness for reducing pain (see Ciraulo, Ciraulo, Sands, Knapp, & Sarid-Segal, 2005 for review). The reasons for being prescribed current medications were not assessed in Study Two, but it is possible that this

may partially explain why approximately 20% of participants had a current prescription for a benzodiazepine, despite overdose risks when also being prescribed methadone. Although Study Two results and clinical implications are limited by not evaluating the role of current pain in the relationship between current psychiatric symptoms and current substance use, investigation regarding how pain may affect the relationship is an interesting area for possible future research.

The second possible limitation of Study Two was that a medical file review regarding other medical comorbidities (e.g., HIV, Hepatitis C), or treatments being received by participants (e.g., pegintron alpha-2b treatment for hepatitis; Merck, 2010) was not conducted. As outlined in both major publications of psychiatric diagnostic guidelines (i.e., *DSM-IV-TR*, APA, 2000; *ICD-10*, World Health Organization, 1993), presence of psychiatric symptoms may indicate the presence of a psychiatric disorder, may be reflective of ongoing substance use (e.g., in the case of substance-induced psychiatric symptoms), or may be reflective of a general medical condition (e.g., thyroid condition, HIV, epilepsy; Williams & Shepherd, 2000; Talbot-Stern, Green & Royle, 2000). Information regarding current medical conditions was not assessed and controlled for in Study Two. Similarly, treatment of medical conditions such as HIV and hepatitis C are known to influence psychiatric symptoms (Turjanski & Lloyd, 2005; Neri, Pulvirenti & Bertino, 2006; Merck, 2010). The conditions of HIV and hepatitis C are known to occur at elevated rates among clients who enrol in low-threshold MMT; Millson and colleagues (2006) found that 6% of clients entering low-

threshold MMT were known to have HIV and approximately 50% were known to have hepatitis C. It is possible if such common medical/physical factors were controlled for in the present study, different results and/or relationships between psychiatric symptoms and substance use may have been obtained.

A third possible limitation of Study 2 relates to the differing restrictiveness of PDSQ criteria for screening positive for different disorders. It is of note, that screening positive for depression was comparatively low with respect to other psychiatric disorders when compared to previous MMT literature (e.g. Callaly et al., 2001). Depression is typically one of the most commonly diagnosed disorders in MMT populations, whereas disorders such as psychosis and OCD are comparatively less common (Gelkopf et al., 2006; Callaly et al., 2001). It is of note that the depression subscale of the PDSQ contains many more items (i.e., 21 items), and requires more items to be endorsed (i.e., nine) for an individual to screen positive, relative to other disorders assessed. For example, the somatization disorder subscale is five items long and requires only one item to be positively endorsed in order for an individual to screen positive. Consequently, depression symptomatology in the present sample may be relatively low in comparison to the other disorders assessed due to its more restrictive criteria, and not actually reflective of a "true" lower symptom prevalence in comparison to other disorders assessed in the present study.

A fourth possible limitation of the study was that the side effects related to methadone may be influencing, or even confounding, the psychiatric symptom reporting of the present sample. That is, methadone may have unpleasant side

effects for some individuals, such as drowsiness, decreased sex drive, and impaired concentration (Brown, Balousek, Mundt & Fleming, 2005; Brown, Benn, & Jansen, 1975). Such side effects share similarities to some symptoms of depression (APA, 2000). Consequently, depression symptomatology in MMT samples may be reflective of methadone side effects as opposed to an independent psychiatric condition. Indeed, as noted above, in samples of MMT clients, depression is typically one of the most prevalent disorders in this population (e.g., Callaly et al., 2001; Gelkopf et al., 2006). However, research also suggests that psychiatric symptoms may predate the onset of participants' opioid use (Callaly et al., 2001) or be substance-induced (Gelkopf et al., 2006). In the present study there were no relationships between psychiatric symptom (including depression) and MMT variables.

Similarly, a fifth possible limitation of Study Two was that side effects of MMT could also be accounting for the some of the observed substance use patterns. That is, participants in the present study may have been attempting to use stimulant substances to self-medicate the sedative side effects of methadone. Other researchers have noted ongoing use of cocaine, or even alcohol, in MMT clients may be indicative of this motivation (Fischer et al., 2005). However, the supplementary analyses of any associations between MMT and current substance use variables were not supportive of this possibility. Instead, the results suggest that not being stabilized on a dose of methadone (i.e., early on in treatment, while the methadone dose is increasing) is related to ongoing prescription opioid use. Fischer and colleagues (2005) posit that the ongoing

alcohol use by MMT clients in treatment during the 1970s, and ongoing cocaine use by MMT clients in the present day, are possibly indicative of self-medication of the side effects of methadone (e.g., drowsiness). However, there was no indication of any MMT variables being related to ongoing cocaine use. Further, the observed pattern of alcohol use and MMT variables is opposite to what would have been predicted by Fischer and colleagues (2005). That is, if alcohol was being used by participants to self-medicate the side-effects of methadone, one would presume the side effects of methadone to increase with increasing methadone doses, and thus alcohol use to be more likely. However, in Study Two, past 30 day alcohol use was associated with a *lowe*r MMT dose. Thus, it is possible that ongoing alcohol use more likely represents a possible attempt to self-medicate opioid withdrawal symptoms until the person is stabilized on an appropriate methadone dosage as opposed to self-medication of drowsiness/depressive side effects from methadone use. Unfortunately multiple and logistic regressions could not able to be conducted investigating how MMT variables may have influenced results predicting ongoing substance use and ongoing psychiatric symptoms due to insufficient sample size. Fischer and colleagues' (2005) hypothesis that the side effects of methadone may be influencing ongoing substance use, as well as possibly psychiatric symptoms, is compelling, and has important treatment implications. Consequently future longitudinal research with low-threshold MMT samples, and larger samples in particular, would be particularly beneficial to examine this hypothesis further.

A sixth possible limitation of the Study Two was that, although the likelihood to use various substances in the past 30 days was evaluated, the extent of this substance use (e.g., number of days the substance was used, substance quantity/dose) was not examined further. Such analyses were not conducted due to a methodological issue. As outlined previously in Section 2.2.3, the number of days/past 30 of prescribed and non-prescribed benzodiazepine and prescription opioid use was not able to be conclusively determined. It is possible different relationships between current psychiatric symptoms and substance use may have been elucidated if extent of current substance use could have been evaluated (e.g., generalized anxiety symptoms could be predictive of any non-prescribed benzodiazepine use; however, PTSD symptoms could be predictive of the frequency of use, with increased symptoms predicting increased use).

Related to the seventh possible study limitation, although any prescribed and non-prescribed benzodiazepine use were evaluated, it could not be determined if all prescribed benzodiazepine users were using their benzodiazepines as prescribed. It is possible prescribed individuals may have been using their medications for non-prescribed reasons and/or in non-prescribed ways. Future research evaluating motivations to use benzodiazepines in the past 30 days, and whether one was prescribed or not, could better evaluate this complexity. It would also provide important directions for future treatment interventions. Additionally, as mentioned in the Study Two Manuscript (see Section 6.2.5), evaluating specific occasions of use, or

assessing benzodiazepine use longitudinally would also assist in further investigating the maintaining factors between benzodiazepine use and psychiatric symptoms in MMT clients.

A eighth possible study limitation not discussed in the Study Two manuscript was the grouping of prescription benzodiazepines and prescription opioids into general classes. The rationale for assessing these prescription medications in this manner is outlined in Section 2.2.3 (Prescription Drug Use History). While not asking about the use history of every prescription medication enabled the study interviews to be more feasible, and may have made the data more valid and reliable (based on participant feedback regarding participant fatigue and not being able to recall use of all the different medications) it also prevented an analysis and comparison of problems associated with different medications. For example, benzodiazepines may be short- or long-acting. The pharmacokinetics of a substance affect how it is used, and its abuse liability (Griffiths & Johnson, 2005; Ciraulo et al., 2005). It would be particularly of interest to determine what types of benzodiazepines may be commonly prescribed to MMT clients, and what medications may have been obtained without a prescription. It is unclear if use of different benzodiazepines might be associated with different psychiatric symptoms in methadone clientele. Previous studies with methadone clients suggest there may be some important differences in how different benzodiazepines are used (Iguchi, Handelsman, Bickel & Griffiths, 1993). Different benzodiazepines have different pharmacokinectics, side effects and ease of ceasing use (Ciraulo et al., 2006); thus, it is possible that

there may be different consequences (including psychiatric) associated with use of different benzodiazepine medications. Such relationships were not able to be evaluated in the present study. It is also likely that the issues outlined above between different types of benzodiazepine medications can be extended to examining prescription opioids used while enrolled in MMT as well.

Related to the Study Two limitation outlined above; the ninth major Study Two limitation was that it was unknown how accurate the Study Two participants were in their abilities to distinguish between benzodiazepines and similar sedative substances (e.g., barbiturates), or substances that may be prescribed for similar reasons (e.g., quetiapine). It was hypothesized by the author that participants could effectively discriminate between these medications based on spontaneous comments made by the first participants interviewed in response to the presentation of NSDUH photo cards (see Section 2.2.3) of different medications (e.g., readily identifying some medications as being only available in the USA; identifying cards as depicting all benzodiazepine type medications) and during other interview portions (e.g., frequently referring to the group of “benzo” medications). However, there are no published, empirical studies, to the knowledge of the author, evaluating the ability and knowledge of clients to discriminate between different sedative substances. The extensive substance and prescription drug use histories of the sample suggest that participants were likely quite knowledgeable regarding different substances. Additionally their recall regarding benzodiazepine use was also quite reliable across different interviews. However, it is possible that some participants may not have been as

knowledgeable as others, may have been misinformed (e.g., another client, friend or dealer may have mistakenly informed them that quetiapine was a benzodiazepine when it is an atypical antipsychotic). This may have introduced error into Study Two in that some participants may have reported benzodiazepine use in the past 30 days that was actually another sedative or a mild antipsychotic (e.g., quetiapine) medication. This could have negatively affected Study Two results since atypical antipsychotics and other medications do not produce the same symptoms of withdrawal as benzodiazepines. Thus, prevalence regarding use of benzodiazepines by the sample may be slightly over-estimated due to some participants erroneously including their use of sedating, non-benzodiazepine substances in reporting their benzodiazepine use. Further, relationships between different types of benzodiazepine use (e.g., prescribed or non-prescribed) and psychiatric symptoms may have been underestimated in that increased error and variability may have contributed to lower effect sizes (thus some relationships between benzodiazepine use and psychiatric symptoms were undetected due to insufficient power).

A tenth possible study limitation of Study Two was that a number of the participants included in Study Two were currently prescribed psychiatric medication, such as antidepressants (e.g., the selective serotonin reuptake inhibitor citalopram) and/or antipsychotics (e.g., the atypical antipsychotic quetiapine; see Table 6.1). Taking psychiatric medication was not controlled for in regression analyses because of statistical power concerns (i.e., having a sufficient number of participants for the desired number of predictors). It is

possible that the results could change if this variable was included in analyses. Future research examining relationships between ongoing psychiatric symptoms and substance use in MMT clients should evaluate the possible contributing (or attenuating or null) effect of psychiatric medication on the relationship. Related to this, particularly given the chaotic lifestyles of low threshold MMT clients (Marshall, 2004), future research should also evaluate the extent to which clients take their psychiatric medication on a regular basis and as prescribed.

In addition to the identified issues of the modified PDSQ in the Study Two manuscript (see Section 6.2.5) as being heavily weighted on anxiety disorders and the possibility of being over inclusive, an eleventh limitation is that there are some other concerns about the modification and administration of the measure that may have influenced Study Two results. The original version of the PDSQ was designed for participants to read and fill out independently. Due to literacy concerns with the present sample, all measures were administered verbally to participants. However, this may have resulted in underreporting of psychiatric symptoms due to social desirability concerns dampening reporting of psychiatric symptoms in the interview format (Moum, 1998). Additionally, by restricting the reporting period to one month for some types of symptoms, instead of six months as in the original version, the modified PDSQ measure could further underestimate the presence of psychiatric symptoms relative to the validated, original version of the PDSQ. However, the test-retest reliability portion of Study Two found high correlations not only for number of symptoms reported, but fairly good levels of agreement in terms of screening positive for many different

disorders assessed between the two versions (see Section 3.6). On the other hand, the levels of agreement and reliability between the two versions of the PDSQ were poor for some disorders. Those disorders with few items on the PDSQ, or where endorsement of only one item resulted in a positive screen, tended to have lower levels of agreement between the two versions (see Table 3.6). Additionally, even the original version of the PDSQ cannot be considered to be diagnostic. Instead a positive screen on the PDSQ is indicative of an increased high likelihood to be experience enough symptoms to warrant receiving a diagnosis relative to someone who did not screen positive on the measure. While some research has found the PDSQ to have good sensitivity and negative predictive values in substance dependent populations (Zimmerman et al., 2004), other research has found it to have low accuracy for screening some disorders (i.e., panic disorder; Castel, Rush, & Scalco, 2008). Despite these possible limitations, the PDSQ clearly measured some level of specific psychiatric symptomatology and current distress in the present study given the large effect sizes.

As mentioned in Chapter Four, it should also be noted that the generalizability of the present study sample is somewhat limited. The participants are part of a unique population enrolled in low-threshold MMT in Eastern Canada. Participants likely represent those who were unable to abide by other methadone program guidelines (see Table 4.1), and thus the present results cannot be considered to be generalizable to all individuals enrolled in MMT. Furthermore, the present sample was over-representative of those

enrolled in the low-threshold MMT clinic who were on daily methadone administration (see Section 4.2.3.1), and thus the results likely represent those participants who are least able to maintain abstinence from substances. That is, this sample may biased by sample selection effects such that it represent individuals enrolled in low-threshold MMT who are have the most severe substance use problems (e.g., psychological dependence to many different substances; high level of physical dependence to substances) and/or psychiatric issues. Furthermore, it is important to note that the present sample represents those enrolled in treatment for their opioid use. Thus, the present results cannot be considered to extend to all substance users and/or those experiencing psychiatric issues. Individuals who are not enrolled in MMT but are using substances such as non-prescribed benzodiazepines and/or experiencing psychiatric symptoms may have a different pattern of relationships between their substance use and psychiatric symptoms. However, despite these limitations to the generalizability of the findings to other samples, the present study provides insight into a highly vulnerable population of individuals who have high treatment needs. Given that almost half of the sample (46.8%, n=35/77) was enrolled in previous programs, this data may provide some insight into issues experienced by individuals who may be unsuccessfully abstaining from substances in other MMT programs and/or reporting psychiatric symptoms.

6.4 Summary of Study Two Findings

The hypotheses of Study Two related to the four main study questions were largely supported. Both psychiatric symptom reporting and ongoing substance use were highly prevalent in the sample of low-threshold MMT clients in Halifax, Nova Scotia. Relationships between non-prescribed benzodiazepine use and anxiety type symptoms, alcohol use and social anxiety symptoms were observed. Relationships between psychiatric symptoms and substance use were not observed for other commonly used substances like cannabis or crack. This is particularly of interest given the negative MMT outcomes association with ongoing cocaine use. There were no psychiatric symptom and substance use relationships observed for psychiatric symptoms like psychosis, hypochondriasis, and somatization, even though fairly large proportions (i.e., one third or more) of the sample reported experiencing such symptoms.

CHAPTER 7 GENERAL DISCUSSION

The primary objectives of this manuscript-based thesis were to: 1) examine prescription opioid use, specifically hydromorphone use, characteristics in a sample of individuals who later enrolled in treatment for their opioid use; and 2) gain insight into co-occurring psychiatric and substance use issues faced by prescription opioid users in treatment. In an effort to answer questions related to these two objectives, a sample of 82 participants enrolled in a low threshold MMT program in Halifax, Nova Scotia was obtained and participants were interviewed about these issues. The specific hypotheses, methods, results, and discussions have been outlined in the previous chapters. The present chapter will summarize the main novel contributions of the thesis research to the literature in addition to summarizing the limitations and future directions for research and clinical practice.

7.1 Summary of Main Novel Findings

The present thesis made a number of novel contributions to the literature. First, the present research was able to systematically and quantitatively investigate substance use and psychosocial variables in a unique, underserved, and vulnerable population. The low-threshold MMT clinic where participants were recruited serves injection drug users who are street-entrenched, poly-substance using, HIV- , Hepatitis B- and/or C-infected (or at risk of such

infection), have been or are currently involved with the criminal justice system, and/or have significant comorbid mental health problems (Marshall, 2004). Many participants (43.6%, *n*=34/78) had been enrolled in previous MMT programs and the sample obtained was also over-representative of those who had daily-witnessed ingestion status (94.9%, *n*=74/78, of the sample had this status versus 37%, *N*=70/190, of all clients enrolled at the clinic). That is, despite an average duration of approximately 3 years enrolled in the current program, participants in the sample had failed to obtain or maintain privileges such as take-home or carry doses of methadone through abstaining from substances; thus, they remain on daily witnessed ingestion status. The reliability assessment conducted as part of the thesis found that the present sample of clients were able to recall past 30 day substance use, current psychiatric symptoms and, for the most part, characteristics of specific occasions of hydromorphone use with acceptable levels of reliability. While limitations to the present interview methods have been noted in previous chapters, the present research suggests that further substance use and psychiatric research with this population is feasible and likely to be reliable.

A second novel contribution of the thesis was that Study One was the first study to describe how a prescription opioid is used by individuals who go on to develop opioid problems, and the specific contexts (aka microenvironments) in which such use occurs. Knowledge of the use characteristics and microenvironment of an occasion of substance use, particularly for under-researched substances (Fischer, Rehm et al., 2008), is particularly important to

understanding substance use initiation, progression, and possible areas for prevention and intervention (DiClemente, 2003).

Third, the findings of Study One suggested that experience with hydromorphone use is prevalent among low-threshold MMT clients in Halifax, Nova Scotia, and it was found to be the most commonly preferred opioid of choice reported by participants. Interestingly, early, but not later, hydromorphone use characteristics varied between those who did and did not have an initial prescription for the substance. This study provides additional rationale and suggestions for further investigations in comparing hydromorphone and heroin use given the findings that indicate both substances may be used in a similar manner by some individuals, and for similar reasons.

Fourth, the main novel contribution to the literature of Study Two was that it was the first study to examine the relationship between current psychiatric symptoms and current substance use in MMT clients who have prescription opioid use histories. Further, it was also the first study to investigate the relationships between current psychiatric symptoms and current substance use for a variety of different psychiatric symptoms and a variety of different substances. It was found that prescription opioid users enrolled in a low-threshold MMT program had similar rates of psychiatric symptom reporting and current substance use to previously investigated populations of heroin users from more traditional, higher-threshold MMT programs, and largely heroin-dependent clients in low-threshold MMT programs. It was also found that non-prescribed benzodiazepine use, in particular, appears to be associated with a variety of

current mood and anxiety symptoms. In turn, generalized anxiety symptoms were found to be associated with non-prescribed benzodiazepine use. Current cocaine use, despite extensive research documenting its association with negative outcomes in MMT, was not found to be predictive of, or be predicted by, current psychiatric symptoms – at least not those examined in the present study.

The fifth main, novel contribution was that a large proportion (approximately 20%) of MMT clients in Study Two reported having current prescriptions for benzodiazepines. Although ongoing benzodiazepine use in MMT has been previously identified as a major clinical issue (e.g., Brands, Blake et al., 2008), no studies in the literature have evaluated differences in prescribed and non-prescribed benzodiazepine use and psychiatric symptoms in MMT clients. While the use of any benzodiazepines can be considered to be risky for any individual taking methadone (Caplehorn & Drummer, 2002; Wolff, 2002), Study Two found that it was non-prescribed benzodiazepine use in particular that was significantly associated with increased psychiatric symptoms.

7.2 General Limitations for Studies One and Two

Limitations of the present thesis studies have been discussed at length in the preceding chapters. However there are some possible limitations across both studies that are of particular note. First, although the test-retest reliabilities obtained for the thesis study measures were found to be acceptable overall, reliability for some variables was quite poor (e.g., presence of others during

hydromorphone use occasions, screening positive for some psychiatric symptoms). It is possible poor reliability for these few variables may have been be a result of the method of assessing reliability (e.g., influence of a second interviewer, recalling details during the first interview negatively influencing recall on the second interview), but it may also reflect issues with the study measures. For example, in heavy opioid users it is possible that the first use of one particular opioid medication is not well remembered because participants' opioid use is extensive and different opioids may be have been frequently substituted for each other based on availability. It is possible that only the occasions of first and most recent use of any opioid are particularly salient in the minds of this population and the interview questions regarding hydromorphone use were too specific. It is also possible that recall of specific opioid use occasions by individuals with extensive opioid use histories may be impaired due to the neurological effects associated with prolonged substance use (Schafer, Lucente, Rustine & Brown, 1994; Eber & Schmitt, 1997; Mintzer & Stitzer, 2002; Oliveira, Scheuer & Scivoletto, 2007). Previous research that found reliable recall for specific occasions of use asked participants to recall occasions of use that were quite recent (i.e., typically within the past month) and participants did not have as extensive substance use histories (Barrett et al., 2005). It is also possible that the relatively long duration of the study interviews (approximately two hours) were too exhaustive for participants and thus the resulting fatigue may have impaired some of their responses to study measures. Additionally, the test-retest reliability interval between the two interviews was relatively short. Additional

research is needed to determine if the reliability of participants recall will be maintained over longer intervals between interviews. Conclusions based on the current studies' results warrant some caution, and, as with all research, replication is needed to better establish the reliability and validity of the present findings.

A third limitation common to both studies was that a medical file review and assessment of pain were not conducted. Many MMT clients have pain (Rosenblum et al., 2003; Barry et al., 2009), and given the majority of participants received prescriptions for opioids (87.2%, *n*=68/78) in addition to using them without a prescription (98.7%, *n*=77/78), it is possible that pain may have been an important factor in their opioid use. It is also likely that some participants in the present sample had chronic pain conditions at the time of the interview. The connections between chronic pain and psychiatric symptoms, and between chronic pain and substance use, are well demonstrated (see Sections 4.4.3 and 6.3.3). Not being able to evaluate the possible mediating or moderating effects of pain with respect to opioid use behaviour and current issues faced by prescription opioid users in treatment limits the interpretation of the study results. However this study limitation also provides an interesting direction for future research.

A fourth important limitation to note across both studies was that the sample was relatively unique. The present sample was comprised of individuals who had extensive substance use histories and were also prescription opioid users who later entered a specialized treatment program for their opioid use.

The sample cannot be considered to be representative of all prescription opioid users, all individuals who develop problems with opioid medications, all individuals enrolled in MMT, or all individuals enrolled in low-threshold MMT. However, no studies to date have systematically and quantitatively examined how prescription opioid users use a particular prescription opioid and few studies to date have specifically evaluated prescription opioid users in treatment. Thus, the present studies still represent an important first step in describing this population and the nature of prescription opioid use. Further, the sample likely represents those who are unsuccessful in other MMT programs and likely have a number of treatment and service needs (e.g., housing, treatment of HIV, hepatitis, assistance to navigate criminal justice system; Marshall, 2004). Understanding how these individuals initiated into the use of an opioid, and current issues they face in treatment, has applications in the development of future research and interventions.

7.3 Future Directions of Research

There are a number of directions for future research in the area of prescription opioid use and issues faced by clients enrolled in MMT. Many of these have been discussed in preceding chapters, but directions that are likely to be most fruitful based on theory and clinical applications are outlined below.

First, establishing a standardized, well validated method to examine the microenvironment, or specific occasions of substance use has important

implications. Substances are frequently used in a polysubstance context (Barrett et al., 2006; Gossop et al., 2006; Leri et al., 2003) and concurrent use of substances can produce different subjective effects than when a substance is used in isolation (McCance-Katz, Kosten, & Jallow, 1998). However, substances are frequently studied by researchers individually. Improving understanding of occasions where individuals initiate into the use of a particular substance (or substances) is important in the development of effective prevention programs to delay or stop the onset of use of substances. Further investigations of specific substance use occasions would also assist in understanding how and why individuals continue to use substances despite negative consequences and/or risk of such consequences (i.e., through investigating specific occasions of more recent use). For example, by evaluating individuals' reasons for using a substance in different situations, important motivational aspects of substance use and/or risks associated with relapse could be further evaluated. Additionally, by systematically gathering data on specific use occasions, it would be possible to evaluate if the presence of certain factors (e.g., negative mood state, use of particular substances) are more likely to be associated with use, relapse to use, overdose, and/or with risky administration practices. Such knowledge is essential in the development and refinement of substance use interventions. For example, knowing motivational influences during an occasion of relapse is helpful in determining healthier replacement activities that also satisfy the motivations for why someone used a substance on that occasion. The present research formed an important basis to further refine the current occasions of substance use

assessment tool for use with individuals who have extensive substance use histories.

The present thesis research lacked a pain assessment measure and medical information (e.g., from health records) regarding participants' history of acute and/or chronic pain conditions. Future research investigating prescription opioid use should assess the influence of pain on how prescription opioids are used, and how pain may affect the ongoing psychiatric and substance use issues experienced by prescription opioid users enrolled in MMT. Of course, the study of pain is complex. For example, pain can present in acute and/or chronic forms, be cancer or non-cancer related, there are emotional as well as physical pain symptoms, and there is often a need to rule out somatic or factitious disorders. Additionally, the study of pain may be limited by types of information available for participants, such as incomplete information in health records, multiple health records held in several different jurisdictions, or the use of aliases by participants. However, there is potential for far-reaching implications and applications of such research to many different medical contexts. Pain is ubiquitous across different medical conditions and health care settings, and, as mentioned in Chapter One, opioid medications are frequently prescribed for pain, and concern about patients' use is common. Better understanding of the interplay between pain, opioid use, and development of substance use problems and psychiatric symptoms is greatly needed.

The third major direction for future research on the basis of the present research findings is further investigation of specific prescription opioids,

particularly hydromorphone. Most prescription opioid use studies to date aggregate prescription opioids as a class and do not assess the use of individual medications. While there are likely important methodological and practical reasons for doing this (see Section 2.2.3), prescription opioids vary greatly in formulation, onset of action, duration of action, side effects, and potency (Epstein et al., 2005). The present study, and previous research (e.g., Oviedo-Joekes et al., 2010), have demonstrated some interesting similarities between the use of hydromorphone and heroin. Further research examining how or why different individuals may choose to use, or prefer, different opioids could be particularly important in determining risk liabilities and approval of medications for market. Further, through comparing different opioids, which have different pharmacokinectic properties (e.g., μ-opioid receptor affinity, action on κ-opioid receptors), and different societal stigma regarding their use (e.g., heroin versus hydromorphone), insight could be gained in understanding how these different pharmacokinectic and social factors may interact in the development of a substance use problem.

The fourth major direction for future research is examining the association between benzodiazepine use and psychiatric symptoms in MMT clients. Despite many negative outcomes associated with ongoing use of many different substances in MMT, particularly for cocaine (Condelli et al., 1991; Stitzer & Chutuape, 1999), non-prescribed benzodiazepine use was associated with almost all psychiatric symptoms assessed. This pattern of relationships may have been found because the PDSQ primarily assesses a large number of

anxiety disorders and few disorders that, theoretically, would not be associated with benzodiazepine use. Additionally, the directionality of the association between benzodiazepine use and psychiatric symptoms is not clear. It could be the participants are attempting to self medicate their anxiety symptoms by using benzodiazepines, or that their benzodiazepine use is exacerbating or causing anxiety symptoms, or that there is an underlying vulnerability to both benzodiazepine use and anxiety symptoms. Regardless of the basis for the relationship, given the high risks associated with taking benzodiazepines while on MMT (e.g., Caplehorn & Drummer, 2002; Iguchi et al., 1993; Wolff, 2002), further investigations into this association (e.g., motivations to use benzodiazepines, investigations of specific occasions of use) could have important implications in terms of reducing the harms associated with benzodiazepine use and improving the quality of life of MMT clients (e.g., through reduction of psychiatric symptoms).

7.4 Clinical Implications

There are a number of clinical implications from the present thesis research. First, Study Two found that substance use and psychiatric issues faced by MMT clients with prescription opioid use histories were very similar to those documented in previous MMT research with heroin-using samples and high- or low-threshold treatment philosophies. That is, treatment needs previously documented for heroin users in traditional MMT programs (e.g., Darke

et al., 1993; Ward et al., 1998a; King & Brooner, 1999; Gelkopf et al., 2006) may also extend to this population of low-threshold MMT clients with prescription opioid use histories (e.g., need for mental health treatment, need for intervention to assist with reducing use/harms associated with use of other substances).

Second, the findings of the thesis studies suggest that screening MMT clients for mental health problems is particularly important to clinical practice. Regardless of whether the symptoms may be substance induced, related to a medical condition such as chronic pain or hepatitis C treatment, or reflect an underlying vulnerability to both psychiatric symptoms and substance misuse, MMT clients in the present sample are experiencing noted levels of psychiatric distress. Psychiatric comorbidity has been found to influence MMT outcome (e.g., Gelkopf et al., 2006) and given the high prevalence of psychiatric symptom reporting in the present sample, there is a demonstrated need to help clients manage their psychiatric symptoms. This may improve outcomes in the MMT program, improve clients' quality of life, and, in turn, possibly decrease harms associated with ongoing benzodiazepine use (e.g., risk of overdose).

Third, the present thesis findings suggest possible directions for future intervention development for MMT clients. Given that almost 90% of the sample reported receiving a prescription for opioids in their lifetime, and previous research has found over one third of MMT clients have ongoing severe chronic pain (Rosenblum et al., 2003), it is possible that chronic pain conditions are also prevalent in the present sample. While additional research is needed, assessment of chronic pain and psychoeducation regarding how to manage

chronic pain (beyond opioid medication treatment) could be beneficial to this population in improving their quality of life. Similarly, a large percentage of the most recent use occasions of hydromorphone (75.0%, *n*=57/76) were found to have occurred after entry to the current MMT program, and the most recent use characteristics were similar to those previously found to be harmful in using other substances (e.g., injecting , co-using with other substances). Possible interventions to reduce such harms and/or reduce possible reasons for continued use in MMT (e.g., to manage pain, reduce withdrawal symptoms while methadone dose is escalated) could be beneficial in reducing ongoing opioid use and in improving clients' quality of life.

Additionally, ongoing benzodiazepine use in MMT was associated with anxiety symptoms (and vice versa). Developing interventions to assess whether improving anxiety management skills may also assist in decreasing concurrent substance use is a particularly interesting future clinical direction. Similarly, assisting clients with benzodiazepine tapering (Ciraulo et al., 2005) and/or providing psychoeducation to clients regarding the risks associated benzodiazepine use (e.g., overdose) and rebound anxiety symptoms could potentially have beneficial long-term effects on anxiety symptoms and are areas for future evaluative interventions. A good starting point for the development of such an intervention may be Otto and Pollack's (2009) cognitive-behavioural treatment program for benzodiazepine discontinuation. While it has not been assessed for use with individuals with substance use disorders, it has been found

to be more effective for the discontinuation benzodiazepine use than a medically-supervised taper with individuals with panic disorder (Otto et al., 1993)

A fourth implication of the present thesis findings is how they may relate to the proposed revisions for the upcoming version of the *DSM*. One of the proposed modifications is the possible addition of "cross cutting" symptom assessment (APA, 2010a). That is, symptoms of depression, anxiety and substance use would be assessed using standardized measures (APA, 2010b), regardless of the individual's primary diagnosis. As mentioned previously in this thesis, the present thesis sample is highly specialized and not representative of all individuals with substance use disorders, or psychiatric disorders. However, the present thesis results support such comprehensive, ongoing assessment. As already mentioned relatively high proportions of this low-threshold MMT sample were currently reporting psychiatric symptoms, particularly depression and anxiety, as well as substance use. Use of a standardized, widely-used measure to regularly assess and monitor such symptoms would be particularly helpful not only in identifying clients in need of additional supports but also to compare different clinical populations and clinical interventions to each other. This may assist in improving allocation of scarce treatment resources across mental health and substance use programs and in the evaluation of such clinical interventions and programming.

7.5 Conclusion

The main novel findings of the thesis were that: 1) Many substance use and psychiatric symptom variables are able to be reliably recalled by a unique population of substance-using individuals enrolled in a low-threshold MMT program; 2) Investigations of specific prescription opioids (instead of the general class) is possible, and can reveal interesting information regarding the contexts of initiation and more recent use. Further, many of these details can be reliably recalled by prescription opioid users; 3) Hydromorphone is a prevalent and highly favoured prescription opioid in low-threshold MMT clients in Halifax, Nova Scotia. There was considerable variability in characteristics of hydromorphone use initiation among individuals enrolled in low-threshold MMT, and these varied by initial prescription status. However, later use of hydromorphone was remarkably consistent across individuals and shared some characteristics previously documented for heroin use; 4) Prescription opioid users in MMT report high rates of current psychiatric symptoms and substance use. Current psychiatric symptoms and substance use appear to be related; 5) Notably, non-prescribed benzodiazepine use predicted depression and anxiety symptoms and general anxiety predicted non-prescribed benzodiazepine use.

While the present research results may not be representative of all prescription opioid users, or all MMT clients, novel findings were obtained with a unique and vulnerable population, specifically with respect to how prescription opioids may be used during specific occasions, and in describing psychiatric and

substance use issues faced by prescription opioid users enrolled in low-threshold MMT.

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APPENDIX A. DEMOGRAPHIC AND METHADONE

HISTORY QUESTIONS

Italics indicate instructions; ***Bold*** *indicates what the interviewer should say.*

*Interviewer:*_____ *Subject ID: Date:*_____ *(mm/dd/yy)*

1. *Gender*: M / F *(circle one)*
2. **How old are you**? *Age:*_____years
3. **What is your ethnicity**: _____

4. What is the highest level of education you have completed *(tick only one; also write in grade/ if completed GED; received some training but did not complete a certain level)*
____ Elementary School
____ Junior High School
____ High School
____ Trade School
____ Community College
____ University
____ Other

5. What is your Marital Status*(tick only one)*
____ Single (never married)
____ Married/Cohabitating
____ Separated/Divorced
____ Widowed

6. What is your Annual Income, stop me when I get there *(read the below options followed by "***per year***")*
____ $0 - $5,000
____ $5, 001-10, 000
____ $10, 001- $20 000
____ $20,001 to $30,000
____ $30,001 to $40,000
____ $40,001 to $50,000
____ $50,001 to $60,000
____ $60,001 to $70,000
____ $70,001 to $80,000
____ more than $80,000

Prescription Medication Questions
I am now going to ask you some questions about your use of prescription medications.

Are you currently taking any medication prescribed by a doctor for any behavioural, emotional or personal difficulties you may have experienced; for example, anxiety, mood, sleep and attention?
Yes ____ No ____
***if they say "nothing", confirm they are prescribed methadone currently:* **"so only a methadone prescription?"**

Please tell me the medications that are currently being prescribed to you for these reasons.

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Are all these medications prescribed by the doctor at Direction 180?*Circle:Yes No*
If not all from Direction 180 Dr/Dr. Fraser specify which are from a non-Direction 180 doctor and relationship with that doctor (e.g., family dr, ER dr, etc). Summarize all current prescriptions to participant

I am now going to ask you some questions about your use of methadone.

Methadone Prescription Drug Interview Schedule	
How old were you when methadone was initially prescribed?	*Age:* _____
In total, for how many months/years have you been prescribed methadone throughout your lifetime?	_____*Years* _____*Months*
Have you been taking methadone consecutively throughout this time period, or have you gone on and off of it? *(if on/off then write down time line)*	

How much methadone are you currently prescribed? **What is your status at Direction 180? Are you on daily ingestion, getting it at the community pharmacy, have carries** *(if carries: for how many days do you get to carry a dose?)* **or something else?** **Have you ever received a prescription for methadone from another program apart from Direction 180?** *If yes, get details of what programs, age when enrolled in program, and how long in each program, how long between each program→ create a timeline* if necessary	*Dose:* *Status at Direction 180:* *Other programs/details:*
How many days in the past 30 days did you use methadone?	
On how many of days in the past 30 days have you used methadone exactly as prescribed?	*Number of days:_____*
When was the last time you took methadone?	

APPENDIX B. SUBSTANCE USE HISTORY AND CURRENT USE MEASURES[18]

Italics indicate instructions; ***Bold*** *indicates what the interviewer should say.*

I am now going to ask you some more information about your drug use in general.

Have you ever smoked cigarettes? *Yes / No (If No, skip to Drug Use Questionnaire Table)*
At what age did you first try smoking cigarettes? _____*years*

Have you smoked any cigarettes in the last 30 days? *Yes / No*
If yes, **how many days? _____**

When was the last time you smoked cigarettes? *(Age is sufficient if not used in past 12 months)* **_____**

[18] *Prescription Drug Use History was administered prior to Substance Use History and Current Use measures.*

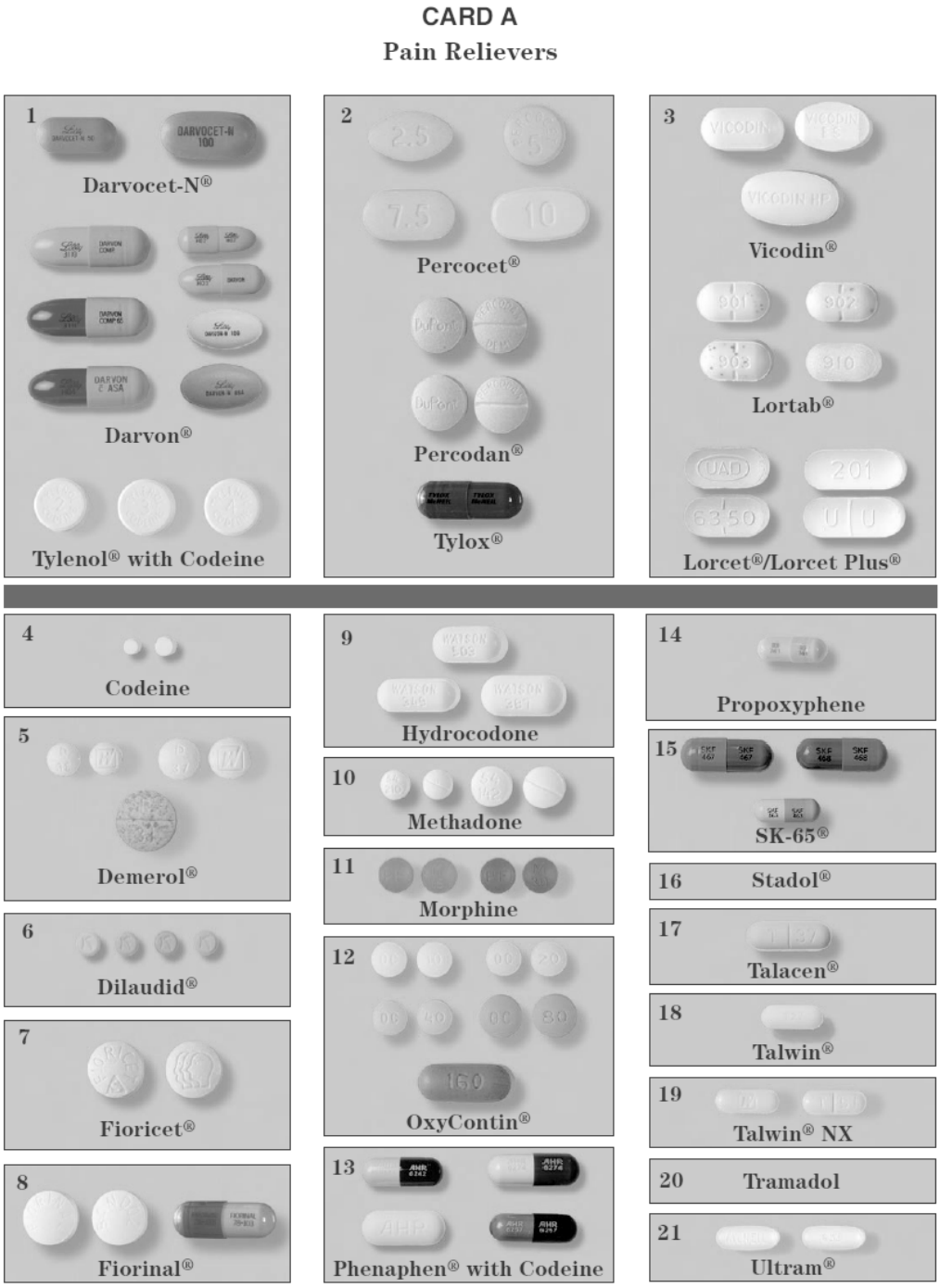
I am now going to read you a list of substances. Please tell me yes or no for whether you have ever used each substance.
(*Go down entire list of substances and indicate ✓ or ✗ for each substance; then, for each substance they have used work across the row asking each question at the top of the column, use clarifications in brackets if necessary)*

DRUG HISTORY CHART

Substance	*Ever used Y(✓) N(✗)*	**How old were you the first time you used _____?**	**In the past 30 days, on how many days did you use____?**	**When was the last time you used _____?** *(Age is sufficient, if not used in past 12 months)*
Alcohol				
Cannabis (pot, marijuana, hash)				
Powder Cocaine (coke, blow, snow)				
Crack				
Amphetamines/ Crystal Meth (methamphetamine; *clarify this is **NOT prescription stimulants***)				
Heroin (*clarify **NOT "synthetic heroin"***)				
MDMA/MDA (ecstasy, E, X)				
GHB (Liquid E)				
Ketamine (Special K)				
Magic Mushrooms (shrooms, psilocybin)				
LSD (acid, blotters, tabs)				
Mescaline				
PCP (angel dust)				
Salvia				

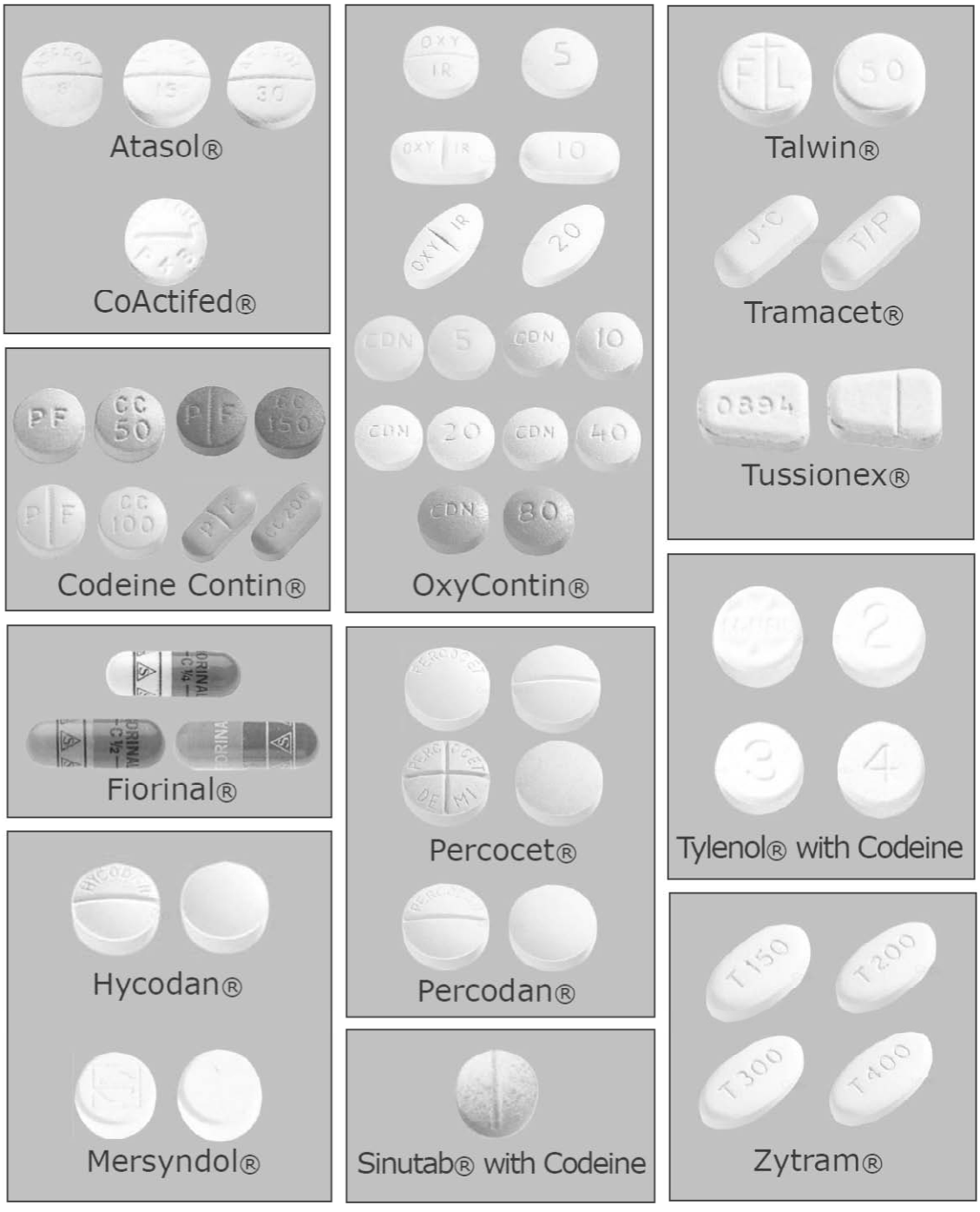
Inhalants such as nitrous oxide, whippets, poppers, amyl nitrate, rush, etc *(circle/write which)*				
Peyote				
Opium				
Have you ever used any other substance in your life that I have not asked you about, including any other prescription drugs in excess of directions or that you took only for the experience of feeling it caused? *(List)*				

APPENDIX C. PRESCRIPTION DRUG PHOTOS[19]



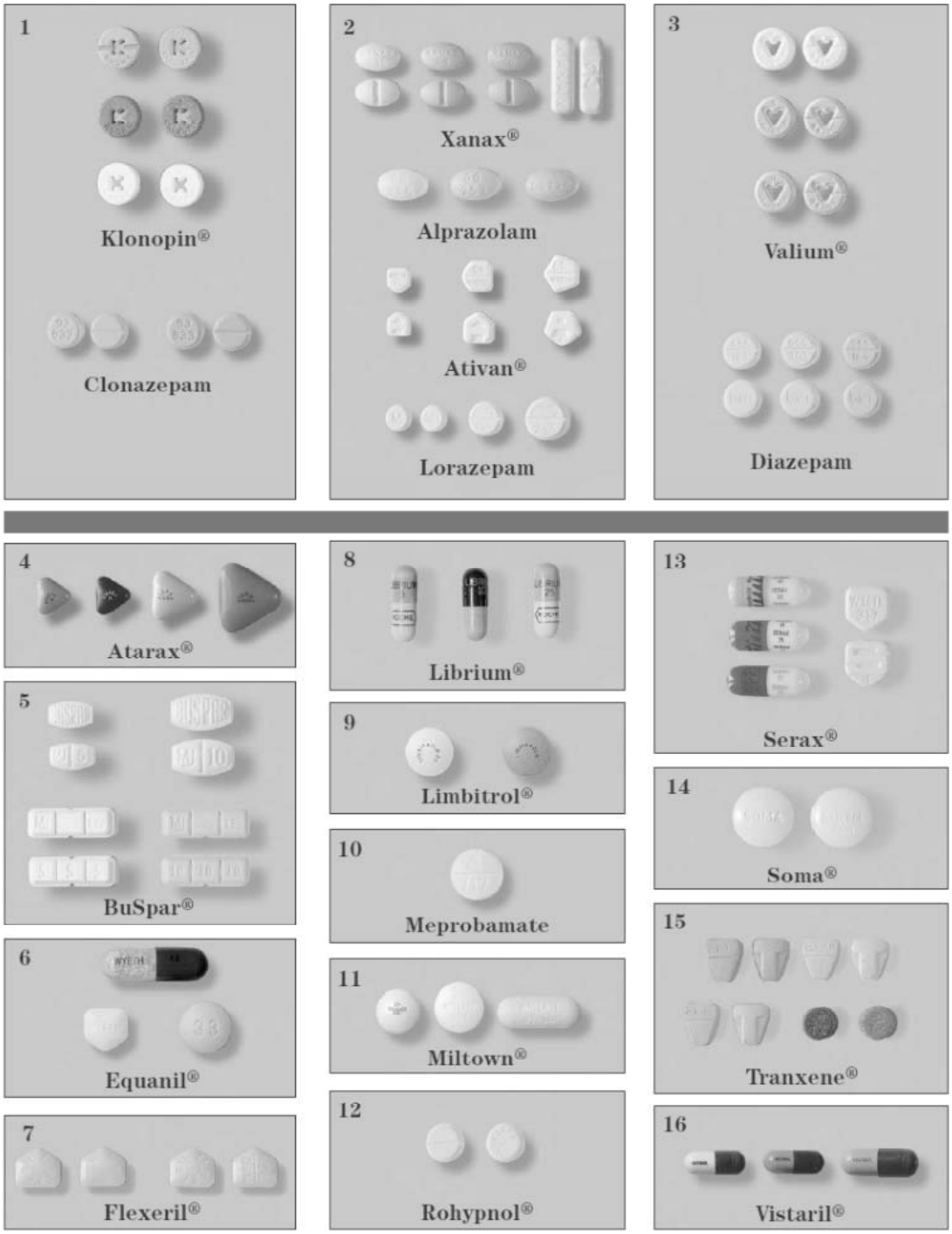
[19] Note:; images of the cards have been slightly reduced in size to fit within the current page formatting requirements

Pain Relievers



CARD B

Tranquilizers

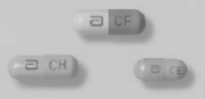


CARD D
Sedatives

1

(picture not available)
Methaqualone (includes Sopor®, Quaalude®)

2



Nembutal® Sodium

(picture not available)
Pentobarbital

Seconal®

(picture not available)
Secobarbital

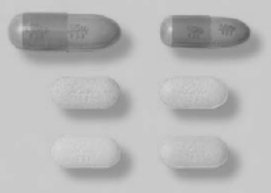
(picture not available)
Butalbital

3

Restoril®

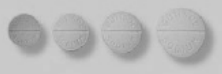
Temazepam

4



Amytal®

5



Butisol®

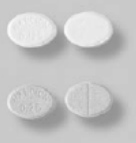
6

Chloral Hydrate

7

Dalmane®

8



Halcion®

9

Phenobarbital

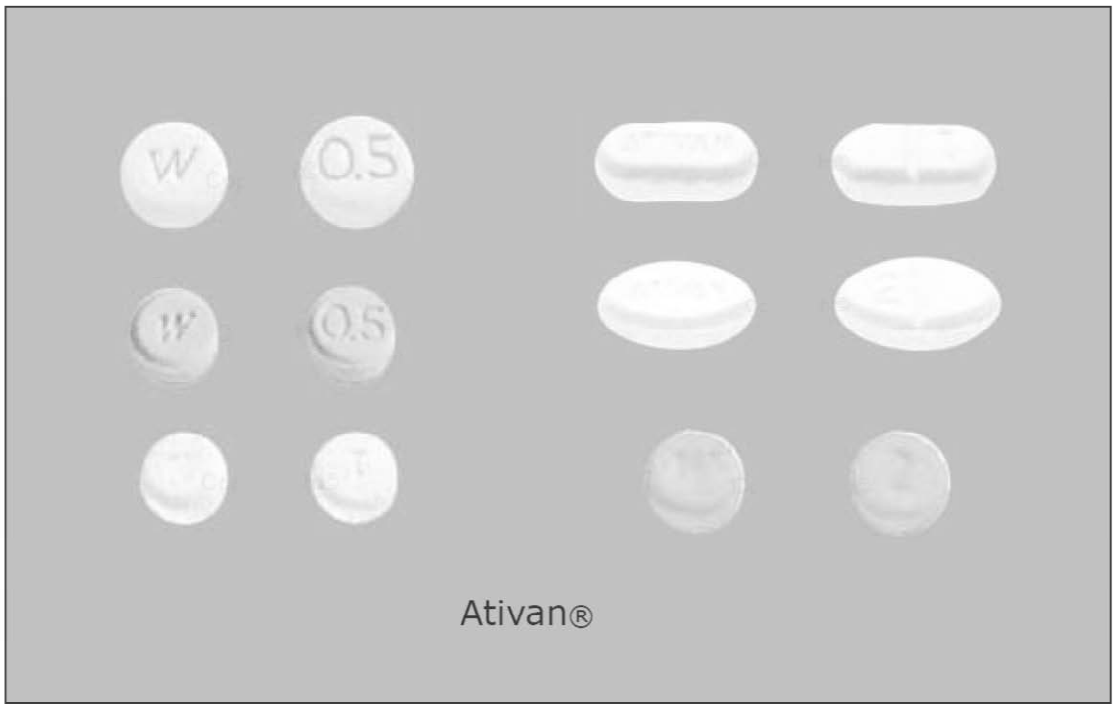
10

Placidyl®

11

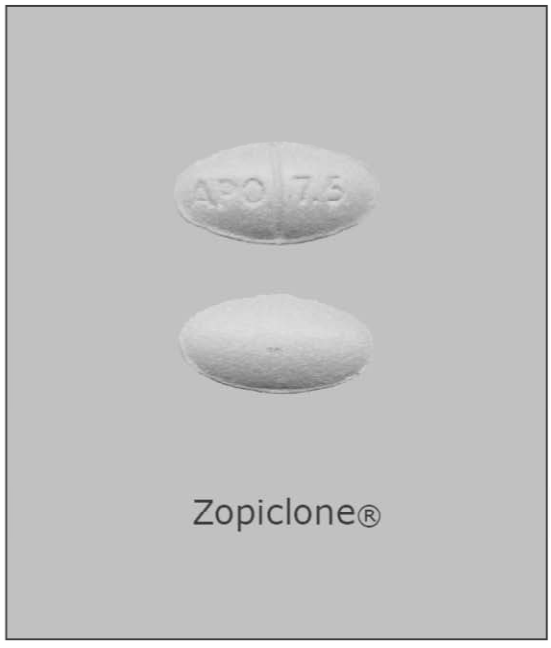
Tuinal®

Tranquilizers/Sedatives



Ativan®

Bellergal®



Zopiclone®

APPENDIX D. PRESCRIPTION DRUG USE HISTORY

MEASURES

Italics indicate instructions; ***Bold*** *indicates what the interviewer should say.*

In addition to *(list current prescriptions)***, have you ever had a prescription for any of the following substances in your lifetime?** *(check)*

- ☐ Tranquilizers (Anti-anxiety) or Sedatives (sleeping pills) such as Valium, Ativan, benzodiazepines, Quaaludes, Halcion)

- ☐ Pain Releivers or Opioids such as oxycontin, dilaudid, percocet, Tylenol 3 or 4

If yes to above: **Now I'm going to show you some pictures of these types of medications.**

Some of the medications come in different forms. Can you tell me if you recognize the medications that you were prescribed? *(show pill cards)* **Are there any other pills on these pages that you remember having a prescription for, that you didn't already mention?**

note: make sure participants were "prescribed" each medication and haven't just "used" it. If at all in doubt, ask: "*did you have a prescription for xxxx?"***

List all previous prescriptions named by the participant:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

If participant indicates yes to any of benzodiazepines/tranquilizers or opioids then write P next to the benzodiazepine and opioid categories on Drug History chart

NON-PRESCRIBED PRESCRIPTION DRUG USE

Please tell me all prescription medications you have used throughout your life without a prescription:

Have you ever used Prescription Tranquilizers (Anti-anxiety) or Sedatives (sleeping pills) such as Valium, Ativan, benzodiazepines, Quaaludes, Halcion without a prescription?

(circle) *YES* *NO*

Now I'm going to show you some of the same photos I just showed you. Can you tell me if you recognize any tranzquilizer/benzodiazepine/sedative medications that you took without a prescription? *Write which medications in the space below or check (use pill cards)*

LIST OF MAIN TRANQUILIZERS / SEDATIVES
_____ Alprazolam (Xanax, Niravam)
_____ Amobarbital (Amytal)
_____ Butabarbital sodium (Busitol)
_____ Buspirone (BuSpar, Buspinol)
_____ Carisoprodol (Soma)
_____ Clorazepate (Tranxene)
_____ Chloral hydrate (Noctec)
_____ Chlordiazepoxide (Librium, Limbitrol)
_____ Clonazepam (Klonopin, Rivotril)
_____ Cyclobenzaprine HCl (Flexeril)
_____ Diazepam (Valium)
_____ Ethchlorvynol (Placidyl)
_____ Flurazepam (Dalmane)
_____ Flunitrazepam (Rohypnol)
_____ Hydroxyzine (Atarax, Vistaril)
_____ Lorazepam (Ativan)
_____ Meprobamate (Equanil, Miltown)
_____ Methaqualone (Sopor, Quaalude)
_____ Oxazepam (Serax)
_____ Pentobarbital Sodium (Nembutal)
_____ Phenobarbital (PB)
_____ Temazepam (Restoril)
_____ Triazolam (Halcion, Novodorm, Songar)
_____ Secobarbital (Seconal)
_____ Secobarbital sodium/amobarbital sodium (Tuinal)

Other tranquilizer/sedative medications? Others not in photos?

_____
_____
_____
_____
_____
_____

(if participant indicates yes to any of the benzodiazepines/tranquilizers then write N next to the benzodiazepine category on Drug History chart)

***prompt for any current or past medication prescriptions held- did they ever use it without a prescription?*

Have you ever used Pain Relievers or prescription opioids such as oxycontin, dilaudid, percocet, Tylenol 3 or 4 without a prescription?

(circle) YES NO

If yes: **Now I'm going to show you some of the same photos I just showed you. Can you tell me if you recognize any opioid medications that you took without a prescription?** *Write which medications in the space below or check*

LIST OF MAIN PRESCRIPTION OPIODS:
_____ *Butalbital (Fioricet, Fiorinal)*
_____ *Butorphanol tartrate (Stadol)*
_____ *Co-codamol (Tylenol with Codeine, Tylenol 3, Phenaphen with Codeine)*
_____ *Codeine*
_____ *Dextropropoxyphene (Darvocet-N)*
_____ *Hydrocodone (Vicodin, Lortab, Lorcet/ Lorcet Plus)*
_____ *Hydromorphone (Dilaudid)*
_____ *Meperidine (Demerol)*
_____ *Methadone (Dolophine, Methadose)*
_____ *Morphine*
_____ *Oxycodone (Percocet, Tylox, Percodan, Percolone,OxyContin)*
_____ *Pentazocine (Talacen, Talwin, Talwin NX)*
_____ *Propoxyphene (Darvon, Dolene, SK-65)*
_____ *Tramadol (Ultracet, Ultram)*
Other opioid medications? Others not in photos?

_____
_____
_____
_____
_____
_____

_____
_____
_____
_____
_____
_____

(if participant indicates yes to any opioids then write N next to the opioid category on Drug History chart

***prompt for any current or past medication prescriptions held- did they ever use it without a prescription?*

I am now going to ask you a few more questions about your use of prescription medications.
Grey areas indicate questions to ask if person has a current prescription

PRESCRIPTION DRUG HISTORY CHART

Substance *Write C if currently prescribed medications in this class* *Write P if participant used medication class with a prescription* *Write N if participant used medication class without a prescription* * * * * * * * *For each class start with confirming previous details:* *If P and N:* **"So for ___, you have been prescribed these as well as taken these without a prescription"** *If only P or only N:* **"So ____, you have only been prescribed/ taken _____ without a prescription; you never took ____ without a prescription/ had a prescription for _____"**	**How old were you the first time you used_____?**		**In the past 30 days, on how many days did you use ___?**	*CURRENT prescriptions:* **In the past 30 days, on how many days did you use ____ exactly as prescribed?**	**When was the last time you used ____?** *(Age is sufficient, if not used in past 12 months)*
	Were you prescribed the medication at this time? *P/N*	**What was the first ____ that you used that first time?**			
Tranquilizers/ Benzodiazepines *(e.g., valium, diazepam, clonazepam NOT Seroquel)*		*Drug*			*Drug*
Prescription Opioids so not methadone, *if relevant**: not heroin,** if relevant* ***not opium*** *if relevant*		*Drug*			*Drug*

★★★**“What was the primary opioid of choice that you use or used in your life?***(to clarify:* ***“opioid means pain reliever substances; so medications like Tylenol 3 or codeine, or a substance like heroin or opium”)”*****?**

_____

APPENDIX E. POLYSUBSTANCE HYDROMORPHONE USE INTERVIEW

I am now going to ask you some questions about your used of Dilaudid/hydromorphone *(use name of hydromorphone medication(s) they report using)*
Grey areas indicate questions to ask if ever had a prescription for medication

Specify drug name:	
Why did you receive your prescription of XXXX? *If unsure, ask if it was prescribed for pain. If so- what was the injury(ies)?*	
How old were you when xxxx was initially prescribed?	*Age:* _____
If prev. indicated they took xxxx without a prescription: **How old were you the first time you took xxxx? Were you prescribed xxxx at this time?** *(write P if prescribed, N if not prescribed)*	
In total, for how many months/years have you been prescribed xxxx throughout your lifetime? What age(s) were you?	_____*Years* _____*Months* _____
Have you been taking xxxx consecutively throughout this time period, or have you gone on and off of it?*(if on/off then write down time line*)	
How many days in the past 30 days did you use xxxx?	
If currently prescribed: **On how many of days in the past 30 days have you used xxxx exactly as prescribed?**	*Number of days:*_____
When was the last time you took xxxx?	*Age:* _____ _____/_____/_____ *. day / month / year*

Think about the LAST time you used xxxx *(prompt with info from earlier in interview).* **Can you remember that instance?** *(if details can not be recalled, ask them about the last recalled time that the substance was used)* (*if can't remember last use and using alternate date ask:* ***When was this?;*** *otherwise write in last use age)* **Do you remember where you were this last time you used xxxx?** Who were you with? Get an e*stimate of number of people*; *# males and females, get relationship (friend, romantic partner, uncle, etc))* Were you the only person using xxxx? *Get # of people also using substance,, # males and females* **What was the primary purpose for using xxxx during this last session?** *(use Purpose Scale Card to clarify)*	*When:*__________________ *Where:*__________________ *With Who:*__________________ *Only person using xxxx?*__________ *Purpose of using xxxx (use Purpose Scale card after)* ____________________________ ________________________
Was xxxx the only substance you were using or were you also using and/or experiencing effects from other substances at the same time? *If yes,* **what other substances were you using with xxxx on this occasion? Any thing else?** *If used xxxx in isolation only ask a) and b) question then dminister to tobacco questions* **Okay, walk me through this session. What substance did you use first?** a) **How much _____ did you consume at this point in time?** *b)* **How did you use _____ at this point in time (e.g., eat/drink, snort, inject, etc)** *If substance used different ways (e.g., snort & inject) then list how much of substance was used each way.* **What substance did you use next?** c) **How much _____ did you consume at this point in time?**	*Other Substances: Yes No* *Other Drug* / *Amount* / *Order* / *Admin Route* ______ ______ ____ ______ ______ ______ ____ ______ ______ ______ ____ ______ ______ ______ ____ ______ ______ ______ ____ ______ ______ ______ ____ ______ ______ ______ ____ ______ ______ ______ ____ ______

d) **How did you use _____at this point in time** (e.g., eat/drink, snort, inject, etc) *If substance used different ways (e.g., snort & inject) then list how much of substance was used each way.* *Use ® to indicate a repeated pattern of use (e.g., alcohol, cannabis, alcohol, cannabis, alcohol…),* *Continue until entire pattern of use during session is recorded.* **Were you also smoking tobacco? If yes: Were you smoking more, less, or the same amount of tobacco compared to usual?** *(circle)*	*Tobacco: None More Less Same (circle)*

Think about the FIRST time you used xxxx *(prompt with info from earlier in interview).* **Can you remember that instance?** *(if details can not be recalled, ask them about the earliest recalled time that the substance was used)*
(*if can't remember first use and using alternate date ask:* ***When was this?;*** *otherwise write in last use age)*
Do you remember where you were this first time you used xxxx?
Who were you with? Get an e*stimate of number of people*; *# males and females, get relationship (friend, romantic partner, uncle, etc))*
Were you the only person using xxxx? *Get # of people also using substance,, # males and females*
What was the primary purpose for using xxxx during this first session? *(use Purpose Scale Card to clarify)*

Was xxxx the only substance you were using or were you also using and/or experiencing effects from other substances at the same time?
If yes, **what other substances were you using with xxxx on this occasion? Any thing else?**

If used xxxx in isolation only ask a) and b) question then Administer to tobacco questions
Okay, walk me through this session. What substance did you use first?
e) **How much _____ did you consume at this point in time?**
f) **How did you use _____ at this point in time (e.g., eat/drink, snort, inject, etc)** *If substance used different ways (e.g., snort & inject) then list how much of substance was used each way.*
What substance did you use next?
g) **How much _____ did you consume at this point in time?**
h) **How did you use _____at this point**

*When:*_____

*Where:*_____

*With Who:*_____

*Only person using xxxx?*_____

Purpose of using xxxx (use Purpose Scale card after)

_____
_____

Other Substances: Yes No

Other Drug	*Amount*	*Order*	*Admin Route*

in time (e.g., eat/drink, snort, inject, etc) *If substance used different ways (e.g., snort & inject) then list how much of substance was used each way.* *Use ® to indicate a repeated pattern of use (e.g., alcohol, cannabis, alcohol, cannabis, alcohol…),* *Continue until entire pattern of use during session is recorded.* **Were you also smoking tobacco? If yes: Were you smoking more, less, or the same amount of tobacco compared to usual?** *(circle)*	*Tobacco: None More Less Same (circle)*

APPENDIX F. MODIFIED PDSQ MEASURE

This form asks you about emotions, moods, thoughts, and behaviours. For each question, tell me *Yes* if it describes how you have been acting, feeling, or thinking. If the item does not apply to you then tell me No. Please answer every question.
(read all questions to participant)

Yes	*No*		**DURING THE PAST 2 WEEKS…**
_Y_	_N_	1.	…did you feel sad or depressed?
_Y_	_N_	2.	…did you feel sad or depressed for most of the day, nearly every day?
_Y_	_N_	3.	…did you get less joy or pleasure from almost all of the things you normally enjoy?
_Y_	_N_	4.	…were you less interested in almost all of the activities you are usually interested in?
_Y_	_N_	5.	…was your appetite significantly *smaller* than usually nearly every day?
_Y_	_N_	6.	…was your appetite significantly *greater* than usual nearly every day?
_Y_	_N_	7.	…did you sleep at least 1 to 2 hours *less* than usual nearly every day?
_Y_	_N_	8.	…did you sleep at least 1 to 2 hours *more* than usual nearly every day?
_Y_	_N_	9.	…did you feel very jumpy and physically restless, and have a lot of trouble sitting calmly in a chair, nearly every day?
_Y_	_N_	10.	…did you feel tired out nearly every day?
_Y_	_N_	11.	…did you frequently feel guilty about things you have done?
_Y_	_N_	12.	…did you put yourself down and have negative thoughts about yourself nearly every day?
_Y_	_N_	13.	…did you feel like a failure nearly every day?
_Y_	_N_	14.	…did you have problems concentrating nearly every day?
_Y_	_N_	15.	…was decision making more difficult than normal nearly every day?
_Y_	_N_	16.	…did you frequently think of dying in passive ways like going to sleep and not waking up?
_Y_	_N_	17.	…did you wish you were dead?
_Y_	_N_	18.	…did you think you'd be better off dead?
_Y_	_N_	19.	…did you have thoughts of suicide, even though you would not really do it?
_Y_	_N_	20.	…did you seriously consider taking your life?
_Y_	_N_	21.	…did you think about a specific way to take your life?

_Y_	_N_	22.	…Have you *ever experienced* a traumatic event such as

combat, rape, assault, sexual abuse, or any other extremely upsetting event?

_Y_	_N_	23.	…Have you *ever witnessed* a traumatic event such as rape, assault, someone dying an accident, or any other extremely upsetting incident?

Yes	*No*		**DURING THE PAST 2 WEEKS…**
_Y_	_N_	24.	…did thoughts about a traumatic event frequently pop into your mind?
_Y_	_N_	25.	…did you frequently get upset because you were thinking about a traumatic event?
_Y_	_N_	26.	…were you frequently bothered by memories or dreams of a traumatic even?
_Y_	_N_	27.	…did reminders of a traumatic event cause you to feel intense distress?
_Y_	_N_	28.	…did you try to block out thoughts or feelings related to a traumatic event?
_Y_	_N_	29.	…did you try to avoid activities, places, or people that reminded you of a traumatic event?
_Y_	_N_	30.	…did you have flashbacks, where it felt like you were reliving a traumatic event?
_Y_	_N_	31.	…did reminders of a traumatic event make you shake, break out into a sweat, or have a racing heart?
_Y_	_N_	32.	…did you feel distant and cutoff from other people because of having experienced a traumatic event?
_Y_	_N_	33.	…did you feel emotionally numb because of having experienced a traumatic event?
_Y_	_N_	34.	…did you give up on goals for the future because of having experienced a traumatic event?
_Y_	_N_	35.	…did you keep your guard up because of having experienced a traumatic event?
_Y_	_N_	36.	…were you jumpy and easily startled because of having experienced a traumatic event?

Yes	*No*		**DURING THE PAST 2 WEEKS…**
_Y_	_N_	37.	…did you often go on eating binges (eating a *very large* amount of food very quickly over a short period of time)?
_Y_	_N_	38.	…did you often feel you could not control how much you were eating during an eating binge?
_Y_	_N_	39.	…did you go on eating binges during which you ate so much that you felt uncomfortably full?
_Y_	_N_	40.	…did you go on eating binges during which you ate a large amount of food even though you didn't feel hungry?
_Y_	_N_	41.	…did you eat alone during an eating binge because you were embarrassed by how much you were eating?
_Y_	_N_	42.	…did you go on eating binges and then feel disgusted with yourself afterward?

_Y_	_N_	43.	…were you very upset with yourself because you were going on eating binges?
_Y_	_N_	44.	…to prevent gaining weight from an eating binge did you go on strict diets or exercise excessively?
_Y_	_N_	45.	…to prevent gaining weight from an eating binge did you force yourself to vomit or use laxatives or water pills?
_Y_	_N_	46.	…was your weight, or the shape of your body, one of the most important things that affected your opinion of yourself?
Yes	*No*		**DURING THE PAST 2 WEEKS…**
_Y_	_N_	47.	…did you worry obsessively about dirt, germs, or chemicals?
_Y_	_N_	48.	…did you worry obsessively that something bad would happen because you forgot to do something important---like locking the door, turning off the stove, or pulling out the electrical cords of appliances?
_Y_	_N_	49.	…were there things you felt compelled to do over and over (for at least ½ hour per day) that you could not stop doing when you tried?
_Y_	_N_	50.	…were there things you felt compelled to do over and over even though they interfered with getting other things done?
_Y_	_N_	51.	…did you wash and clean yourself or things around you obsessively and excessively?
_Y_	_N_	52.	…did you obsessively and excessively check things or repeat actions over and over again?
_Y_	_N_	53.	…did you count things obsessively or excessively?
Yes	*No*		**DURING THE PAST 2 WEEKS…**
_Y_	_N_	54.	…did you get very scared because your heart was beating fast?
_Y_	_N_	55.	…did you get very scared because you were short of breath?
_Y_	_N_	56.	…did you get very scared because you were feeling shaky or faint?
_Y_	_N_	57.	…did you get sudden attacks of intense anxiety or fear that came on from the blue, for no reason at all?
_Y_	_N_	58.	…did you get sudden attacks of very intense anxiety or fear during which you thought something terrible might happen, such as your dying, going crazy, or losing control?
_Y_	_N_	59.	…did you have sudden, unexpected attacks of anxiety during which you had three or more of the following symptoms: heart racing or pounding, sweating, shakiness, shortness of breath, nausea, dizziness, or feeling faint?
_Y_	_N_	60.	…did you worry a lot about having unexpected anxiety attacks?
_Y_	_N_	61.	…did you have anxiety attacks that caused you to avoid certain situations or to change your behavior or normal routine?

Yes	*No*		**DURING THE PAST 2 WEEKS…**
_Y_	_N_	62.	…did things happen that you knew were true, but that other people told you were your imagination?
_Y_	_N_	63.	…were you convinced that other people were watching you, talking about you, or spying on you?
_Y_	_N_	64.	…did you think that you were in danger because someone was plotting to hurt you?
_Y_	_N_	65.	…did you think that you had special powers that other people didn't have?
_Y_	_N_	66.	…did you think that some outside force or power was controlling your body or mind?
_Y_	_N_	67.	…did you hear voices that other people didn't hear, or see things that other people didn't see?

NOTE: MOST OF THE FOLLOWING QUESTIONS REFER TO THE PAST MONTH

Yes	*No*		**DURING THE PAST MONTH…**
_Y_	_N_	68.	…did you regularly avoid any situations because you were afraid they'd cause you to have an anxiety attack?
		69.	…did any of the following make you feel fearful, anxious, or nervous because you were afraid you'd have an anxiety attack in the situation?
_Y_	_N_	a.	going outside far away from home
_Y_	_N_	b.	being in crowded places
_Y_	_N_	c.	standing in long lines
_Y_	_N_	d.	being on a bridge or in a tunnel
_Y_	_N_	e.	traveling on a bus, train, or plane
_Y_	_N_	f.	driving or riding in a car
_Y_	_N_	g.	being home alone
_Y_	_N_	h.	being in wide-open spaces (like a park)
_Y_	_N_	70.	…did you almost always get very anxious as soon as you were in any of the above situations?
_Y_	_N_	71.	...did you avoid any of the above situations because they made you feel anxious or fearful?

Yes	*No*		**DURING THE PAST MONTH…**
_Y_	_N_	72.	...did you worry about embarrassing yourself in front of others?
_Y_	_N_	73.	...did you worry a lot that you might do something to make people think that you were stupid or foolish?
_Y_	_N_	74.	...did you feel very nervous in situations where people might pay attention to you?
_Y_	_N_	75.	...were you extremely nervous in social situations?
_Y_	_N_	76.	...did you regularly avoid any situations because you were afraid you'd do or say something to embarrass yourself?
		77.	...did you worry a lot about doing or saying something to embarrass yourself in any of the following situations?

_Y_	_N_	a.	public speaking
_Y_	_N_	b.	eating in front of other people
_Y_	_N_	c.	using public restrooms
_Y_	_N_	d.	writing in front of others
_Y_	_N_	e.	saying something stupid when you were with a group of people
_Y_	_N_	f.	asking a question when in a group of people
_Y_	_N_	g.	business meetings
_Y_	_N_	h.	parties or other social gatherings
_Y_	_N_	78.	…did you almost always get very anxious as soon as you were in any of the above situations?
_Y_	_N_	79.	...did you avoid any of the above situations because they made you feel anxious or fearful?

Yes	*No*		**DURING THE PAST MONTH...**
_Y_	_N_	80.	...did you think that you were drinking too much?
_Y_	_N_	81.	...did anyone in your family think or say that you were drinking too much, or that you had an alcohol problem?
_Y_	_N_	82.	...did friends, a doctor, or anyone else think or say that you were drinking too much?
_Y_	_N_	83.	...did you think about cutting down or limiting your drinking?
_Y_	_N_	84.	...did you think that you had an alcohol problem?
_Y_	_N_	85.	...because of your drinking did you have problems in your marriage; at your job; with your friends or family; doing household chore; or in any other important areas of your life?

Yes	*No*		**DURING THE PAST MONTH…**
_Y_	_N_	86.	...did you think that you were using drugs too much?
_Y_	_N_	87.	...did anyone in your family think or say that you were using drugs too much, or that you had a drug problem?
_Y_	_N_	88.	...did friends, a doctor, or anyone else think or say that you were using drugs too much?
_Y_	_N_	89.	...did you think about cutting down or limiting your drug use?
_Y_	_N_	90.	...did you think you had a drug problem?
_Y_	_N_	91.	...because of your drug use did you have problems in your marriage; at your job; with your friends or family; doing household chores; or in any other important areas of your life?

Yes	*No*		**DURING THE PAST MONTH…**
_Y_	_N_	92.	...were you a nervous person on most days?
_Y_	_N_	93.	…did you worry a lot that bad things might happen to you or someone close to you?
_Y_	_N_	94.	…did you worry about things that other people said you shouldn't worry about?
_Y_	_N_	95.	…were you worried or anxious about a number of things in your daily life on most days?

_Y_	_N_	96.	…did you often feel restless or on edge because you were worrying?
_Y_	_N_	97.	…did you often have problems falling asleep because you were worrying about things?
_Y_	_N_	98.	…did you often feel tension in your muscles because of anxiety or stress?
_Y_	_N_	99.	…did you often have difficulty concentrating because your mind was on your worries?
_Y_	_N_	100.	…were you often snappy or irritable because you were worrying or feeling stressed out?
_Y_	_N_	101.	…was it hard for you to control or stop your worrying on most days?

Yes	*No*		**DURING THE PAST MONTH…**
_Y_	_N_	102.	…have you had a lot of stomach and intestinal problems such as nausea, vomiting, excessive gas, stomach bloating, or diarrhea?
_Y_	_N_	103.	…have you been bothered by aches and pains in many different parts of your body?
_Y_	_N_	104.	...Do you get sick more than most people?
_Y_	_N_	105.	...Has your physical health been poor *most of your life*?
_Y_	_N_	106.	...Are your doctors *usually* unable to find a physical cause for your physical symptoms?

Yes	*No*		**DURING THE PAST MONTH…**
_Y_	_N_	107.	...did you often worry that you might have a serious medical illness?
_Y_	_N_	108.	...was it hard to stop worrying that you have a serious medical illness?
_Y_	_N_	109.	...did your doctor say that you didn't have a serious medical illness but it was still hard to stop thinking about it?
_Y_	_N_	110.	...did you worry so much about having a serious illness that it interfered with your activities or it caused problems?
_Y_	_N_	111.	...did you visit the doctor a lot because you were worried that you had a serious physical illness?

APPENDIX G. ORIGINAL PDSQ MEASURE

This form asks you about emotions, moods, thoughts, and behaviours. For each question, tell me *Yes* if it describes how you have been acting, feeling, or thinking. If the item does not apply to you then tell me No. Please answer every question.
(read all questions to participant)

Yes	*No*		**DURING THE PAST 2 WEEKS…**
_Y_	_N_	1.	…did you feel sad or depressed?
_Y_	_N_	2.	…did you feel sad or depressed for most of the day, nearly every day?
_Y_	_N_	3.	…did you get less joy or pleasure from almost all of the things you normally enjoy?
_Y_	_N_	4.	…were you less interested in almost all of the activities you are usually interested in?
_Y_	_N_	5.	…was your appetite significantly *smaller* than usually nearly every day?
_Y_	_N_	6.	…was your appetite significantly *greater* than usual nearly every day?
_Y_	_N_	7.	…did you sleep at least 1 to 2 hours *less* than usual nearly every day?
_Y_	_N_	8.	…did you sleep at least 1 to 2 hours *more* than usual nearly every day?
_Y_	_N_	9.	…did you feel very jumpy and physically restless, and have a lot of trouble sitting calmly in a chair, nearly every day?
_Y_	_N_	10.	…did you feel tired out nearly every day?
_Y_	_N_	11.	…did you frequently feel guilty about things you have done?
_Y_	_N_	12.	…did you put yourself down and have negative thoughts about yourself nearly every day?
_Y_	_N_	13.	…did you feel like a failure nearly every day?
_Y_	_N_	14.	…did you have problems concentrating nearly every day?
_Y_	_N_	15.	…was decision making more difficult than normal nearly every day?
_Y_	_N_	16.	…did you frequently think of dying in passive ways like going to sleep and not waking up?
_Y_	_N_	17.	…did you wish you were dead?
_Y_	_N_	18.	…did you think you'd be better off dead?
_Y_	_N_	19.	…did you have thoughts of suicide, even though you would not really do it?
_Y_	_N_	20.	…did you seriously consider taking your life?
_Y_	_N_	21.	…did you think about a specific way to take your life?

_Y_	_N_	22.	…Have you *ever experienced* a traumatic event such as combat, rape, assault, sexual abuse, or any other extremely

upsetting event?

_Y_ _N_ 23. …Have you *ever witnessed* a traumatic event such as rape, assault, someone dying an accident, or any other extremely upsetting incident?

Yes *No* **DURING THE PAST 2 WEEKS…**

_Y_ _N_ 24. …did thoughts about a traumatic event frequently pop into your mind?

_Y_ _N_ 25. …did you frequently get upset because you were thinking about a traumatic event?

_Y_ _N_ 26. …were you frequently bothered by memories or dreams of a traumatic even?

_Y_ _N_ 27. …did reminders of a traumatic event cause you to feel intense distress?

_Y_ _N_ 28. …did you try to block out thoughts or feelings related to a traumatic event?

_Y_ _N_ 29. …did you try to avoid activities, places, or people that reminded you of a traumatic event?

_Y_ _N_ 30. …did you have flashbacks, where it felt like you were reliving a traumatic event?

_Y_ _N_ 31. …did reminders of a traumatic event make you shake, break out into a sweat, or have a racing heart?

_Y_ _N_ 32. …did you feel distant and cutoff from other people because of having experienced a traumatic event?

_Y_ _N_ 33. …did you feel emotionally numb because of having experienced a traumatic event?

_Y_ _N_ 34. …did you give up on goals for the future because of having experienced a traumatic event?

_Y_ _N_ 35. …did you keep your guard up because of having experienced a traumatic event?

_Y_ _N_ 36. …were you jumpy and easily startled because of having experienced a traumatic event?

Yes *No* **DURING THE PAST 2 WEEKS…**

_Y_ _N_ 37. …did you often go on eating binges (eating a *very large* amount of food very quickly over a short period of time)?

_Y_ _N_ 38. …did you often feel you could not control how much you were eating during an eating binge?

_Y_ _N_ 39. …did you go on eating binges during which you ate so much that you felt uncomfortably full?

_Y_ _N_ 40. …did you go on eating binges during which you ate a large amount of food even though you didn't feel hungry?

_Y_ _N_ 41. …did you eat alone during an eating binge because you were embarrassed by how much you were eating?

_Y_ _N_ 42. …did you go on eating binges and then feel disgusted with yourself afterward?

_Y_ _N_ 43. …were you very upset with yourself because you were going

			on eating binges?
_Y_	_N_	44.	…to prevent gaining weight from an eating binge did you go on strict diets or exercise excessively?
_Y_	_N_	45.	…to prevent gaining weight from an eating binge did you force yourself to vomit or use laxatives or water pills?
_Y_	_N_	46.	…was your weight, or the shape of your body, one of the most important things that affected your opinion of yourself?
Yes	*No*		**DURING THE PAST 2 WEEKS…**
_Y_	_N_	47.	…did you worry obsessively about dirt, germs, or chemicals?
_Y_	_N_	48.	…did you worry obsessively that something bad would happen because you forgot to do something important---like locking the door, turning off the stove, or pulling out the electrical cords of appliances?
_Y_	_N_	49.	…were there things you felt compelled to do over and over (for at least ½ hour per day) that you could not stop doing when you tried?
_Y_	_N_	50.	…were there things you felt compelled to do over and over even though they interfered with getting other things done?
_Y_	_N_	51.	…did you wash and clean yourself or things around you obsessively and excessively?
_Y_	_N_	52.	…did you obsessively and excessively check things or repeat actions over and over again?
_Y_	_N_	53.	…did you count things obsessively or excessively?
Yes	*No*		**DURING THE PAST 2 WEEKS…**
_Y_	_N_	54.	…did you get very scared because your heart was beating fast?
_Y_	_N_	55.	…did you get very scared because you were short of breath?
_Y_	_N_	56.	…did you get very scared because you were feeling shaky or faint?
_Y_	_N_	57.	…did you get sudden attacks of intense anxiety or fear that came on from the blue, for no reason at all?
_Y_	_N_	58.	…did you get sudden attacks of very intense anxiety or fear during which you thought something terrible might happen, such as your dying, going crazy, or losing control?
_Y_	_N_	59.	…did you have sudden, unexpected attacks of anxiety during which you had three or more of the following symptoms: heart racing or pounding, sweating, shakiness, shortness of breath, nausea, dizziness, or feeling faint?
_Y_	_N_	60.	…did you worry a lot about having unexpected anxiety attacks?
_Y_	_N_	61.	…did you have anxiety attacks that caused you to avoid certain situations or to change your behavior or normal routine?

Yes	*No*		**DURING THE PAST 2 WEEKS…**
_Y_	_N_	62.	…did things happen that you knew were true, but that other people told you were your imagination?
_Y_	_N_	63.	…were you convinced that other people were watching you, talking about you, or spying on you?
_Y_	_N_	64.	…did you think that you were in danger because someone was plotting to hurt you?
_Y_	_N_	65.	…did you think that you had special powers that other people didn't have?
_Y_	_N_	66.	…did you think that some outside force or power was controlling your body or mind?
_Y_	_N_	67.	…did you hear voices that other people didn't hear, or see things that other people didn't see?

NOTE: MOST OF THE FOLLOWING QUESTIONS REFER TO THE PAST 6 MONTHS

Yes	*No*		**DURING THE PAST 6 MONTHS…**
_Y_	_N_	68.	…did you regularly avoid any situations because you were afraid they'd cause you to have an anxiety attack?
		69.	…did any of the following make you feel fearful, anxious, or nervous because you were afraid you'd have an anxiety attack in the situation?
_Y_	_N_	a.	going outside far away from home
_Y_	_N_	b.	being in crowded places
_Y_	_N_	c.	standing in long lines
_Y_	_N_	d.	being on a bridge or in a tunnel
_Y_	_N_	e.	traveling on a bus, train, or plane
_Y_	_N_	f.	driving or riding in a car
_Y_	_N_	g.	being home alone
_Y_	_N_	h.	being in wide-open spaces (like a park)
_Y_	_N_	70.	…did you almost always get very anxious as soon as you were in any of the above situations?
_Y_	_N_	71.	...did you avoid any of the above situations because they made you feel anxious or fearful?

Yes	*No*		**DURING THE PAST 6 MONTHS…**
_Y_	_N_	72.	...did you worry about embarrassing yourself in front of others?
_Y_	_N_	73.	...did you worry a lot that you might do something to make people think that you were stupid or foolish?
_Y_	_N_	74.	...did you feel very nervous in situations where people might pay attention to you?
_Y_	_N_	75.	...were you extremely nervous in social situations?
_Y_	_N_	76.	...did you regularly avoid any situations because you were afraid you'd do or say something to embarrass yourself?
		77.	...did you worry a lot about doing or saying something to embarrass yourself in any of the following situations?

_Y_	_N_	a.	public speaking
_Y_	_N_	b.	eating in front of other people
_Y_	_N_	c.	using public restrooms
_Y_	_N_	d.	writing in front of others
_Y_	_N_	e.	saying something stupid when you were with a group of people
_Y_	_N_	f.	asking a question when in a group of people
_Y_	_N_	g.	business meetings
_Y_	_N_	h.	parties or other social gatherings
_Y_	_N_	78.	…did you almost always get very anxious as soon as you were in any of the above situations?
_Y_	_N_	79.	...did you avoid any of the above situations because they made you feel anxious or fearful?

Yes	*No*		**DURING THE PAST 6 MONTHS…**
_Y_	_N_	80.	...did you think that you were drinking too much?
_Y_	_N_	81.	...did anyone in your family think or say that you were drinking too much, or that you had an alcohol problem?
_Y_	_N_	82.	...did friends, a doctor, or anyone else think or say that you were drinking too much?
_Y_	_N_	83.	...did you think about cutting down or limiting your drinking?
_Y_	_N_	84.	...did you think that you had an alcohol problem?
_Y_	_N_	85.	...because of your drinking did you have problems in your marriage; at your job; with your friends or family; doing household chore; or in any other important areas of your life?

Yes	*No*		**DURING THE PAST 6 MONTHS…**
_Y_	_N_	86.	...did you think that you were using drugs too much?
_Y_	_N_	87.	...did anyone in your family think or say that you were using drugs too much, or that you had a drug problem?
_Y_	_N_	88.	...did friends, a doctor, or anyone else think or say that you were using drugs too much?
_Y_	_N_	89.	...did you think about cutting down or limiting your drug use?
_Y_	_N_	90.	...did you think you had a drug problem?
_Y_	_N_	91.	...because of your drug use did you have problems in your marriage; at your job; with your friends or family; doing household chores; or in any other important areas of your life?

Yes	*No*		**DURING THE PAST 6 MONTHS…**
_Y_	_N_	92.	...were you a nervous person on most days?
_Y_	_N_	93.	…did you worry a lot that bad things might happen to you or someone close to you?
_Y_	_N_	94.	…did you worry about things that other people said you shouldn't worry about?
_Y_	_N_	95.	…were you worried or anxious about a number of things in your daily life on most days?

_Y_	_N_	96.	…did you often feel restless or on edge because you were worrying?
_Y_	_N_	97.	…did you often have problems falling asleep because you were worrying about things?
_Y_	_N_	98.	…did you often feel tension in your muscles because of anxiety or stress?
_Y_	_N_	99.	…did you often have difficulty concentrating because your mind was on your worries?
_Y_	_N_	100.	…were you often snappy or irritable because you were worrying or feeling stressed out?
_Y_	_N_	101.	…was it hard for you to control or stop your worrying on most days?

Yes	*No*		**DURING THE PAST 6 MONTHS…**
_Y_	_N_	102.	…have you had a lot of stomach and intestinal problems such as nausea, vomiting, excessive gas, stomach bloating, or diarrhea?
_Y_	_N_	103.	…have you been bothered by aches and pains in many different parts of your body?
_Y_	_N_	104.	...Do you get sick more than most people?
_Y_	_N_	105.	...Has your physical health been poor *most of your life*?
_Y_	_N_	106.	...Are your doctors *usually* unable to find a physical cause for your physical symptoms?

Yes	*No*		**DURING THE PAST 6 MONTHS…**
_Y_	_N_	107.	...did you often worry that you might have a serious medical illness?
_Y_	_N_	108.	...was it hard to stop worrying that you have a serious medical illness?
_Y_	_N_	109.	...did your doctor say that you didn't have a serious medical illness but it was still hard to stop thinking about it?
_Y_	_N_	110.	...did you worry so much about having a serious illness that it interfered with your activities or it caused problems?
_Y_	_N_	111.	...did you visit the doctor a lot because you were worried that you had a serious physical illness?

APPENDIX H. COPYRIGHT PERMISSION LETTER FOR STUDY ONE MANUSCRIPT

Below is the scanned license agreement between Ms. Heather Grace Fulton the publisher, Lippincott, Williams, and Wilkins, regarding the manuscript, "*Prescription Opioid Misuse: Characteristics of Earliest and Most Recent Remembered Hydromorphone Use*" featured in Chapter 4 of the present thesis. This article is currently in press in the *Journal of Addiction Medicine*. The license agreement was negotiated with the publishing staff, Silvia Serra (Silvia.Serra@wolterskluwer.com) and Natalie McGroarty (Natalie.McGroarty@wolterskluwer.com).

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For the article Prescription Opioid Misuse: Characteristics of Earliest and Most Recent Remembered Hydromorphone Use, Fulton HG, Barrett SP, MacIsaac C, and Stewart SH (currently in press) in the Journal of Addiction Medicine

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Andrew Richardson

VP of Business Development

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Heather Fulton

APPENDIX I. COPYRIGHT PERMISSION LETTER FOR STUDY TWO MANUSCRIPT

NOTE: Below are the emails exchanged between the Ms. Heather Grace Fulton and the publisher (BioMed Central) of the manuscript, "*The Relationship Between Self-Reported Substance Use And Psychiatric Symptoms In Low-Threshold Methadone Maintenance Treatment Clients*" featured in Chapter 6 of the present thesis. This article was published in the *Harm Reduction Journal*, an open access journal. The authors retained copyright for this article. Please see the websites in the emails below for further information if required.

From: journals@biomedcentral.com [mailto:journals@biomedcentral.com]

Sent: October-04-11 9:07 AM

To: heather.fulton@dal.ca

Subject: RE: (4th request) 00383682: Copyright for Fulton et al., 2011 [ref:00D2CUt.5002IDdOO:ref

Dear Heather,

Thank you for your message, and please accept my apologies for the delay in getting back to you. I have been following up on this with colleagues, as I was unsure of the procedure.

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I hope that this helps, and please do not hesitate to get in touch if you have any questions.

With best wishes,

Matthew Landau
Editorial Assistant

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Manuscript ID:

From: Heather Fulton

Email address: heather.fulton@dal.ca

Journal:

Date of query: 19/09/2011

Question/Comment:

To Whom It May Concern:

I am preparing my Ph.D. thesis for submission to the Faculty of Graduate Studies at Dalhousie University and am seeking your permission to include my paper as a chapter in my thesis:

“The relationship between self-reported substance use and psychiatric symptoms in low-threshold methadone maintenance treatment clients” by Fulton HG, Barrett SP, MacIsaac C & Stewart SH; 2011, 8:18.

Here is a link to a pdf of this article in the Harm Reduction Journal:

http://www.harmreductionjournal.com/content/pdf/1477-7517-8-18.pdf

If this is possible, my Faculty has a formal letter that needs to be signed and dated, and then included in the thesis. I have attached it to this email. If possible, I was hoping a member of your editorial staff could print, sign, and scan a PDF version to email back to me.

If this is NOT possible, could you also please let me know.

If you have any questions or concerns at all, please feel free to contact me.

Best wishes,

Heather Fulton

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