PERSONALITY, MOTIVES AND PATTERNS OF PRESCRIPTION ANXIOLYTIC AND SEDATIVE MISUSE

by

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ABSTRACT

Misuse of prescription anxiolytic and sedative medication is a widespread phenomenon in Canada and a topic of increasing concern among health care providers. While anxiolytics and sedatives have important therapeutic uses in the treatment of anxiety and insomnia, these substances have psychoactive properties that render them vulnerable to misuse. Understanding the correlates and contexts of misuse is essential for developing targeted treatment and prevention strategies. This dissertation is comprised of a series of four studies conducted with adults in the Halifax Regional Municipality, recruited from the community and from a local substance use disorder treatment program. Study 1 investigated misuse of anxiolytics and sedatives among currently prescribed users of these medications in the general community. Misuse and diversion were associated with a more extensive history of other substance use and with personality dimensions, including hopelessness and impulsivity. Study 2 investigated motives for misuse among non-prescribed anxiolytic and sedative users recruited from the community. This study also included non-prescribed stimulant medication users to facilitate comparisons across differing classes of psychiatric medications. Non-therapeutic motives were associated with substance use history and, for anxiolytics and sedatives, with the personality dimension sensation-seeking. Study 3 involved an analysis of prescription regimens and misuse among all participants of Studies 1 and 2 who had ever held a prescription for an anxiolytic or sedative. Misuse of benzodiazepine anxiolytics and sedatives was more frequent than that of non-benzodiazepines, but was unrelated to prescription regimen. Study 4 examined the misuse of quetiapine, an atypical antipsychotic medication with anxiolytic and sedative effects, among clients of a methadone maintenance program. Misuse of quetiapine was widespread, but was typically associated with therapeutic motives. Quetiapine misuse was linked with a history of misusing other anxiolytic and sedative drugs. Collectively, these studies provide evidence that anxiolytic and sedative misuse is a heterogeneous phenomenon encompassing varying patterns of use and motives for misuse. Furthermore, these investigations suggest that anxiolytic and sedative misuse is linked to individual-level and medication-related variables. By providing a more comprehensive characterization of this important public health issue, these findings have practical implications in both clinical and research contexts.

LIST OF ABBREVIATIONS AND SYMBOLS USED

ADHD	Attention-deficit/hyperactivity disorder
AHA	Assessment of Hyperactivity and Attention
ANOVA	Analysis of variance
aOR	Adjusted odds ratio
AS	Anxiety Sensitivity subscale of the SURPS
B	Beta weight; standardized logistic regression coefficient
b.i.d.	*Bis in die;* twice-daily administration of medication
BZ	Benzodiazepine
CAD	Canadian dollars
CI	Confidence interval
CNS	Central nervous system
d	Cohen's *d*, a measure of effect size
df	Degrees of freedom
DAWN	Drug Abuse Warning Network
DMT	Dimethyltryptamine
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders (4th Edition, Text Revision)
DXM	Dextromethorphan
F	Fisher's *F* ratio
GAD	Generalized anxiety disorder
H	Hopelessness subscale of the SURPS
IMP	Impulsivity subscale of the SURPS
LSD	Lysergic acid diethylamide
M	Mean
MDMA	3,4-methylenedioxymethamphetamine
MTF	Monitoring the Future
N	Total sample size
n	Subsample size
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
Non-BZ	Non-benzodiazepine
ns	Not statistically significant
NSDUH	National Survey on Drug Use and Health
OCD	Obsessive-compulsive disorder
OR	Odds ratio
p	Probability of Type I error
PCP	Phencyclidine
PDSQ	Psychiatric Diagnostic Screening Questionnaire
p.r.n.	*Pro re nata;* as-needed administration of medication
r	Pearson product-moment correlation
SD	Standard deviation

SSRI	Selective serotonin reuptake inhibitor
SS	Sensation Seeking subscale of the SURPS
SURPS	Substance Use Risk Profile Scale
t	Computed value of *t* test
t.i.d.	*Ter in die;* thrice-daily administration of medication
US	United States of America
α	Alpha; index of internal consistency
χ^2	Computed value of chi-square test

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CHAPTER 1 Introduction

1.1 Introduction Overview

This dissertation focuses on the misuse of prescription anxiolytic and sedative medication among adults recruited from the community and from a substance use treatment program in the Halifax Regional Municipality in Nova Scotia, Canada. This document is comprised of four empirical studies investigating patterns of anxiolytic and sedative misuse, individual-level correlates of misuse, and medication-related factors relating to misuse. This introductory chapter provides background on anxiolytics and sedatives and the misuse of these drugs, including a review of definitional issues that have complicated empirical studies of prescription drug misuse. This chapter also discusses intrapersonal variables of relevance to anxiolytic and sedative misuse, including motives for use and personality traits. This is followed by a review of medication characteristics that are potentially relevant to misuse. Finally, each of the studies included in this dissertation is introduced, accompanied by a discussion of the overall goals and objectives of this program of research.

1.2 Anxiolytics and Sedatives: Terminology, Therapeutic Indications, Adverse Effects, and Misuse Potential

In Canada, the cost of anxiolytic and sedative medications represents the third largest expenditure on psychiatric and neurological drugs, and in Nova Scotia, per capita costs of these medications exceed the national average by 17 percent (Morgan, Raymond, Mooney & Martin, 2008). Epidemiological data indicate that in 2011, 12 percent of Canadian women and 6 percent of men used a prescription anxiolytic or sedative (Health

Canada, 2012). While referring, respectively, to the pharmacological management of anxiety and sleep disorders, anxiolytic and sedative medications are frequently discussed together as drugs from these classes are often prescribed interchangeably (Becker, Fiellin & Desai, 2007; Brust, 2004; Roehrs & Roth, 2004). They may also be referred to by a variety of other terms, including tranquilizers, depressants, anti-anxiety drugs, and hypnotics (Kulkarni & Mehendale, 2005). To maintain consistency, the terminology "anxiolytics and sedatives" will be used throughout this document.

1.2.1 Benzodiazepines

One of the most widely used classes of anxiolytic and sedative medication is the benzodiazepines (BZs), which were first marketed in the 1960s and rapidly grew in popularity (Brust, 2004; Busto, 1999). BZs were favoured over their predecessors, including barbiturates, as they were more efficacious in alleviating anxiety and had a safer side effect profile than barbiturates, which were known to have a low threshold for overdose and a higher risk for dependence (Lader, 1978; 2007; Longo & Johnson, 2000). BZs act as central nervous system (CNS) depressants, producing their effects by potentiating the inhibitory neurotransmitter γ-aminobutyric acid (GABA; Brust, 2004). BZs are most commonly used therapeutically in the treatment of anxiety disorders and insomnia (Busto, 1999; Romach, Busto, Somer, Kaplan & Sellers, 1995) but may also be used as muscle relaxants, anticonvulsants, to induce anesthesia, and to ameliorate symptoms of alcohol withdrawal, including seizures (Brust, 2004; Dell'osso & Lader, 2013; Kulkarni & Mehendale, 2005; Lader, 2007).

In addition to their beneficial therapeutic uses, there are a number of potential adverse effects of BZ use. Administration of BZs can induce anterograde amnesia

(Buffett-Jerrott & Stewart, 2002) and chronic use is associated with impairments in a range of neurocognitive domains, including visuospatial ability and sustained attention (Barker, Greenwood, Jackson & Crowe, 2004a; Curran, 1992). Evidence suggests that BZ-related cognitive deficits, particularly memory deficits, can persist even after BZs are discontinued (Barker, Greenwood, Jackson & Crowe, 2004b). BZs can also cause psychomotor retardation, including drowsiness and daytime sedation, ataxia, motor incoordination, muscle weakness, and slowed reaction time (Longo & Johnson, 2000). This can increase the risk of falls and accidents and has been linked with impaired driving skills and motor vehicle crashes (Barbone et al., 1998; Smink, Egberts, Lusthof, Uges & de Gier, 2010). Although BZs typically have a low toxicity profile when used alone, they interact synergistically with alcohol and other CNS depressants, which can result in respiratory depression and hypotension (Kulkarni & Mehendale, 2005). Furthermore, prolonged use of BZs is associated with physical dependence, manifested as tolerance to the drugs' effects and withdrawal upon discontinuation, even when used at typical therapeutic doses (Busto, 1999, Lader, 2007). Evidence suggests that the clinical efficacy of BZs declines over time (Lader, 1999; 2007), with many users experiencing tolerance to both the sedative and anxiolytic effects of these drugs (Longo & Johnson, 2000). It is common for BZ users to experience withdrawal symptoms (e.g., increased anxiety, sleep disturbance, nausea, perceptual disturbances, or seizures) and many have great difficulty discontinuing BZ use (Brust, 2004). Despite best practice guidelines recommending that BZs be restricted to short-term use (Canadian Psychiatric Association, 2006), and although first-time BZ users tend to report a desire to minimize their use of these medications (Anthierens et al., 2007), many become long-term users. In

one large study, more than 80 percent of BZ users reported taking their medication for longer than the recommended duration (Manthey et al., 2011). Among a sample of psychiatric inpatients, less than 5 percent of BZ users had initiated use within the previous month (Haw & Stubbs, 2007).

In addition to these adverse side effects, the psychoactive properties of BZs also make them vulnerable to misuse[1] (O'Brien, 2005; Becker et al., 2007). The primary determinants of a drug's liability for misuse include its reinforcing effects (i.e., its capacity to maintain problematic self-administration) and its toxicity (i.e., adverse effects to the individual and/or society from its use; Griffiths & Johnson, 2005). In a review of studies utilizing BZ self-administration paradigms with humans and laboratory animals, Roache and Meisch (1995) concluded that BZs have moderate reinforcing effects and potential for misuse, which tends to be elevated in users with a history of alcohol abuse or illicit drug use. Increased misuse liability of BZs has also been reported among patients receiving methadone maintenance treatment (e.g., Farré et al., 1998) with correspondingly high prevalence of BZ misuse reported in this population (Chen et al., 2011). Despite these serious concerns with BZ use and misuse, these drugs continue to be prescribed frequently and many clinicians view them favourably (Baldwin & Talat, 2012; Cloos & Ferreira, 2009; Lader, 2007).

1.2.2 Non-Benzodiazepine Anxiolytics and Sedatives

Non-benzodiazepine (non-BZ) anxiolytics and sedatives fall within a variety of chemical classes. Some share properties with BZs while others are structurally and

[1] Prescription drug misuse is distinct from physical dependence, which is a normal physiological consequence of BZ use, as noted above. The terminology used in the prescription drug misuse literature varies considerably and will be discussed in more detail in Section 1.5.

pharmacologically distinct (Lader, 1988). Among the more common non-BZ drugs currently in use are the so-called "Z-drugs," including zopiclone, eszopiclone, zolpidem, and zalepon, which are primarily prescribed for insomnia and are described as having better safety and tolerability profiles than BZs (Licata & Rowlatt, 2008). Despite having distinct molecular structures, the Z-drugs have similar pharmacological properties to BZs, including potentiation of GABA (Lader, 1988). Other anxiolytic and sedative drugs include those affecting serotonin neurotransmission (e.g., buspirone, trazodone; Lader, 1988) and those with antihistaminic properties (e.g., diphenhydramine, hydroxyzine; Brust, 2004). The atypical antipsychotic drug quetiapine (Seroquel™) has effects on dopaminergic, serotonergic, histaminic, and alpha-adrenergic systems (Gugger & Cassagnol, 2008), and its off-label use in the treatment of insomnia and anxiety disorders has become increasingly common (Wu, Wang, Katz & Farley, 2013; Yost & White, 2010). The sedative and anxiolytic effects of quetiapine make this substance a suitable candidate for consideration within the group of non-BZs.

As with BZs, non-BZ anxiolytic and sedative drugs have therapeutic benefits but can involve adverse side effects for users (Glass, Lanctôt, Herrmann, Sproule & Busto, 2005), including psychomotor impairment (Gustavsen, Hjelmeland, Bernard & Mørland, 2011), daytime sedation (Mendelson, 2005), short-term memory deficits (Noble, Langtry & Lamb, 1998), increased risk for motor vehicle collisions (Barbone et al., 1998), and development of physical dependence (Aranko, Henriksson, Hublin & Seppäläinen, 1991; Flynn & Cox, 2006; Jones & Sullivan, 1998). Although the use of quetiapine for anxiety and insomnia typically involves dosages lower than those used to treat psychosis, serious metabolic side effects (e.g., obesity, diabetes, elevated blood lipid levels) can occur even

at reduced doses (Cates, Jackson, Feldman, Stimmel & Woolley, 2009; Miodownik & Lerner, 2006), which has contributed to controversy surrounding its off-label use (Coe & Hong, 2012; Gugger & Cassagnol, 2008).

Non-BZs are often discussed as favourable alternatives to BZs in terms of misuse potential (e.g., Soyka, Bottlender & Möller, 2000). However, as noted by Brust (2004, p. 214), "the lexicon of abused drugs is replete with agents initially touted as nonaddicting."[2] Correspondingly, numerous concerns have been raised about misuse of non-BZs. In particular, there is now substantial evidence for misuse of the Z-drugs (e.g., Aranko et al., 1991; Cimolai, 2007; Hajak, Müller, Wittchen, Pittrow & Kirch, 2003; Jaffe et al., 2004; Morinan & Keaney, 2010; Rooney & O'Connor, 1998; Sikdar, 1998; Victorri-Vigneau, Dailly, Veyrac & Jolliet, 2007). Several studies have documented misuse liabilities of the Z-drugs comparable to those of common BZs (Griffiths & Johnson, 2005; Rush, Baker & Wright, 1999; Rush, Frey & Griffiths, 1999). Although non-BZ anxiolytics and sedatives whose actions are not mediated by GABA appear to have a lower liability for misuse (Rush, Baker & Wright, 1999), certain subpopulations, including those with a history of alcohol or illicit drug misuse, may also be at risk to misuse such compounds (Fischer & Boggs, 2010; Jaffe et al., 2004; Myrick, Markowitz & Henderson, 1998; Quintero, 2009).

Since the 1990s, clinical practice guidelines have moved towards recommending selective serotonin reuptake inhibitors (SSRIs) in the pharmacological management of anxiety disorders (Lader, 2007). A key difference between SSRIs and other drugs with anxiolytic properties is that it can take several weeks of continuous SSRI use to produce a

[2] Interestingly, this observation also applies to the BZs, which when originally developed were thought to present minimal risk for side effects, including addiction (Lader, 2011).

therapeutic effect (Canadian Psychiatric Association, 2006). This delay in reinforcement theoretically reduces the potential for development of psychological dependence. Furthermore, SSRIs typically lack the positive subjective effects that characterize drugs with misuse liability (e.g., elation, euphoria; Zawertailo, Busto, Kaplan & Sellers, 1995). For the purposes of this dissertation, and consistent with the prescription anxiolytic and sedative misuse literature,[3] SSRIs will not be included within the anxiolytic and sedative drugs investigated in this thesis.

1.3 An "Epidemic" of Prescription Drug Misuse[4]

1.3.1 Prevalence and Scope of Anxiolytic and Sedative Misuse

Prescription drug misuse has garnered substantial attention from the media in recent years, with indications of rising prevalence and high-profile overdose cases leading to increasing recognition of this issue (e.g., Blanco et al., 2007; Hertz & Knight, 2006; McCarthy, 2007). In Canada, prescription drug misuse has been termed a "public health and safety crisis" (National Advisory Committee on Prescription Drug Misuse, 2013, p. 8). Recent data from the United States (US) indicate that nonmedical use of psychotherapeutics is second only to marijuana use in terms of current (past month) prevalence and recent (past year) incidence of use (Substance Abuse and Mental Health Services Administration, 2011a). Anxiolytics and sedatives are among the classes of psychotherapeutic drugs most implicated in this "epidemic" of misuse (Compton & Volkow, 2006, p. S4), with estimates placing nonmedical use of anxiolytics and sedatives

[3] For example, the National Survey of Drug Use and Health (NSDUH) does not include SSRIs within the anxiolytic and sedative medications assessed in its epidemiological surveys of prescription drug misuse (e.g., Substance Abuse and Mental Health Services Administration, 2008).

[4] In this review of the literature, the terminology employed by the source material to refer to prescription drug misuse is retained.

at a higher rate of prevalence than cocaine, hallucinogens, inhalants, and heroin (SAMHSA, 2011a). In a large study of US adults, the lifetime prevalence rate of anxiolytic and sedative use without a valid prescription was 7.1 percent (Goodwin & Hasin, 2002). Similarly, among a nationally representative sample of college students in the US, approximately 7.8 percent reported non-prescribed BZ use (McCabe, 2005). Becker et al. (2007) found a prevalence of 2.3 percent for past-year nonmedical anxiolytic or sedative use in US adults, of whom nearly 10 percent met Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV diagnostic criteria for a substance use disorder involving these drugs (American Psychiatric Association, 1994). Although much of the population-level monitoring of prescription drug misuse has taken place in the US, concerns with anxiolytic and sedative misuse have been reported internationally (e.g., Albsoul-Younes, Wazaify, Yousef & Tahaineh, 2010; Assanangkornchai, Sam-Angsri, Rerngpongpan & Edwards, 2010; Ghandour, El Sayed & Martins, 2012; United Nations Office on Drugs and Crime, 2012) and available data from Canada correspond with US findings (Currie, Schopflocher & Wild, 2011; Health Canada, 2012). In Nova Scotia, over 50 percent of respondents to a recent survey of front-line health care workers and substance users reported that problem use of prescription depressants (i.e., anxiolytics and sedatives) represents a "very serious" concern in the region (Black, Simon & Gilbert, 2012). A survey of Nova Scotian adolescents (Grade 7 to 12) found that 3 percent had used anxiolytics or sedatives without a doctor's prescription within the past year (Poulin & Elliott, 2007).

The misuse of psychoactive prescription drugs has been attributed to their widespread availability (DeSantis, Webb & Noar, 2008), to greater social acceptability

than illicit drugs (DeSantis et al., 2008; Hernandez & Nelson, 2010), and to a perception that misuse of prescription drugs is less subject to legal consequences than illicit drug use (Inciardi, Surratt, Cicero & Beard, 2009; Quintero, 2009). Acquisition of misused prescription drugs may occur through prescription fraud and forgery, obtaining prescriptions from multiple physicians ("doctor shopping"), thefts, and online pharmacies (NACPDM, 2013; Weekes, Rehm & Mugford, 2007). One study found that street values for anxiolytic and sedative medications were inexpensive and comparable to pharmacy prices (Sajan, Corneil & Grzybowski, 1998). Evidence suggests, however, that one's own prescription or diversion from users with legitimate prescriptions, including friends and family members, represent the most common sources of misused prescription medication (Barrett, Darredeau, Bordy & Pihl, 2005; McCabe & Boyd, 2005; SAMHSA, 2011a).

1.3.2 Harms Associated with Anxiolytic and Sedative Misuse

A belief that prescription medications are less harmful than illicit drugs has also been noted as a contributor to prescription drug misuse (Arria, Caldeira, Vincent, O'Grady & Wish, 2008; Hertz & Knight, 2006; Quintero, 2009). Contrary to this perception of safety, misuse of prescription drugs, including anxiolytics and sedatives, can have devastating effects for individuals and their families (e.g., NACPDM, 2013). As described above, anxiolytics and sedatives can have serious side effects even when used according to therapeutic guidelines. When these drugs are misused, the potential harms are magnified. For example, misuse of an anxiolytic or sedative may involve using higher than recommended doses or co-administering it with other psychoactive substances (Compton & Volkow, 2006; NACPDM, 2013), which can greatly increase the risk for accidents, overdose, or adverse drug interactions (Becker et al., 2007; Griffiths &

Johnson, 2005). Misuse may also occur when users alter the route of administration, such as taking anxiolytics and sedatives intranasally or by intravenous injection, the latter of which can result in vascular trauma (Lader, 1996).

At the societal level, prescription drug misuse results in lost productivity and increased demand for treatment resources (NACPDM, 2013). The US-based Drug Abuse Warning Network (DAWN) reports that about half (50.5 percent) of all hospital emergency room visits for drug abuse in 2011 involved nonmedical use of pharmaceuticals (SAMHSA, 2013). Anxiolytic and sedative misuse specifically has been implicated in an increasing number of emergency department visits (Coben et al., 2010). Evidence suggests that prescription drug misuse can increase the risk of developing DSM-IV-TR (APA, 2000) abuse and dependence involving prescription drugs (McCabe, West, Morales, Cranford & Boyd, 2007). Paralleling the rising prevalence of prescription drug misuse, rates of substance use disorders involving prescription drugs have increased in recent years, with a particularly significant increase in sedative abuse and dependence (Blanco et al., 2007). Moreover, admissions to treatment programs for problem anxiolytic and sedative use more than tripled from 1998 to 2008, rising substantially more than the increase in admission rates for other substances (SAMHSA, 2011b). Finally, prescription drug misuse has also been reported as a possible precursor to illicit drug use (Inciardi et al., 2009).

1.4 Characteristics and Correlates of Anxiolytic and Sedative Misuse

Despite these concerns, surprisingly little is known about misuse of anxiolytics and sedatives. Compared to other frequently misused medication classes, including opioids and stimulants, anxiolytics and sedatives have received less attention from

researchers (Ford, 2008). Furthermore, much of the empirical research on anxiolytic and sedative misuse is comprised of epidemiological, survey-based studies. While such research is essential for estimating prevalence and tracking trends in misuse at the population level, its ability to provide insight into the diverse behaviours and individual-level factors associated with prescription drug misuse is limited (Boyd & McCabe, 2008). Detailed investigation of the patterns and predictors of prescription drug misuse is crucial for informing prevention and intervention efforts. Existing knowledge on correlates of anxiolytic and sedative misuse is reviewed in the following sections.

1.4.1 Sociodemographic Factors

Higher prevalence rates of alcohol and illicit drug use, abuse, and dependence among men are consistently reported in the literature (Brady, Grice, Dustan & Randall, 1999). However, relationships between sex and anxiolytic and sedative misuse are less consistent. Some studies have reported higher rates of anxiolytic and sedative misuse among men (Goodwin & Hasin, 2002; Griffiths & Johnson, 2005; McCabe, Teter & Boyd, 2006), others have reported higher rates among women (Becker et al., 2007; Simoni-Wastila, Yang & Lawler, 2008), and still others have reported equivalent rates among men and women (Boyd, McCabe, Cranford & Young, 2006; Ford & McCutcheon, 2012). More men than women seek treatment for anxiolytic and sedative-related substance use disorders; however, women seeking treatment for anxiolytic and sedative-related problems outnumber women seeking treatment for all other forms of problem substance use, suggesting that anxiolytic and sedative misuse among women is of significant concern (SAMHSA, 2011b). Women receive proportionately more

prescriptions for anxiolytics and sedatives than men (Health Canada, 2012) and how this greater relative exposure to these medications may relate to misuse is unclear.

Past research has highlighted adolescents, young adults, and older adults as age groups at elevated risk for anxiolytic and sedative misuse (Simoni-Wastila & Yang, 2006; Simoni-Wastila et al., 2008; Victorri-Vigneau et al., 2013). However, prescription drug misuse is best conceptualized within a developmental framework, as patterns of misuse appear to manifest differently across age groups (for a review, see McLarnon, Barrett, Monaghan & Stewart, [2012], Appendix A). At present, trajectories of anxiolytic and sedative misuse across the lifespan are inadequately understood.

Several studies have indicated that White and Hispanic ethnic groups are at elevated risk for prescription anxiolytic and sedative misuse (Becker et al., 2007; Ford & McCutcheon, 2012; Goodwin & Hasin, 2002; Simon-Wastila et al., 2008). However, among adults with concurrent substance use and mental health disorders, Brunette, Noordsy, Xie and Drake (2003) found no relationship between demographic variables and BZ abuse.

Findings relating socioeconomic factors to anxiolytic and sedative misuse are also mixed. Becker et al. (2007) reported that unemployment, lack of insurance, and recent arrest were positively related to anxiolytic and sedative misuse, while level of education and household income were unrelated. Conversely, Simoni-Wastila et al. (2008) reported higher rates of anxiolytic and sedative misuse among US youth with health insurance as compared to those with no insurance. Goodwin and Hasin (2002) found anxiolytic and sedative misuse to be associated with lower income but higher level of education. Youth

from higher-income families had higher rates of misuse of Ambien (a non-BZ) than those from lower-income families (Ford & McCutcheon, 2012).

1.4.2 Comorbid Psychopathology

Mental health and substance use disorders are highly comorbid (Kessler, Chiu, Demler, Merikangas & Walters, 2005). Thus, it is not surprising that anxiolytic and sedative misuse has been associated with mental health difficulties. Becker et al. (2007) found elevated panic symptoms and overall psychological distress among participants reporting past-year nonmedical anxiolytic and sedative use compared to those reporting no nonmedical use. Goodwin and Hasin (2002) reported associations between anxiolytic and sedative misuse and major depression, agoraphobia, antisocial personality disorder, suicidal ideation, and family history of psychopathology. Non-BZ misuse has been related to mental health concerns in general (Hajak et al., 2003) and depression in particular (Ford & McCutcheon, 2012). Among a sample of adults with concurrent disorders, higher levels of affective symptoms predicted development of BZ-related substance use disorders (Brunette et al., 2003) and among individuals admitted to substance use treatment programs, those seeking treatment for BZ-related issues were reportedly more likely to have a comorbid psychiatric disorder than those admitted for all other substances (SAMHSA, 2011b). While longitudinal data is sparse, one study found that any lifetime nonmedical use of anxiolytics and sedatives predicted onset of psychopathology in those with no history of mental health difficulties (Schepis & Hakes, 2011). Among participants with a history of any mental health diagnosis, nonmedical anxiolytic use predicted recurrence of previous psychopathology and onset of new forms of psychopathology, including non-prescription drug substance use disorders (Schepis &

Hakes, 2011). These preliminary findings suggest that misuse of prescription anxiolytics and sedatives may increase risk for subsequent onset and recurrence of mental health and substance use difficulties. Although findings from existing research provide compelling evidence for a relationship between anxiolytic and sedative misuse and other psychopathology, no consistent pattern is evident.

1.4.3 Other Substance Use and Risk-Taking Behaviours

Anxiolytic and sedative misuse has been widely reported in polysubstance contexts. Due to their synergistic effects with other CNS depressants, anxiolytics and sedatives may be taken to augment the euphoric effects of alcohol or opioids, including methadone (Longo & Johnson, 2000; O'Brien, 2005). Anxiolytics and sedatives may also be administered to offset the negative side effects of stimulant drugs (Compton & Volkow, 2006) or to alleviate withdrawal from other substances (Longo & Johnson, 2000). Consistent with this, in a large sample of drug users, BZs were highly rated as "secondary" drugs of choice (Morgan, Noronha, Muetzelfeldt, Fielding & Curran, 2013). In a study of individuals seeking treatment for BZ-related substance use problems, the vast majority (95 percent) reported misuse of at least one other substance in addition to BZs (SAMHSA, 2011b). In this study, 82 percent reported primary abuse of another substance with secondary abuse of BZs and 13 percent reported primary abuse of BZs with secondary abuse of another substance, most commonly opioids, alcohol, marijuana or cocaine (SAMHSA, 2011b). These forms of polysubstance use put users at increased risk for adverse consequences from drug interactions.

Correlational studies provide further support for a relationship between anxiolytic and sedative misuse and other substance use. Misuse of anxiolytics and sedatives is

associated with alcohol abuse and dependence, cigarette use, illicit drug use, younger age of initiating illicit substance use, and IV drug use (Becker et al., 2007; McCabe et al., 2006; Simoni-Wastila et al., 2008). Misuse of sedatives and anxiolytics is also associated with more problematic use of other substances, including alcohol and tobacco (Becker et al., 2007). Use of BZs without a valid prescription is reportedly associated with an increased risk of other licit and illicit substance use, as well as a range of high-risk behaviours, including frequent binge drinking and being a passenger with an impaired driver (McCabe, 2005). Non-BZ misuse has also been linked to a history of illicit drug and alcohol misuse (Ford & McCutcheon, 2012; Hajak et al., 2003).

Although the association between anxiolytic and sedative misuse and other substance use appears to be robustly supported by previous research, findings for other potential correlates of misuse are inconsistent. Consequently, there is little consensus in terms of the factors associated with misuse of prescription anxiolytics and sedatives at an individual level (McCabe, 2005). One possible explanation for the lack of consistency in previous research originates with researchers' definitions of prescription drug misuse, which tend to vary across studies.

1.5 Defining Prescription Drug Misuse

The lack of a uniform definition for prescription misuse has long been identified as an impediment to conducting comprehensive evaluations of the literature, interpreting study findings, and comparing findings across studies (Cole & Chiarello, 1990; Shader & Greenblatt, 1993). A review of the recent scientific literature reveals an array of terminology used to refer to prescription drug misuse (Barrett, Meisner, & Stewart, 2008). Terms such as "misuse," "nonmedical use," "illicit use," "recreational use," and

"abuse" are frequently used interchangeably and many studies lack clarity about the operational criteria for the terminology employed. The following sections discuss some common approaches to defining prescription drug misuse.

1.5.1 Prescription Drug Abuse, Dependence, and the DSM

The DSM-IV-TR (APA, 2000) provides specific criteria for diagnosing substance use disorders, including Sedative, Hypnotic, or Anxiolytic Dependence and Sedative, Hypnotic, or Anxiolytic Abuse. Dependence is defined as a cluster of cognitive, behavioural and physiological symptoms indicating recurrent, compulsive use of a substance despite significant substance-related problems (APA, 2000), similar to the concept of addiction (O'Brien, Volkow & Li, 2006). As noted previously, regular use of anxiolytics or sedatives can induce physiological adaptations, including increased tolerance and a withdrawal syndrome when the substance is discontinued, even when used according to therapeutic guidelines (Lader, 2007). DSM-IV-TR substance dependence can involve symptoms of physical tolerance and withdrawal, but these are not required for a diagnosis and are insufficient grounds for a diagnosis unless accompanied by at least one additional symptom (APA, 2000). Physical dependence alone does not imply addiction, and the use of the term dependence within the anxiolytic and sedative misuse literature can thus be misleading if interpreted to involve intentional misuse. Within the DSM-IV-TR framework, substance abuse is defined as a maladaptive pattern of substance use resulting in significant negative physical, social, interpersonal or legal consequences (APA, 2000). However, in the prescription drug misuse literature, it is common to find the term abuse employed to refer to recreational use or equated to non-prescribed use (e.g., Compton & Volkow, 2006; Griffiths & Johnson, 2005; O'Brien,

2005), and substantially less common to find it describing substance abuse as defined by DSM-IV-TR criteria (e.g,. Dåderman & Edman, 2001; Lavie, Fatséas, Denis & Auriacomb, 2009). This idiosyncratic usage of the terms abuse and dependence within the prescription drug misuse literature is one source of confusion and inconsistency around terminology.

The most recent update to the DSM (DSM-V; APA, 2013a) merged the categories of substance abuse and substance dependence into a single diagnosis of substance use disorder. This change was prompted by a desire to more accurately reflect the symptoms of problematic substance use and to minimize confusion around the term dependence (APA, 2013b). The discussion in this section upholds the distinction between abuse and dependence, as defined by the DSM-IV, as the published research to date has employed this distinction.

1.5.2 Non-Prescribed Use

Defining misuse of prescription drugs as any use without a physician's prescription is an approach employed in numerous studies (e.g., Boyd, McCabe, Cranford & Young, 2007; Kelly & Parsons, 2007; McCabe, 2005; McCabe et al., 2006) as well as in the Monitoring the Future (MTF) study, a large-scale epidemiological survey in the US. Respondents of the MTF are instructed to report on their use of medications "on your own—that is, without a doctor telling you to take them" (Johnston, O'Malley, Bachman & Schulenberg, 2009). This approach is problematic as equating prescription drug misuse with non-prescribed use excludes prescribed use that deviates from the physician's recommendations, such as by exceeding the recommended dosage or deviating from the normal route of administration (Barrett et al., 2008). This characterization also fails to

distinguish between respondents' motives for use. For example, a non-prescribed anxiolytic or sedative may be used to alleviate physical or psychological discomfort, for intoxicating purposes, or to modulate the effects of other drugs. These types of misuse are likely to have differing patterns of social, familial, and individual predictors (Compton & Volkow, 2006), but are grouped together using this form of classification.

1.5.3 Comprehensive Definitions of Misuse

Increasing recognition of the inconsistency in terminology has impelled researchers and policymakers to work towards consensus. As a result of such a collaboration, the Canadian Centre on Substance Abuse proposed a definition of prescription drug misuse as use "that is associated with increased risk for harm, such as: obtaining the drugs from illegitimate sources, deviating from accepted medical practice and/or scientific knowledge, or taking the drugs for purposes which are not therapeutic" (CCSA, 2012). Comparable comprehensive definitions of prescription drug misuse have been employed in epidemiological research. The National Survey of Drug Use and Health (NSDUH) is annual study in the US that tracks trends in drug use and associated harms at a population level. The NSDUH uses the term "nonmedical" use of psychotherapeutics, defined as "use without a prescription of the individual's own or simply for the experience or feeling the drugs caused" (SAMHSA, 2011b). The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), also conducted in the US, defines nonmedical prescription drug use as "without a prescription, in greater amounts, more often, or longer than prescribed, or for a reason other than a doctor said you should use them" (Blanco et al., 2007). Within the scientific literature, similar broad definitions of prescription drug misuse have been widely adopted (e.g., Arria, Caldeira,

O'Grady et al., 2008; Arria, O'Grady, Caldeira, Vincent & Wish, 2008; Currie et al., 2011; Nattala, Leung, Abdallah, Murthy & Cottler, 2012).

The formulation of clearly operationalized definitions of prescription drug misuse allows for systematic estimation of anxiolytic and sedative misuse prevalence at a population level and for cross-study comparisons of investigations employing similar methodology. However, comprehensive definitions have been critiqued for being overly inclusive. For example, the NESARC definition is based in part on prescription status (i.e., non-prescribed medication use), in part on users' behaviours (i.e., use of a medication in greater amounts or more frequently than prescribed), and in part on users' subjective motives (i.e., use of a medication for a reason other than that recommended by the prescribing physician). The complex structure of this comprehensive definition means that respondents are required to recall multiple pieces of information to answer one question (Boyd & McCabe, 2008). Further complicating matters for researchers, a study participant's affirmative response provides no information about which aspects of the definition were endorsed, or even if the participant met more than one (or all) of the stipulated conditions (Boyd & McCabe, 2008). Ultimately, comprehensive definitions capture a heterogeneous collection of possible behaviours and motivations under a single descriptive term that is likely to be of little predictive value, making it difficult for researchers to parse out specific patterns of prescription drug misuse and identify factors associated with specific forms of misuse (Barrett et al., 2008).

As the body of literature has grown, it has become increasingly clear that unitary definitions of misuse inadequately represent the heterogeneity among various forms of prescription drug misuse (Barrett et al., 2008; Fischer & Rehm, 2007). Researchers have

called for more refined assessment of prescription drug misuse and for research questions that disaggregate specific elements of misuse, including motives, prescription status, and varying misuse behaviours (Boyd & McCabe, 2008; McCabe, Cranford, Boyd & Morales, 2008). Gaining a better characterization of anxiolytic and sedative misuse through this approach has the potential to increase our understanding of etiological pathways to prescription anxiolytic and sedative misuse, to better understand the health consequences of misuse, and to inform the development of effective prevention and intervention programs, thereby assisting treatment providers in addressing clients' individual needs (SAMHSA, 2011a).

1.6 Motives for Anxiolytic and Sedative Misuse

The importance of considering motives in empirical investigations of anxiolytic and sedative misuse is illustrated in the preceding discussion. In the context of substance use, motives can be defined as the reasons underlying an individual's decision to use a substance (Cox & Klinger, 1988). Motives have been studied extensively within the literature on alcohol, tobacco and illicit drug use. Understanding the motives underlying substance use behaviour can provide information about the antecedents of substance use, patterns of use, probable consequences, and the types of interventions that may be useful (Cooper, 1994; Cox & Klinger, 1988; Kuntsche, Knibbe, Gmel & Engels, 2005). Moreover, in addition to predicting substance use outcomes, varying motives for alcohol and drug use have been linked to distinct cognitive and affective correlates (Comeau, Stewart & Loba, 2001; Scott, Hides, Allen & Lubman, 2013; Zvolensky et al., 2007).

Researchers have described two broad subtypes of prescription drug misuse, characterized by either therapeutic or non-therapeutic motives and associated with

distinct patterns of use (Boyd & McCabe, 2008; Griffiths & Johnson, 2005). Non-therapeutic motives are thought to be associated with use of the drug in social contexts, concurrent use of other substances, alternate routes of administration, and intermittent but heavy usage (Boyd & McCabe, 2008; Busto et al., 1986; Griffiths & Johnson, 2005). In contrast, therapeutically motivated prescription drug misuse is considered an attempt to ameliorate unpleasant psychological or physical symptoms, with motives corresponding with the drug's pharmaceutical indication (McCabe, Boyd & Teter, 2009). According to this model, therapeutic misuse may involve chronic usage but generally does not involve dose escalation, co-administration of other substances, or alternate routes of administration (Boyd & McCabe, 2008). While therapeutic misuse may appear to be less harmful than non-therapeutic misuse, there are risks to the user regardless of motive (Goldsworthy, 2010). Self-medication has been linked to the development of substance dependence and exacerbation of mental health symptoms (Busto et al., 1986; Robinson, Sareen, Cox & Bolton, 2011) and even therapeutic use of anxiolytics and sedatives puts users at risk of experiencing adverse side effects of these drugs, including memory impairments, accidents, and withdrawal (Griffiths & Weerts, 1997). It is important to note that motive for use is independent of prescription status, and both prescribed and non-prescribed users may report therapeutic or non-therapeutic motives (Boyd & McCabe, 2008).

A growing body of research has documented a variety of specific therapeutic and non-therapeutic motives for anxiolytic and sedative misuse. Therapeutic motives include ameliorating symptoms of insomnia or anxiety, relieving stress, and coping with feelings of depression. Non-therapeutic motives for anxiolytic and sedative misuse include

intoxication (i.e., getting high), increasing sociability, experimentation/curiosity, and safety compared to street drugs (Boyd et al., 2006; Holloway & Bennett, 2012; Morgan et al., 2013; Nattala et al., 2012; Pedersen & Lavik, 1991; Quintero, 2009; Victorri-Vigneau et al., 2007). Non-therapeutic motives reported by anxiolytic and sedative users also include modulating the effects of other drugs, including enhancing the effects of alcohol or opioids and counteracting the negative effects of cocaine or amphetamines (Sajan et al., 1998). Individual anxiolytic and sedative users may report multiple motives for use (Pedersen & Lavik, 1991). For example, in a sample of patients receiving opioid maintenance treatment, Fatséas, Lavie, Denis and Auriacombe (2009) found that a majority of BZ users (53 percent) reported both therapeutic and "hedonic" motives for BZ use, while 32 percent reported exclusively therapeutic motives and 15 percent reported exclusively hedonic motives. In this study, therapeutic BZ use was defined as use aimed at reducing negative affective states, feelings of tension, or withdrawal symptoms, while hedonic BZ use was defined as use aimed at pursuing pleasure only. Endorsing a greater number of motives for anxiolytic and sedative misuse has been associated with heavier use (Nattala, Leung, Abdallah & Cottler, 2011) and co-administration of anxiolytics and sedatives with alcohol (Nattala et al., 2012).

Although clinical observations and theoretical predictions suggest that therapeutic and non-therapeutic forms of anxiolytic and sedative misuse are likely to be associated with differing sets of predictors at the individual level (Compton & Volkow, 2006), only a small number of studies have explicitly investigated this. In a study of anxiolytic and sedative misuse among adolescents, Pedersen and Lavik (1991) presented a classification of four groups: non-users, prescribed users, non-prescribed "self-medication" users, and

non-prescribed "intoxication" users. Intoxication users of both sexes reported the highest levels of alcohol and cannabis consumption. Among adolescent girls, all anxiolytic and sedative users had higher levels of mental health symptoms than non-users; however, the pattern was less clear for boys. In the study by Fatséas et al. (2009) described above, patterns of BZ use differed between motive groups, with exclusively hedonic users more likely than exclusively therapeutic users to report using BZs in combination with other substances, obtaining BZs on the black market, and using alternate routes of administration. Interestingly, Fatséas et al. found no differences between motive groups in terms of demographic variables or substance use history. However, this study focused on a relatively small sample of opioid-dependent individuals, and as such, findings may not be representative of other groups of anxiolytic and sedative users.

In a study of university students reporting non-prescribed anxiolytic or sedative use, McCabe et al. (2009) generated three subtypes: "self-treatment," "recreational," and "mixed". Findings suggested that the recreational and mixed subtypes were more prevalent among men, while the self-treatment subtype was more prevalent among women. Consistent with predicted associations between non-therapeutic motives for anxiolytic and sedative use and other substance use, higher levels of recent binge drinking and past-year illicit drug use were found among the recreational subtype as compared to the self-treatment subtype. However, all anxiolytic and sedative users, regardless of subtype, had higher rates of alcohol- and drug-related problems than anxiolytic and sedative non-users. Although McCabe et al.'s study provides empirical support for heterogeneity in anxiolytic and sedative misuse, the method of classifying the subtypes complicates interpretation of the results. The self-treatment subtype was defined

partly by motive and partly by patterns of use, containing only users who reported motives consistent with the main pharmaceutical indications of anxiolytic and sedative drugs and no alcohol co-administration. For example, an individual who reported exclusively therapeutic motives but used alcohol concurrently with an anxiolytic would be classified within the mixed subtype. However, subtyping did not take into account routes of administration of anxiolytics and sedatives or co-administration with substances other than alcohol. Thus, a respondent who used an anxiolytic intranasally, or a sedative to induce sleep following cocaine use, could have been classified within the self-treatment subtype. This approach makes it difficult to discern from these data whether problematic use of other substances can be meaningfully differentiated based on motive for anxiolytic and sedative use.

Gaining insight into the characteristics that differentiate therapeutic and non-therapeutic motives for use of anxiolytics and sedatives has important implications, including predicting risk for adverse consequences, detecting individuals in need of treatment for other conditions (e.g., anxiety disorders) and developing targeted strategies for intervention that better meet clients' needs by addressing underlying motives for misuse (Boyd & McCabe, 2008; Rigg & Ibañez, 2010).

1.7 Personality and Motivational Models of Substance Use

Personality traits encompass a range of individual differences in patterns of thinking, feeling, and behaving (Caspi, Roberts & Shiner, 2005). These characteristics are commonly described in terms of broader higher-order traits that subsume narrower lower-order traits. Personality differences have been related to health outcomes based on their associations with behaviours that can affect health positively or negatively, including

social relationships, exercise, eating habits, and substance use (Caspi et al., 2005). Multiple etiological frameworks for substance use propose that personality characteristics can reflect individual variation in susceptibility for the use and misuse of different substances (e.g., Conway, Swendsen, Rounsaville & Merikangas, 2002; Grekin, Sher & Wood, 2006; McGue, Slutske, & Iacono, 1999; Sher, Bartholow & Wood, 2000).

Numerous studies have yielded evidence for cross-sectional and longitudinal relationships between higher-order personality traits and substance use. For instance, the five-factor model of personality is an empirically supported taxonomy comprising the traits extraversion, neuroticism, conscientiousness, agreeableness, and openness to experience (McCrae & Costa, 1987; 1997). Low conscientiousness, low agreeableness and high neuroticism have been correlated with higher rates of alcohol use (Malouff, Thorsteinsson, Rooke, & Schutte, 2007). Similarly, in a cross-sectional study of young adults, higher neuroticism and lower conscientiousness were associated with non-prescribed anxiolytic and sedative use (Benotsch, Jeffers, Snipes, Martin & Koester, 2013). In a 9-year longitudinal study, higher baseline levels of neuroticism and lower levels of conscientiousness predicted prescription drug misuse at follow-up (Turiano, Whiteman, Hampson, Roberts & Mrozczek, 2012). Eysenck's (1990) personality theory, focusing on the three higher-order dimensions of extraversion, neuroticism, and psychoticism, has also been applied to the understanding of substance use, with high neuroticism and psychoticism scores being particularly implicated in problematic alcohol and drug use (e.g., Sher et al., 2000).

While personality constructs have been described as "distal" to drug use and abuse behaviours (Sher et al., 2000), evidence suggests that personality factors can

differentiate substance users based on their motives for use of various substances. Cloninger (1987) proposed a typology of alcoholism that classified alcoholics into two groups based on age of onset of alcohol use and common comorbid conditions. Type I alcoholism was characterized by a later age of onset and proneness to anxiety and depression. Type II alcoholism tended to have an earlier age of onset and was linked to impulsivity and antisociality. These groups were differentiated in terms of three personality dimensions: novelty seeking, harm avoidance, and reward dependence. Type I alcoholism was associated with lower novelty seeking, higher harm avoidance, and higher reward dependence. Type II demonstrated an inverse pattern, being associated with higher novelty seeking, lower harm avoidance, and lower reward dependence (Cloninger, 1987). Motives for alcohol use also differed between groups. Use of alcohol to cope with negative life events was more characteristic of Type I, while Type II was associated with use of alcohol for its stimulating or enhancing effects (Cloninger, 1987).

Building on Cloninger's work, more recent investigations of individual differences in the development of substance use problems have demonstrated relationships between more specific personality dimensions and motives for substance use. This research has informed the development of a motivational theory proposing that different personality traits are linked to susceptibilities for use of substances with varying reinforcing properties (Conrod, Pihl, Stewart & Dongier, 2000). Within this theoretical framework, Conrod, Pihl et al. developed a system of classifying substance-abusing individuals, focusing on four personality dimensions thought to relate to vulnerability for problematic use of different drug classes: anxiety sensitivity (AS), hopelessness (H), sensation seeking (SS), and impulsivity (IMP). AS describes a tendency to fear that

anxiety, particularly its accompanying sensations of physiological arousal, will lead to social embarrassment, illness, or loss of control. H describes a tendency towards a pessimistic outlook and sadness. SS describes a propensity to seek out exciting or exhilarating experiences, including the use of substances with euphoric subjective effects. IMP describes a pattern of behavioural disinhibition coupled with difficulty in anticipating long-term negative consequences of one's behaviour. This conceptualization considers personality traits as relatively stable constructs that act as risk factors for substance use (Conrod, Pihl et al., 2000; Conrod, Stewart et al., 2000).

Research has provided empirical support for this motivational theory. The AS personality dimension has been positively associated with the use of substances that can ameliorate anxiety, including alcohol, tobacco, anxiolytics, and sedatives (Woicik, Stewart, Pihl & Conrod, 2009; Stewart & Kushner, 2001). High AS individuals have higher rates of anxiety and somatization disorders (Conrod, Pihl et al., 2000; Conrod & Woicik, 2002) and alcohol users with high levels of AS tend to report motives for use indicating a desire to reduce negative affective states (Stewart & Zeitlin, 1995). AS is inversely related to the use of marijuana and stimulants, possibly because the physiological sensations induced by these substances would be experienced as aversive by high-AS individuals (Woicik et al., 2009). The H dimension is associated with low self-esteem and vulnerability for depression. High levels of H have been associated with problematic use of substances to ameliorate these forms of negative affect, including alcohol and opioids (Conrod, Pihl et al., 2000; Woicik et al., 2009). High levels of SS have been associated with increased quantity and frequency of alcohol consumption, use of alcohol for its euphoric effects (Conrod, Pihl et al., 2000; Krank et al., 2011), and

misuse of prescription stimulant and analgesic medications (Arria, Caldeira, Vincent et al., 2008; Herman-Stahl, Krebs, Kroutil & Heller, 2007; Jardin, Looby & Earleywine, 2011). IMP has been associated with problem alcohol use, polysubstance use, illicit stimulant drug use (Krank et al., 2011; Conrod, Pihl et al., 2000), and problem gambling (Verdejo-García, Lawrence & Clark, 2008). IMP has also been specifically linked to risk for early-onset substance problems (Pulkkinen & Pitkänen, 1994).

Although research on personality and substance use largely focuses on higher-order personality traits, lower-order traits may provide greater accuracy in terms of prediction of behavioural outcomes (Paunonen & Ashton, 2001). Conrod, Stewart et al. (2000) argue that by the use of specific, narrowly defined constructs, this motivational model improves incrementally upon more general descriptors of personality (e.g., neuroticism) and motives for substance use (e.g., tension reduction). These personality dimensions have shown greater specificity for various forms of substance use and misuse than other, broader, models of personality risk (Conrod & Woicik, 2002; Krank et al., 2011), suggesting that this motivational framework is well suited for examining prescription anxiolytic and sedative misuse.

1.8 Beyond Individual Differences

Etiological models of substance use posit that both internal (or endogenous) factors and external (or exogenous) factors play a role in the development and maintenance of problematic substance use (Sloboda, Glantz & Tarter, 2012). While the preceding discussion has focused on internal factors that vary across individuals, including personality traits and psychopathology, external variables are also related to risk for prescription drug misuse, abuse and dependence (Compton & Volkow, 2006).

These encompass characteristics of the drugs themselves, including their pharmacological properties and manner of administration (Ballantyne & LaForge, 2007). These factors are discussed with reference to anxiolytics and sedatives in the following sections.

1.8.1 Characteristics of Anxiolytic and Sedative Medications

Pharmacological properties, drug formulation and route of administration all contribute to a drug's misuse liability. In particular, pharmacokinetic factors, including absorption rate and half-life, are important determinants of reinforcing effects in laboratory studies (Busto, Lanctôt, Bremner & Sellers, 1995; Victorri-Vigneau et al., 2007). Anxiolytics and sedatives vary in terms of such properties (Brust, 2004), and those with higher potency, rapid onset, and shorter duration of action are thought to have a greater potential for misuse, abuse, and dependence (APA, 2000; Roache & Meisch, 1995). Interestingly, post-marketing studies of misused medications suggest that the relationship between pharmacological properties and misuse liability demonstrated in controlled research settings may have limited predictive validity for real-world patterns of misuse (Grudzinskas, et al., 2006), suggesting a need for more ecologically-valid investigations of anxiolytic and sedative medication misuse.

1.8.2 Prescription Regimens

Prescription regimens have received little attention within the literature. Because of their rapid onset, anxiolytics and sedatives may be prescribed on a short-term or *p.r.n.* ("as-needed") basis. As anxiety disorders frequently present with a variable course, patients often prefer medications that can be taken intermittently (Longo & Johnson, 2000), allowing them to control the timing and dosage of medication administered (Westra & Stewart, 2002). Although formal practice guidelines recommend regularly

scheduled administration paradigms (Canadian Psychiatric Association, 2006; e-CPS, 2012), evidence suggests that many physicians routinely instruct their patients to take these medications as needed (Westra & Stewart, 2002). One study of long-term BZ use among patients with panic disorder found that only five percent reported using their medications exclusively on a regularly-scheduled basis (Westra & Stewart, 2002) and another study reported that BZ users tend to shift from regularly scheduled to as-needed use over time (Romach et al., 1995). In addition to enhancing patients' perceived control over their symptoms, physicians who advocate *p.r.n.* use argue that this manner of medication administration can reduce frequency of medication use, promote exposure to anxiety-inducing stimuli, attenuate the development of dependence, and facilitate discontinuation (Kaplan & DuPont, 2005; Westra & Stewart, 2002). However, available evidence provides little support for these assertions. *P.r.n.* users often administer their medications in a symptom-contingent manner, which has been criticized for inducing conditioned drug tolerance (Dammen, Haug, & Götestam,1994). *P.r.n.* anxiolytic use has also been associated with hypervigilance towards cues of physical threat on a selective attention task (Stewart, Westra, Thompson & Conrad, 2000) and poorer outcomes from cognitive-behavioural therapy (Westra, Stewart & Conrad, 2002). Furthermore, among a sample of psychiatric inpatients, *p.r.n.* use of anxiolytics and sedatives was associated with a history of recreational drug use (D'Mello, Lyon, Colenda & Fernandes, 2000).

There is a dearth of research on relationships between manner of anxiolytic and sedative self-administration and misuse of these drugs. The greater flexibility with *p.r.n.* administration suggests the potential for use of anxiolytics and sedatives in ways that are inconsistent with therapeutic guidelines. Examples could include administering these

medications in excess quantities on sporadic occasions or diverting doses to other people. Examining this assumption in a sample of anxiolytic and sedative users is an important gap in the literature.

1.9 Overarching Goals of the Current Research

Notwithstanding limitations in the way prescription drug misuse has been defined in the literature, existing research suggests that misuse of prescription anxiolytic and sedative medications constitutes a significant public health issue. This dissertation research was designed to address gaps in the existing literature resulting from inconsistencies in how prescription drug misuse has been operationalized and from the tendency for this phenomenon to be presented as a unitary construct, rather than as a complex assortment of behaviours and motivations. Thus, one goal was to investigate heterogeneity in patterns of misuse and diversion within adult Canadian prescribed and non-prescribed anxiolytic and sedative users. A further goal was to examine individual difference variables and medication-related factors that may be related to various forms of misuse. These studies build upon prior research by seeking evidence for a heterogeneous conceptualization of anxiolytic and sedative misuse in terms of motives for use and the contexts and manner in which these substances are misused.

1.9.1 Forms of Anxiolytic and Sedative Misuse Assessed

In this series of studies, misuse encompasses the use of an anxiolytic or sedative medication that was not prescribed to the user as well as use in a way other than that intended by the prescriber (Boyd & McCabe, 2008). Examples of the latter assessed in these studies include the use of a medication in quantity or frequency exceeding the

prescribed guidelines, the use of a medication by an alternate route of administration, and the deliberate co-administration of a medication with another psychoactive substance. Separately evaluating these forms of misuse was intended to identify heterogeneity within anxiolytic and sedative misuse and allow for analysis of specific correlates of these behavioural patterns. Diversion, defined as provision of a medication by a prescribed user to another individual, is also investigated. Although some past research has defined prescription drug misuse to include deviating from recommended guidelines by taking *less* of a medication than prescribed (e.g., Holloway & Bennett, 2012), taking a reduced dosage of an anxiolytic or sedative was not assessed as a form of misuse in the present studies. The rationale for this decision is that taking less of a medication would not be associated with the same potential risks and harms as those associated with medication overuse, such as overdose or development of dependence symptoms.

1.9.2 Study Descriptions

This document is comprised of four empirical studies involving adults recruited from the general community and an outpatient substance use treatment program in the Halifax Regional Municipality. In Study 1, patterns of anxiolytic and sedative misuse and diversion were investigated among adults (N=67) in the community with current prescriptions for these medications. Objectives for this study included investigating associations between personality dimensions, motives, and misuse behaviours. In Study 2, patterns of non-prescribed anxiolytic and sedative use were examined among community-recruited adults. This study also included a sample of non-prescribed stimulant users to allow for comparisons across classes of prescription psychiatric medications (total N=71). Objectives included identifying distinct patterns of use and

individual difference correlates of therapeutic and non-therapeutic motives. Study 3 focused on medication characteristics, including prescription regimens and misuse of BZ and non-BZ anxiolytics and sedatives, among all participants of Study 1 and the subset of Study 2 participants with histories of prescribed anxiolytic and sedative use (total N=85). Finally, in Study 4, misuse of a specific non-BZ was evaluated among a high-risk substance-using population, thereby extending research to a group of anxiolytic and sedative users that has received little attention in the literature. The sample for this study (N=74) was drawn from a community-based methadone maintenance program. Specific hypotheses are discussed in the introduction section for each study. In general, therapeutic and non-therapeutic motives were expected to be differentially linked to substance use history, personality, comorbid psychopathology, and patterns of misuse.

1.9.3 Advancing Theory

This project advances the theoretical conceptualization of prescription drug misuse that proposes that subtypes of misuse, classified based on motive for use and prescription status, can be differentially linked to other substance use and substance-related harms (Boyd & McCabe, 2008). This research also advances existing theory by applying the motivational model of substance abuse proposed by Conrod, Pihl et al. (2000) to the misuse of prescription anxiolytics and sedatives. Although researchers have identified motives for use as an important factor to consider when examining prescription drug misuse (e.g., McCabe et al., 2009), no published studies to date have assessed the association between personality characteristics, motives, and anxiolytic and sedative misuse.

CHAPTER 2 Study 1: Medication Misuse and Diversion in Adult Prescribed Users of Anxiolytics and Sedatives[5]

2.1 Abstract

Study Objective: To identify patterns of misuse and diversion of anxiolytic and sedative drugs among a sample of prescribed users. ***Design:*** Cross-sectional study. ***Setting****:* General population of a mid-sized city in Atlantic Canada. ***Participants****:* Sixty-seven adults (aged 19–61 years) with current prescriptions for anxiolytic or sedative drugs. ***Intervention:*** Face-to-face interviews and questionnaires were used to gather information on demographics as well as variables relating to drug misuse and diversion such as personality dimensions, psychiatric symptoms, and other substance use. ***Measurements and Main Results:*** Of the 67 participants, 36 (54%) reported misusing their drugs on at least one occasion, and 35 (52%) reported diverting their drugs at least once. A variety of forms of anxiolytic or sedative misuse were reported, including exceeding the recommended dosage (28 participants [42%]), deliberately using the drug with alcohol or another drug (27 [40%]), or taking it by an alternate route of administration (5 [7%]). Misuse and diversion were associated with a history of substance use and substance-related problems, as well as personality characteristics

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relating to impulsivity and hopelessness. Diversion was associated with an increased likelihood of having taken any psychoactive prescription drug without having a valid prescription for it. ***Conclusion:*** A variety of forms of drug misuse and diversion occurred among this population of adult prescribed users of anxiolytics or sedatives. Likelihood of engaging in misuse or diversion was associated with a range of individual differences, including other substance use, substance use disorders, and personality characteristics. Despite the modest sample size and cross-sectional design, this study identified substantial heterogeneity in prescription anxiolytic and sedative misuse, suggesting that the use of clearly defined operational criteria will be essential in future efforts to further characterize this phenomenon.

2.2 Introduction

Anxiolytic and sedative medications have important applications in the treatment of anxiety and sleep disorders (Busto, 1999; Nowell et al., 1997; O'Brien, 2005; Romach et al., 1995). In addition to having beneficial clinical effects, these drugs have been shown to be vulnerable to misuse (Becker et al., 2007; Hertz & Knight, 2006; O'Brien, 2005), which is associated with a range of negative consequences, including cognitive and psychomotor impairment (Buffett-Jerrott & Stewart, 2002; Lader, 1999; Stewart, 2004), harmful interactions with alcohol or other drugs (Brust, 2004; Lader, 1999), and risk for accidents and overdose (Busto, Kaplan, & Sellers, 1980; Coben et al., 2010; Griffiths & Weerts, 1997; Lader, 1999). Despite increasing recognition of all forms of prescription drug misuse and indications that anxiolytic and sedative misuse is becoming more widespread (Blanco et al., 2007; Hertz & Knight, 2006; Riggs, 2008), little is known about the individual demographic and clinical characteristics associated with misuse of these drugs (McCabe, 2005; Boyd & McCabe, 2008).

Concerns about misuse of anxiolytics and sedatives in the general population have tended to focus on two broad but distinct domains: overuse by the person for whom the drug was prescribed, and use that is inconsistent with the drug's prescribed purpose. These forms of misuse can be differentiated based on whether the person's primary motive in taking the drug is therapeutic or non-therapeutic (O'Brien, 2005; Farnsworth, 1990; Griffiths & Weerts, 1997). Therapeutic misuse is typically motivated by a desire to alleviate symptoms of a mental or physical health concern, which may be manifested as use exceeding the recommended dose, frequency, or duration of use (Boyd & McCabe, 2008). This form of misuse does not usually involve ingesting the drugs with other

substances or taking them by alternate routes of administration (Boyd & McCabe, 2008). Therapeutic anxiolytic or sedative misuse is often described in the context of long-term pharmacologic management of anxiety or sleep disorders, in which prolonged prescribed use of anxiolytics and sedatives results in physical symptoms of dependence and a potentially dangerous withdrawal syndrome (Brust, 2004; Griffiths & Johnson, 2005; Lader, 1999). Barbiturates (Brust, 2004; Morgan, 1990) and benzodiazepines (Busto, 1999; Busto & Sellers, 1991; O'Brien, 2005) have been identified as drugs of greatest concern in this respect. More recently, concerns with the use of non-benzodiazepine alternatives have also surfaced (Cimolai, 2007; Curran & Musa, 2002; Hajak et al., 2003; Jones & Sullivan, 1998; Rush, Baker, & Wright, 1999).

Non-therapeutic misuse of anxiolytics and sedatives has been associated with very different patterns and contexts of use, including use to obtain a euphoric effect, concurrent polysubstance use, parenteral routes of administration[6], and intentionally increased dosages (Barrett et al., 2008; Lader, 1999; O'Brien, 2005). However, it is difficult to draw comparisons between the individuals who engage in these distinct forms of anxiolytic or sedative misuse, as non-therapeutic misuse is often discussed as exclusively relating to persons who obtain the drug from illegitimate sources, whereas therapeutic misuse is typically considered as only relating to those with prescriptions for the drugs (O'Brien, 2005).

Studies of non-therapeutic misuse that focus exclusively on users of non-prescribed drugs exclude individuals with a valid prescription who intentionally

[6] Parenteral administration refers to the introduction of a substance into the body by a means other than the digestive system. In the case of prescription anxiolytics and sedatives, which are normally taken orally, parenteral routes include injection, inhalation (smoking), and intranasal use.

administer their drug in ways that are inconsistent with the recommended guidelines for use (Barrett et al., 2008; Kelly & Parsons, 2007; McCabe, 2005; McCabe, 2008; McCabe et al., 2006). Among the studies that have limited their samples to individuals who report use of such drugs outside the confines of a physician's prescription, associations have been found between use of non-prescribed anxiolytics or sedatives and increased levels of psychiatric symptomatology, substance use, and other risky behaviours (Goodwin & Hasin, 2002; McCabe, 2005; McCabe et al., 2006).

To our knowledge, little research attention has been directed toward examining motives for anxiolytic and sedative misuse among those for whom the drugs were prescribed or toward investigating specific forms of drug misuse in this population, such as exceeding the recommended dosage, deviating from the normal route of administration, or co-administering the drug with alcohol or other drugs. In part, this may be because much of our current knowledge is derived from large epidemiologic surveys. Although useful for collecting data from large numbers of respondents, these types of studies are often not well suited to gathering this type of detailed information (Barrett et al., 2008). These studies have also been criticized for grouping together heterogeneous subtypes of prescription drug misuse; for example, failing to differentiate between users based on prescription status or motives for use (Boyd & McCabe, 2008).

Specific predictors of diversion of anxiolytics and sedatives by those for whom the drugs were prescribed have also received relatively scant attention. This is an interesting omission, considering that anxiolytic or sedative misuse is often discussed in the context of diversion of these drugs to users without prescriptions (Fatséas, Lavie, Denis, & Auriacombe, 2009; McCabe, 2005). In some past investigations, the analysis

has included all individuals who reported being approached to share or sell their drug (McCabe et al., 2006), which does little to elucidate the factors relating to actual diversion. Among persons taking prescribed stimulant drugs, use of non-prescribed stimulants (Poulin, 2001), misuse of one's own drug (Darredeau, Barrett, Jardin, & Pihl, 2007), comorbid mental illness (Wilens, Gignac, Swezey, Monuteaux, & Biederman, 2006) and younger age at first prescription (Darredeau et al., 2007) have been identified as significant predictors of diversion. It is unknown whether a similar set of variables may relate to anxiolytic and sedative diversion among prescribed users, or if the factors relating to anxiolytic and sedative diversion are specific to those types of medication.

Researchers have begun to note the importance of differentiating the social, psychological, motivational, and demographic predictors associated with varying forms of prescription drug misuse (Barrett et al., 2008; Boyd & McCabe, 2008; Compton & Volkow, 2006). In the broader literature on addiction, the observed heterogeneity among substance users has prompted numerous investigations of individual difference factors relating to drug and alcohol use. These efforts have provided strong empirical support for relationships between various personality characteristics, motives for substance use, and development of substance use problems (Jaffee & D'Zurilla, 2009; Martin & Sher; 1994; Sher et al., 2000). For example, there is evidence linking the specific personality dimensions of anxiety sensitivity, sensation seeking, impulsivity, and hopelessness to distinct patterns of motivational correlates, substance use, and psychiatric symptoms (Conrod & Woicik, 2002; Conrod, Pihl et al., 2000). Relationships have been demonstrated between sensation seeking and misuse of prescription stimulants (Arria, Caldeira, Vincent et al., 2008; Low & Gendaszek, 2002) and analgesics (Arria, Caldeira,

Vincent et al., 2008); however, these studies included non-prescribed use of these drugs in their definitions of misuse. One group of authors found that anxiety sensitivity and hopelessness were related to higher frequencies of use of a broad category of sedative drugs involving both prescription anxiolytics and opioids (Woicik et al., 2009).

To our knowledge, the specific personality and motivational factors associated with misuse and diversion of anxiolytic and sedative drugs in particular have not been examined. Therefore, in this study, we aimed to identify patterns and correlates of anxiolytic and sedative misuse and diversion in an adult community sample of individuals for whom these drugs were prescribed. It was expected that misuse and diversion would be related to use of alcohol and other drugs, greater prevalence of psychiatric symptoms, and personality characteristics associated with risk for substance use. Individuals reporting misuse of their own drugs were also expected to be more likely to have engaged in diversion and to have used anxiolytic and/or sedative drugs without a prescription. These proposed associations were expected to vary depending on the users' motives. Individuals who had misused their drug for reasons that are inconsistent with the drug's typical therapeutic purpose were expected to report higher levels of other substance use, psychopathology, and personality risk variables compared with those who had engaged in those behaviours for exclusively therapeutic purposes.

2.3 Method

2.3.1 Study Participants

Men and women aged 18 years or older were recruited from the general population of the Halifax Regional Municipality of Nova Scotia, Canada, based on current use of a prescribed anxiolytic or sedative drug to treat symptoms of anxiety or

disrupted sleep. Recruitment took place through advertisements on community bulletin boards and Internet classified advertising sites. Additional recruitment took place through the Dalhousie University Department of Psychology Research Participation System (Halifax, Canada). These strategies were based on methods used in the past to successfully recruit prescribed (Barrett, Darredeau et al., 2005) and non-prescribed (Darredeau et al., 2007) users of prescription psychiatric drugs. Eligible medications included benzodiazepines and non-benzodiazepines with hypnotic, sedative, or anxiolytic effects. Because drugs in these categories are often prescribed interchangeably for treatment of anxiety and insomnia (Brust, 2004), no differentiation was made at the time of recruitment. Participants received $10 CAD compensation for each hour of study participation or one credit point toward psychology undergraduate courses. Written informed consent was obtained from all participants. Institutional approval was obtained from the Dalhousie University Health Sciences Research Ethics Board.

2.3.2 Study Measures

2.3.2.1 Polysubstance and Prescription Drug Use Interview

A structured, face-to-face interview that was adapted from an existing measure (Barrett, Darredeau et al., 2005; Barrett, Gross, Garand, Pihl, 2005; Darredeau et al., 2007; see Appendix B) was used to gather information about prescription drugs. Past research suggests that this measure is a reliable means of collecting accurate, in-depth substance use details (Barrett, Gross et al., 2005). To assist with recollection, participants were prompted with cards depicting commonly prescribed sedatives, anxiolytics, stimulants, and analgesics. These cards were adapted from the NSDUH (SAMHSA, 2008) and were supplemented with images from the *Compendium of Pharmaceuticals*

and Specialties (Canadian Pharmacists Association, 2008). Participants reported their age at first prescription, drug dose and frequency, and duration of use. They provided information about instances of prescription drug misuse (i.e., using alternate routes of administration, deliberate co-administration with other substances, or exceeding recommended dosages) and diversion (i.e., selling, trading, or giving away their medication).

Participants were presented with a list of motives based on past research (McCabe, Teter, & Boyd, 2005; McCabe, Cranford, Boyd, & Teter, 2007) and asked to report their primary motives for engaging in anxiolytic or sedative misuse. Participants were given the option of providing a different motive for use if they thought that their motive was not adequately captured in the existing list. These motives were subsequently categorized as therapeutic or non-therapeutic. Therapeutic use was operationally defined as use corresponding to the drug's pharmaceutical indication— typically, to reduce anxiety or help induce sleep. Non-therapeutic use was operationally defined as being inconsistent with the drug's pharmaceutical indication. Specific non-therapeutic motives included the following: to achieve intoxication, to increase or decrease the effects of another drug, to fit in with peers, or to explore the drug's effects out of curiosity. For the purposes of the analysis, individuals who reported ever having used an anxiolytic or sedative with non-therapeutic intent were classified as non-therapeutic users. Therapeutic users were considered to be those individuals who exclusively used anxiolytic or sedative drugs with therapeutic intent and according to recommended guidelines. This approach was based on methods of categorization of prescription drug users that was employed in past research (Boyd et al., 2006; Darredeau et al., 2007).

2.3.2.2 Drug List Questionnaire

This measure (see Appendix B) was adapted from the *Addiction Severity Index* (McLellan, Luborsky, Woody & O'Brien, 1980) and was used to collect information about participants' use of licit and illicit substances, excluding prescription drugs. For each substance used, participants were asked to report their age at first and last use, period of heaviest use, and estimated total number of lifetime uses.

2.3.2.3 Substance Abuse and Dependence Questionnaire

Past and present DSM-IV-TR (APA, 2000) substance abuse and dependence were assessed by using a protocol adapted from the NSDUH (SAMHSA, 2008; see Appendix B). Substance abuse questions were asked of all participants who had used a substance at least 10 times in their lifetime. Both abuse and dependence questions were asked if participants had used the substance at least 10 times during any 30-day period.

2.3.2.4 Substance Use Risk Profile Scale

Assessment of four personality dimensions— anxiety sensitivity, hopelessness, impulsivity, and sensation seeking—was carried out by using the *Substance Use Risk Profile Scale* (SURPS), a validated 28-item self-report tool (Conrod & Woicik, 2002; see Appendix C).

2.3.2.5 Psychiatric Diagnostic Screening Questionnaire

The *Psychiatric Diagnostic Screening Questionnaire* (PDSQ) is a validated self-report measure used to screen for symptoms of DSM-IV-TR Axis I disorders under the categories of mood, anxiety, eating, psychosis, somatoform, hypochondriasis, and substance use (Zimmerman & Mattia, 2001; see Appendix D).

2.3.3 Study Procedures

Interviews were conducted in a standardized format in the following sequence: demographic details, polysubstance interview, drug list questionnaire, and substance abuse and dependence questionnaire. Participants then completed the PDSQ and SURPS. All measures were completed in a single session lasting approximately two hours.

2.3.4 Statistical Analysis

The data were analyzed using SPSS statistical software, version 16.0 (SPSS Inc., Chicago, IL). A series of bivariate analyses was conducted to compare groups delineated by presence or absence of misuse or diversion, and across therapeutic and non-therapeutic motives for misuse. Independent-samples *t* tests were used to examine differences in SURPS dimensions and total number of substances used, and chi-square analyses were used to examine differences across categoric demographic, substance use, and diagnostic categories. To account for the increased possibility for error associated with multiple analyses, the alpha level used to determine statistical significance for the above analyses was set at 0.01.

Stepwise binary logistic regression using the likelihood ratio method was used to evaluate the best predictors of anxiolytic or sedative misuse and diversion, with each coded as a dichotomous outcome. For each regression, all variables found to be significant or marginally significant (*p* value between 0.01 and 0.05) in the preceding bivariate analyses were entered as possible predictors. An a priori power analysis using an alpha of 0.05, a power of 0.8, and an effect size of 0.8 (Cohen's *d*), based on past studies of prescription drug misuse (Barrett, Darredeau et al., 2005; Darredeau et al.,

2007; McCabe et al., 2009), yielded a desired sample size of at least 54 participants for chi-square (χ^2) tests, 50 for *t* tests, and 58 for regression analyses.

2.4 Results

2.4.1 Participant Characteristics

Sixty-seven participants were recruited, ranging in age from 19 to 61 years (M=28.7 years, SD=10.9). Fifty-six participants (84%) were female. Sixty-three participants (94%) were Caucasian, a proportion representative of the overall population of the municipality (Statistics Canada, 2007). All participants had at least a high school education, and 39 (58%) were currently enrolled as postsecondary students. On average, participants had received 2.3 (SD=1.8) different anxiolytic or sedative prescriptions during their lifetime, with the earliest prescription at a mean age of 21.5 years (SD=6.1).

2.4.2 Anxiolytic and Sedative Misuse

Participants reported engaging in a variety of forms of drug misuse (Figure 2.1). The most common forms of misuse reported were exceeding the drug's recommended dosage or deliberately co-administering the drug with another substance. Of the 28 individuals (42%) who reported exceeding their drug's recommended dosage, 14 (21%) admitted to doing so for non-therapeutic purposes at least once. The substances most commonly co-administered with anxiolytics or sedatives were alcohol by 25 participants (37%), cannabis by 16 (24%), cocaine by six (9.0%), amphetamine by six (9.0%), and 3,4-methylenedioxymethamphetamine (MDMA) by six (9.0%). Using a prescribed anxiolytic or sedative by an alternate route of administration was less common than other forms of misuse. All five participants (7.5%) who reported alternate routes of

administration had used the medication intranasally, whereas one (1.5%) also reported injecting the medication.[7]

Individuals who had misused a prescribed anxiolytic or sedative tended to be younger at the time of their first prescription (M=19.8 years, SD=4.8), compared with individuals who never misused their drug (M=23.4 years, SD=6.8), $t(65)=2.49$, $p=0.015$. Younger age at first prescription was also related to several specific forms of misuse, including using an alternate route of administration, deliberately co-administering the drug with other substances, and exceeding the recommended dosage for non-therapeutic reasons. No other significant demographic differences were found for prescription anxiolytic or sedative misuse.

Participants were compared across substance use variables, psychiatric symptomatology, and personality indices based on whether they reported ever using their medication in a way that was not prescribed (Table 2.1). Misuse of anxiolytics or sedatives was strongly related to participants' lifetime histories of other substance use. On average, participants who reported misusing a prescribed anxiolytic or sedative had used a significantly greater number of illicit drugs than those who had never misused their medication. A strong relationship was demonstrated between cocaine and anxiolytic or sedative misuse. Individuals who had used cocaine were almost five times more likely to have misused an anxiolytic or sedative than those who had never used cocaine (Table 2.1). In particular, those who had used cocaine were more likely to report misuse by exceeding the drug's recommended dosage, $\chi^2=9.72$, $p=0.003$. Participants who had met diagnostic criteria for cocaine abuse were over 13 times more likely to report taking an

[7] Percentages refer to the proportion of the overall sample (N=67) reporting each specific form of misuse.

anxiolytic or sedative in excess amounts for non-therapeutic reasons, χ^2=11.82, p=0.004. Anxiolytic or sedative misuse was also significantly associated with a history of regular tobacco use, LSD use, and cannabis abuse. Trends indicating similar relationships were apparent for many of the other substance use and substance use disorder variables (Table 2.1).

Consistent with this pattern, participants reporting any form of anxiolytic or sedative misuse were over 5 times more likely to report problem drug use on the PDSQ than were those who had never misused their medication (Table 2.1). Those reporting misuse were over twice as likely to screen positive for major depressive disorder and post-traumatic stress disorder; however, these trends did not attain statistical significance. There were no other significant group differences on the psychiatric conditions assessed by the PDSQ. Differences in the SURPS personality dimensions were also observed. On average, individuals who had engaged in anxiolytic or sedative misuse obtained significantly higher scores on the impulsivity and hopelessness subscales and trended toward higher scores on the anxiety sensitivity and sensation seeking subscales (Table 2.1). Higher levels of sensation seeking were significantly, and specifically, associated with administering an anxiolytic or sedative by an alternate route of administration, $t(65)$=3.63, p=0.001.

Multiple logistic regression was used to test for unique predictive effects of the variables in question. When controlling for participants' sex and age, the model best predicting general anxiolytic or sedative misuse included two variables: number of illicit drugs used and the SURPS hopelessness subscale, χ^2=20.93, p<0.001. Holding all else constant, an incremental increase in either of these variables was associated with a

significantly greater chance of reporting anxiolytic or sedative misuse. An additional substance used during a participant's lifetime was associated with a 61% increase in the odds of misuse. For the hopelessness subscale, a 1-point elevation was associated with a 22% increase in the odds of misuse. The same two variables were found to be the best predictors of misuse of anxiolytics or sedatives by administering in excess, χ^2=19.37, p=0.001. The number of drugs used and the impulsivity subscale were the best predictors of co-administration of an anxiolytic or sedative with other drugs or alcohol, χ^2=24.96, p<0.001. A two-factor model including the SURPS sensation seeking subscale and PDSQ drinking-related problems was the best fit for predicting anxiolytic or sedative misuse by alternate routes of administration, χ^2=30.18, p<0.001; however, neither of these variables had significant unique predictive effects.

2.4.3 Anxiolytic and Sedative Diversion

Thirty-five (52%) of the 67 participants reported diverting their anxiolytic or sedative drug on at least one occasion (Figure 2.1). All 35 individuals had given away their drug to others. Fewer individuals reported ever selling their drug (4 participants [6.0%]) or trading it for another item (2 participants [3.0%]).[8] No significant differences in diversion based on demographic variables were noted.

Substance use variables, psychiatric symptoms, and personality were compared between participants who reported diverting their anxiolytic or sedative medication and those who reported never diverting (Table 2.2). Diversion was found to be related to a variety of substance use variables, including use of a greater number of illicit drugs, drug-related problems as measured by the PDSQ, cocaine use, and cannabis abuse. Similar

[8] Percentages refer to the proportion of the overall sample (N=67) reporting each specific form of diversion.

relationships were observed for psilocybin use, alcohol abuse, and cocaine abuse, but were not statistically significant. Diversion was also related to certain prescription misuse variables. In particular, diversion was associated with taking a prescribed anxiolytic or sedative in excess for non-therapeutic reasons and with using a psychoactive prescription medication without having a valid prescription for it.[9] A trend was observed on the PDSQ such that individuals who met screening criteria for generalized anxiety disorder were less likely to have diverted their medication. There was also a trend indicating an increased likelihood of diversion among participants with higher scores on the SURPS impulsivity subscale.

Multiple logistic regression was conducted to determine the best predictors of anxiolytic or sedative diversion. When controlling for age and sex, the model best fitting the data included four variables: PDSQ drug-related problems, cannabis abuse, the SURPS impulsivity subscale, and PDSQ generalized anxiety disorder, $\chi^2=31.36$, $p<0.001$. Individuals reporting cannabis abuse were almost nine times more likely to have diverted their medication compared with those with no history of cannabis abuse. Individuals screening positive for PDSQ drug-related problems were almost six times more likely to have diverted than those not reporting such problems. A 1-point increase on the impulsivity subscale was associated with a 24% increased likelihood of diversion. An inverse relationship was observed for PDSQ generalized anxiety disorder, such that individuals who screened positive for this disorder were 83% *less* likely to have diverted their drug than those who did not screen positive.

[9] This includes the use of non-prescribed anxiolytics, sedatives, stimulants, or opioid analgesics.

2.5 Discussion

This study aimed to identify patterns and predictors of anxiolytic or sedative drug misuse and diversion in a sample of adults prescribed these medications. To our knowledge, this investigation is the first to explicitly assess motivations for anxiolytic or sedative misuse in prescribed contexts as well as to examine the role of specific personality variables in indexing risk for anxiolytic or sedative misuse. The results of this study add to the growing body of evidence documenting widespread misuse and diversion of prescription drugs, including anxiolytics and sedatives. More than half of the prescribed anxiolytic and sedative users in this sample reported misusing their medication. One of the main factors associated with misuse was more extensive substance use and use-related problems. This is consistent with the study's predictions and with previous research linking substance use disorders to a higher risk for misusing anxiolytics and sedatives (Brunette et al., 2003; Roache & Meisch, 1995), but expands on past findings by indicating that the number of substances used, irrespective of any documented substance use disorder, is a significant predictor of misuse.

In this study, different forms of anxiolytic and sedative misuse were associated with specific personality characteristics. Hopelessness was associated with an increased likelihood of deliberately exceeding the recommended dosage, impulsivity was related to deliberate co-administration of other drugs or alcohol, and sensation seeking was linked to administration by an alternate route. Such findings highlight the importance of considering different forms of misuse as distinct entities with distinct risk factors. Although anxiety sensitivity was not significantly associated with any of the misuse variables examined in our study, it is important to note that elevated levels of anxiety

sensitivity may be linked to other forms of anxiolytic or sedative drug misuse, such as using the drug in response to intermittent symptoms of anxiety rather than following a recommended regular schedule of administration (Westra & Stewart, 2002).

Consistent with previous literature on prescription drug diversion (Darredeau et al., 2007), diversion of anxiolytics and sedatives was found to be a common occurrence, with over half of the participants reporting giving away their drug on at least one occasion. Other forms of diversion, including selling or trading, were much more infrequent. As with misuse, participants who reported diverting their drugs tended to be more impulsive and to have more extensive substance use histories. They were also more likely to have used a psychoactive prescription drug without a prescription. This finding is perhaps indicative of a general perceived acceptability of sharing prescription drugs among these individuals. Individuals reporting symptoms of generalized anxiety disorder were less likely to report diverting their drug, possibly indicating a reluctance to part with a medication perceived as being essential to treating their anxiety.

2.5.1 Limitations

Several limitations must be taken into account when interpreting these results. The structured interview used in this study was developed to examine multiple forms of prescription drug misuse, including detailed motives for use, and is a time-intensive measure to administer. A trade-off for using this approach was a limited sample size, which restricted the power of the statistical analyses to detect significant effects. This may have obscured potentially important relationships between the variables of interest. The generalizability of the findings may also be limited by the demographic composition of the study participants, who were primarily young, female, Caucasian, urban, and well

educated. Thus, caution should be exercised when applying these results to more diverse groups of anxiolytic or sedative users. Although the participants may not constitute a representative sample of individuals taking anxiolytics or sedatives, due to the voluntary nature of research participation, a truly representative sample may not be feasible to obtain regardless of recruitment strategies. Additional user characteristics not addressed in this analysis may also be related to risk for anxiolytic and sedative misuse or diversion. For example, rates of these behaviours may differ depending on the condition the drug was intended to treat and on the health professional dispensing the prescription. These speculations may form the bases of future investigations in this field.

The approach of defining misuse and diversion categorically constitutes a possible limitation, as it precluded our ability to compare participants based on a quantifiable index of misuse or diversion. Those who engaged in diversion or misuse on a regular basis may have differed from those who diverted or misused on fewer occasions. Furthermore, participants reported only on actual instances of diversion, not on situations in which they may have been approached to divert their drug. Investigating differences between individuals who divert their drugs and those who are presented with the opportunity to divert but elect not to do so represents another promising avenue for future research.

When relying on retrospective self-report measures, there may be concerns about the accuracy of reporting. Participants may under-report or fail to remember past drug use. By requiring in-depth reports on specific, vividly remembered instances of substance use, the recollections of participants in this study were linked to salient events. These types of interview methods have been shown to increase the reliability and validity of

self-reported substance use patterns (Sobell, Brown, Leo, & Sobell, 1996; Sobell, Sobell, Leo, & Cancilla, 1988). To further encourage accuracy in reporting, participants were specifically advised during the consent process that reporting on substance use would place them at no risk of legal action.

The cross-sectional design of this investigation restricts the ability to draw causal inferences about the factors associated with anxiolytic or sedative misuse and diversion. As there was no experimental control over the variables of interest, it is impossible to rule out alternative hypotheses for observed associations. For example, although the theory proposed by Conrod, Pihl et al. (2000) explicitly presents a model of causality such that individual differences in stable, measurable personality characteristics act as risk factors for development of substance use problems, the directionality of the link between personality and anxiolytic or sedative misuse cannot be conclusively determined from a cross-sectional study. Future investigations should incorporate longitudinal designs to increase our understanding of the mechanisms linking individual-level factors to misuse of anxiolytics and sedatives.

2.5.2 Conclusion

To our knowledge, this study is the first to identify characteristics and associated features of various forms of prescription anxiolytic or sedative misuse. A challenge for health care professionals prescribing such drugs is to maximize benefit while minimizing harm—that is, to responsibly provide safe and effective relief of symptoms while minimizing misuse and diversion of the prescribed medications. Clinicians can play a critical role in identifying patients who may be at risk to misuse or divert their drugs. Clinicians should be aware not only of the general abuse liability of these drugs, but also

of the importance of individual differences in risk for misuse and diversion. In particular, the strong association between substance use history and anxiolytic or sedative misuse found in this study suggests that clinicians considering drug options for treatment of anxiety or sleep conditions could employ a few brief screening questions regarding their patients' substance use histories. Identifying individuals who may be at risk, considering alternative treatments where appropriate, and educating patients on the safe and effective use of these drugs may have important effects in decreasing their diversion and misuse in the future.

Table 2.1.
Correlates of misuse of anxiolytics or sedatives among prescribed users.

	Misuse (n=36)	No Misuse (n=31)	Statistical Test	
	No. (%) of Participants		χ^2 (*p* value)	OR
Lifetime substance use history[a]				
Regular tobacco user	22 (61)	7 (23)	10.07 (0.003)	5.39[b]
Tobacco dependence	13/33 (39)	5/28 (18)	3.38 (0.093)	2.99
Alcohol use	36 (100)	30 (97)	1.18 (0.463)	--
Alcohol abuse	18/34 (53)	7/30 (23)	5.87 (0.021)	3.70
Alcohol dependence	12 (33)	8 (26)	0.45 (0.597)	1.44
Cannabis use	33 (92)	20 (65)	7.43 (0.014)	6.05
Cannabis abuse	13/34 (38)	3 (10)	7.13 (0.010)	5.78[b]
Cannabis dependence	12 (33)	3 (10)	5.36 (0.037)	4.67
Cocaine use	17 (47)	5 (16)	7.30 (0.009)	4.65[b]
Cocaine abuse	7/35 (20)	0 (0)	6.94 (0.012)	--
Cocaine dependence	5 (14)	0 (0)	4.65 (0.057)	--
Amphetamine use	6 (17)	1 (3)	3.22 (0.113)	6.00
MDMA use	16 (44)	5 (16)	6.21 (0.018)	4.16
Psilocybin use	21 (58)	8 (26)	7.18 (0.013)	4.03
LSD use	17 (47)	3 (10)	11.21 (0.001)	8.35[b]
Psychiatric symptoms per PDSQ				
Major depressive disorder	17 (47)	8 (26)	3.27 (0.082)	2.57
Post-traumatic stress disorder	18 (50)	8 (26)	4.11 (0.049)	2.88
Obsessive-compulsive disorder	16 (44)	11 (36)	0.56 (0.618)	1.45
Generalized anxiety disorder	19 (53)	18 (58)	0.19 (0.806)	0.81
Social phobia	27 (75)	23 (74)	0.01 (>0.999)	1.04
Panic disorder	17 (47)	9 (29)	2.32 (0.142)	2.19
Agoraphobia	17 (47)	15 (48)	0.01 (>0.999)	0.95
Problem alcohol use	11 (30)	10 (32)	0.02 (>0.999)	0.92
Problem drug use	20 (56)	6 (19)	9.19 (0.003)	5.21[b]
	Mean (SD)		*t* (*p* value)	*r*
SURPS personality dimension score				
SURPS Anxiety Sensitivity	18.75 (3.21)	17.26 (3.15)	1.913 (0.060)[c]	0.23
SURPS Sensation-Seeking	16.42 (3.89)	14.39 (3.22)	2.304 (0.024)[c]	0.27
SURPS Impulsivity	17.47 (4.13)	14.71 (4.11)	2.732 (0.008)[c]	0.32[b]
SURPS Hopelessness	19.31 (4.78)	16.48 (3.51)	2.777 (0.007)[d]	0.33[b]

	Misuse (n=36)	No Misuse (n=31)	Statistical Test	
	Mean (SD)		*t* (*p* value)	*r*
Lifetime number of substances used	5.28 (3.16)	2.52 (1.90)	4.405 (<0.001)[e]	0.50[b]

Note. Tobacco dependence information was unavailable for six participants, alcohol abuse was unavailable for three participants, cannabis abuse was unavailable for two participants, and cocaine abuse was unavailable for one participant. OR = odds ratio; MDMA = 3,4-methylenedioxymethamphetamine; LSD = lysergic acid diethylamide; PDSQ = Psychiatric Diagnostic Screening Questionnaire; SURPS = Substance Use Risk Profile Scale.

[a] For alcohol, cannabis, and cocaine, data are presented on the basis of any lifetime use as well as having met the diagnostic criteria for abuse or dependence.

[b] Statistical significance according to a alpha level of 0.01.

[c] *df*=65.

[d] *df*=63.509.

[e] *df*=58.459.

Table 2.2.
Correlates of diversion of anxiolytics or sedatives among prescribed users.

	Diversion (n=35)	No Diversion (n=32)	Statistical Test	
	No. (%) of Participants		χ^2 (p value)	OR
Lifetime substance use history [a]				
Regular tobacco user	16 (46)	13 (41)	0.176 (0.806)	1.23
Tobacco dependence	12/32 (38)	6/29 (21)	2.067 (0.172)	2.30
Alcohol use	35 (100)	31 (97)	1.110 (0.478)	--
Alcohol abuse	17/33 (52)	8/31 (26)	4.438 (0.043)	3.06
Alcohol dependence	14 (40)	6 (19)	3.605 (0.067)	2.89
Cannabis use	31 (88)	22 (69)	3.973 (0.071)	3.52
Cannabis abuse	14 (40)	2/30 (7)	9.673 (0.003)	9.33[b]
Cannabis dependence	10 (29)	5 (16)	1.612 (0.250)	2.16
Cocaine use	17 (49)	5 (16)	8.228 (0.005)	5.10[b]
Cocaine abuse	7/34 (21)	0 (0)	7.370 (0.011)	--
Cocaine dependence	5 (14)	0 (0)	4.940 (0.054)	--
Amphetamine use	6 (17)	1 (3)	3.511 (0.108)	6.41[c]
MDMA use	14 (40)	7 (22)	2.552 (0.124)	2.38
Psilocybin use	20 (57)	9 (28)	5.734 (0.026)	3.41
LSD use	13 (37)	7 (22)	1.861 (0.194)	2.11
Any prescription anxiolytic or sedative misuse	23 (66)	13 (41)	4.233 (0.052)	2.80
Exceeded recommended dosage of an anxiolytic or sedative	19 (54)	9 (28)	4.703 (0.030)	3.04
Exceeded recommended dosage of an anxiolytic or sedative for non-therapeutic reasons	12 (34)	2 (6)	7.949 (0.006)	7.83[b]
Co-administered an anxiolytic/ sedative with another substance	19 (54)	8 (25)	5.959 (0.024)	3.56
Administered an anxiolytic or sedative by an alternate route	5 (14)	0 (0)	4.940 (0.054)	--
Used an anxiolytic/sedative without a valid prescription	18 (51)	11 (34)	1.980 (0.218)	2.02
Used a psychoactive prescription drug without a valid prescription [d]	29 (83)	16 (50)	8.183 (0.008)	4.83[b]

	Diversion (n=35)	No Diversion (n=32)	Statistical Test	
	No. (%) of Participants		χ^2 (p value)	OR
Psychiatric symptoms per PDSQ				
Major depressive disorder	12 (34)	13 (41)	0.287 (0.622)	0.76
Post-traumatic stress disorder	14 (40)	12 (38)	0.044 (1.000)	1.11
Obsessive-compulsive disorder	13 (37)	14 (44)	0.303 (0.625)	0.76
Generalized anxiety disorder	15 (43)	22 (69)	4.532 (0.049)	0.34
Social phobia	28 (80)	22 (69)	1.117 (0.401)	1.82
Panic disorder	15 (43)	11 (34)	0.506 (0.617)	1.43
Agoraphobia	14 (40)	18 (56)	1.769 (0.225)	0.52
Problem alcohol use	14 (40)	7 (22)	2.552 (0.124)	2.38
Problem drug use	20 (57)	6 (19)	10.376 (0.002)	5.78[b]
	Mean (SD)		t (p value)	r
SURPS personality dimension score				
Anxiety Sensitivity	18.34 (3.41)	17.75 (3.08)	0.744 (0.460)[e]	0.09
Sensation-Seeking	15.91 (4.07)	15.00 (3.27)	1.008 (0.317)[e]	0.12
Impulsivity	17.40 (4.10)	14.88 (4.23)	2.478 (0.016)[e]	0.29
Hopelessness	18.14 (4.73)	17.84 (4.17)	0.273 (0.785)[e]	0.03
Lifetime number of substances used	4.97 (3.33)	2.94 (2.11)	3.013 (0.004)[f]	0.37[b]

Note. Tobacco dependence information was unavailable for six participants, alcohol abuse was unavailable for three participants, cannabis abuse was unavailable for two participants, and cocaine abuse was unavailable for one participant. MDMA=3,4-methylenedioxymethamphetamine; LSD=lysergic acid diethylamide; PDSQ=Psychiatric Diagnostic Screening Questionnaire; SURPS=Substance Use Risk Profile Scale.

[a] For alcohol, cannabis, and cocaine, data are presented on the basis of any lifetime use as well as having met the diagnostic criteria for abuse or dependence.

[b] Statistical significance according to an alpha level of 0.01.

[c] Although the odds ratio for amphetamine suggests that its use is associated with increased risk for diversion, the failure of this result to attain statistical significance is likely due to the low number of participants in both groups who had ever tried amphetamine (6 of those participants who had diverted and 1 of those participants who had never diverted).

[d] Prescription drugs in this category include anxiolytics, sedatives, stimulants, and opioid analgesics.

[e] df=65.

[f] df=58.111.

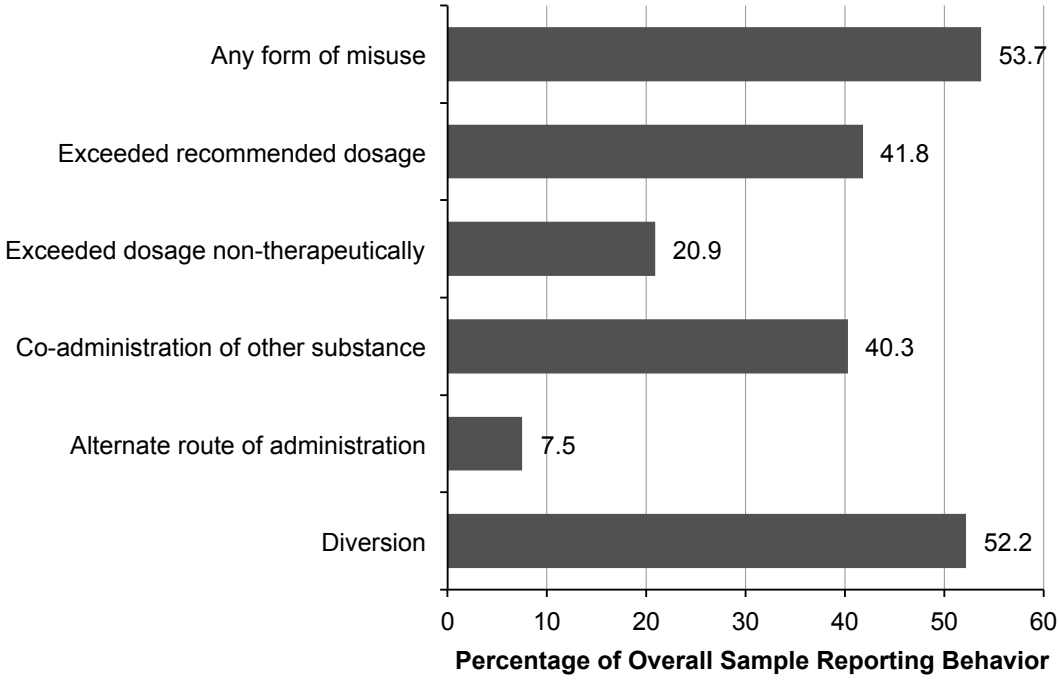

Figure 2.1. Percentages of the overall sample (N=67) reporting various forms of prescription anxiolytic or sedative misuse and diversion

2.6 Linking Statement and Rationale for Study 2

Study 1 aimed to identify patterns and predictors of anxiolytic or sedative drug misuse and diversion in a sample of adults with prescriptions for these drugs. To our knowledge, this investigation was the first to explicitly assess motivations for anxiolytic or sedative misuse in prescribed users, to make comparisons based on specific forms of misuse, and to identify associations between therapeutic and non-therapeutic motives, personality, and other substance use. The focus of Study 2 shifted to examine various forms of anxiolytic and sedative misuse among users of these drugs without valid prescriptions (i.e., non-prescribed users). A number of previous studies of non-prescribed medication use exist in the literature, likely because it is a straightforward way to define prescription drug misuse. Although previous researchers have described various motives for anxiolytic and sedative use among non-prescribed users, very few have empirically investigated the correlates of therapeutic vs. non-therapeutic motives. Of particular concern in Study 2 were relationships between users' motives for taking non-prescribed anxiolytics and sedatives and demographic variables, substance use history, personality, and non-substance psychopathology. Patterns and contexts of non-prescribed use were also examined. To further add to the understanding of anxiolytic and sedative misuse, specifically, participants with histories of non-prescribed stimulant use were also recruited. This provided a basis of comparison for making inferences about relationships specific to medication class. As with Study 1, Study 2 was conducted with the objective of contributing to a more comprehensive picture of heterogeneity in prescription anxiolytic and sedative misuse.

CHAPTER 3 Study 2: Motives for the Non-Prescribed Use of Psychiatric Medications: Relationships with Personality, Psychopathology, Other Substance Use, and Patterns of Use[10]

3.1 Abstract

Objectives: Psychiatric medications are commonly used without a valid prescription for therapeutic and non-therapeutic reasons. This study aimed to examine the associated features of therapeutic and non-therapeutic motives for use among non-prescribed users of anxiolytic, sedative and stimulant medications recruited from the community. ***Method:*** Participants (N=71) completed face-to-face interviews and questionnaires assessing medication use and misuse, other substance use, personality, and non-substance-related psychopathology. Multivariate logistic regression was used to examine factors relating to primary motives for use. ***Results:*** Non-therapeutic motives for use of anxiolytics, sedatives and stimulants were associated with a more extensive history of other substance use, as compared to therapeutic motives. Men were more likely than women to report using anxiolytics and sedatives for non-therapeutic motives. No symptoms of psychopathology, including anxiety disorders or attention-deficit/hyperactivity disorder, were related to motives for non-prescribed medication use.

[10] Adapted from McLarnon, M. E., Darredeau, C., Chan, J., & Barrett, S. P. (2013). Motives for the non-prescribed use of psychiatric medications: Relationships with psychopathology, other substance use and patterns of use. *Journal of Substance Use.* As first author of this article, I contributed to the design of the study, participated in training of research assistants, recruited and screened participants, managed data collection, entered data, conducted analyses, wrote the manuscript, and revised the manuscript in accordance with suggestions from my co-authors, peer reviewer, and journal editor. This study was funded by grants from the Dalhousie Department of Psychiatry Research Fund and the Dalhousie Research Development Fund for the Humanities and Social Sciences.

Although patterns of use tended to correspond with self-reported motives, in some cases, users reported therapeutic motives while describing high-risk patterns of use.

Conclusion: These results demonstrate important heterogeneity within non-prescribed medication users that a unitary conceptualization fails to adequately capture.

3.2 Introduction

While prevalence rates for the use of illicit drugs have stabilized or declined in recent years, misuse of prescription drugs has become a major public health concern (DuPont, 2010; Hernandez & Nelson, 2010). Many psychiatric drugs with beneficial therapeutic applications have psychoactive effects that render them vulnerable to misuse (O'Brien, 2005; Kollins, 2007), including anxiolytic and sedative medications used to treat anxiety disorders and insomnia and stimulants used to treat attention-deficit/hyperactivity disorder (ADHD). Recent epidemiological data indicate lifetime prevalence rates for misuse of anxiolytics, sedatives, and stimulants at 8.7 percent, 3.0 percent, and 8.5 percent, respectively (SAMHSA, 2011a).

One form of misuse involves the administration of medications by users who do not hold valid prescriptions. Non-prescribed use of anxiolytics, sedatives, and stimulants has been attributed, in part, to perceptions of safety relative to illicit drugs (Hertz & Knight, 2006). However, users of non-prescribed medications do not receive information or follow-up care from a health care provider and may thus lack knowledge of contraindications or other precautionary measures (McCabe et al., 2008). They may administer medications in unsafe quantities (DeSantis et al., 2008; White, Becker-Blease, & Grace-Bishop, 2006), through alternative routes of administration, or concurrently with other substances (White et al., 2006; Barrett, Darredeau et al., 2005), putting them at risk for adverse reactions or overdose (Buffet-Jerrott & Stewart, 2002; Cai, Crane, Poneleit, & Paulozzi, 2010; Hall et al., 2008; Hertz & Knight, 2006; Hill, El-Khayat, Sandilands, & Thomas, 2010; Klein-Schwartz, 2002). One study of unintentional pharmaceutical drug overdoses found that in almost half of deaths involving benzodiazepine anxiolytics and

sedatives, the medications were not prescribed to the user (Hall et al., 2008). Even at lower doses, anxiolytics and sedatives can cause memory deficits and other cognitive impairments (Buffet-Jerrott & Stewart, 2002). Acute overuse of prescription stimulants is associated with a number of adverse consequences, including seizure, psychotic symptoms, and cardiac complications (Hertz & Knight, 2006; Hill et al., 2010; Klein-Schwartz, 2002). Non-prescribed stimulants are frequently ingested through alternate routes of administration (White et al., 2006; Barrett, Darredeau et al., 2005), increasing the likelihood of harm to the user. Furthermore, recurrent use of anxiolytics, sedatives or stimulants without the oversight of a prescribing clinician may increase the risk of developing dependence on these medications (Chen, Storr, & Anthony, 2009; McCabe et al., 2007).

A number of studies have specifically examined correlates of non-prescribed anxiolytic, sedative, and stimulant use. Use of these medications without a prescription has been linked with alcohol, tobacco, and illicit drug use and misuse of other classes of prescription drugs (Advokat, Guidry, & Martino, 2005; Goodwin & Hasin, 2002; Kokkevi, Fotiou, Arapaki & Richardson, 2008; Low & Gendaszek, 2002; McCabe et al., 2006). Non-prescribed use has also been associated with other high-risk behaviours, such as binge drinking or being a passenger in a car with an impaired driver (McCabe, 2005; McCabe & Teter, 2007). While these findings consistently place non-prescribed psychiatric medication use within a broader cluster of problematic substance-related behaviours, associations with other possible correlates, including demographic and psychosocial factors, are less well understood.

A limitation of existing literature is that non-prescribed psychiatric medication use is often defined categorically, which may result in heterogeneous motives and patterns of behaviour being grouped under a single descriptive term (Boyd & McCabe, 2008). Understanding motives is crucial for predicting trajectories and consequences of substance use (e.g., Cooper, 1994; Zvolensky et al., 2007). In recent years, the importance of considering users' motives in investigations of prescription drug misuse has been increasingly emphasized (Barrett et al., 2008; Fischer & Rehm, 2007). Motives for non-prescribed use have been described as falling into two broad categories, based on whether the medication is administered with therapeutic or non-therapeutic intent (Goldsworthy, 2010). Therapeutic motives for anxiolytic and sedative use include managing symptoms of insomnia or anxiety (McCabe et al., 2009; Pedersen & Lavik, 1991), reducing stress and tension (Nattala et al., 2011), and treating withdrawal from other substances (Fatséas et al., 2009). Therapeutic motives for non-prescribed stimulant use include improving concentration and attention (Rabiner et al., 2009; Wilens et al., 2008) and controlling hyperactivity (White et al., 2006). Non-therapeutic motives include intoxication (Judson & Langdon, 2009; Kokkevi et al., 2008), altering the effect of other psychoactive substances (Barrett & Pihl, 2002; Nattala et al., 2011), and experimentation or curiosity (Kokkevi et al., 2008; Teter, McCabe, LaGrange, Cranford & Boyd, 2006).

Administration of prescription drugs for non-therapeutic purposes is thought to involve patterns of use similar to those associated with illicit drugs, including use in social contexts, concurrent use of other substances, and alternate routes of administration (Boyd & McCabe, 2008). Conversely, therapeutically motivated non-prescribed use is thought to be more likely to resemble typical prescribed use. While some empirical

results support these hypotheses (e.g., Fatséas et al., 2009; McCabe et al., 2009), other studies have found that users endorsing therapeutic motives may also report co-administration of other psychoactive substances and alternate routes of administration (e.g., Barrett, Darredeau et al., 2005). Furthermore, although therapeutically motivated non-prescribed use is often perceived as more benign than non-therapeutic use (Goldsworthy, 2010), there are risks to the user regardless of motive (McCabe et al., 2008). For instance, use of substances for self-medication purposes has been linked to development of comorbid psychopathology in users with anxiety or substance use disorders. In a longitudinal study, Robinson et al. (2011) reported that endorsement of self-medication motives predicted onset of substance dependence among participants who met criteria for an anxiety disorder at baseline. Self-medication with alcohol or other drugs was found to be a risk factor for incident social phobia among those with no anxiety disorder at baseline, leading these authors to suggest that self-medication may exacerbate subclinical symptoms (Robinson et al., 2011).

Despite calls for more research focused on identifying distinct subtypes of non-prescribed medication users (McCabe et al., 2009), few studies to date have explicitly investigated individual-level characteristics relating to motives for non-prescribed anxiolytic, sedative, and stimulant use. Investigating personality variation among non-prescribed users of psychoactive prescription medications represents one promising avenue for increasing our understanding of these forms of substance use behaviour. Multiple theories of substance use vulnerability propose that personality characteristics can reflect individual variation in susceptibility for the use and misuse of different classes of substances (Conway et al., 2002; Grekin, et al., 2006; Sher et al., 2000). Evidence

suggests that personality traits can differentiate substance users based on their motives for use of substances with varying reinforcing properties (e.g. Comeau et al., 2001; Conrod, Pihl et al., 2000). Studies have provided empirical support for a motivational model of substance use focusing on four personality dimensions related to vulnerability for problematic use of different drug classes: Anxiety sensitivity (AS), hopelessness (H), sensation seeking (SS), and impulsivity (IMP; Conrod, Pihl et al., 2000). This motivational model is well suited for examining links with non-prescribed anxiolytic, sedative, and stimulant use, as these personality dimensions have shown greater specificity for various forms of substance use than other, broader, models of personality risk (Krank et al., 2011).

The present study was designed to explore whether individual difference factors including demographics, personality, non-substance related psychopathology (particularly symptoms of anxiety disorders and ADHD), and other substance use, were differentially associated with motives for non-prescribed use of anxiolytics, sedatives, and stimulants. Based on past research (McCabe, 2005; O'Brien, 2005), we hypothesize that non-therapeutic users will report more extensive substance use histories compared to therapeutic users. We also expect to find differing patterns of psychiatric symptoms between these groups, with therapeutic users reporting higher rates of anxiety disorders and non-therapeutic users reporting more externalizing symptoms. Furthermore, this study aimed to determine whether distinct patterns of use corresponding to self-reported motives would be observed when examining a specific instance of non-prescribed use.

3.3 Method

3.3.1 Participants and Recruitment

Men and women (age 18 and older) were recruited from the general population of Halifax Regional Municipality of Nova Scotia, via advertisements on community and online bulletin boards, on the basis of having ever used an anxiolytic, sedative, or stimulant medication without a valid prescription. Participants provided written informed consent and were compensated $10 Canadian per hour. Institutional approval was obtained from the Dalhousie University Health Sciences Research Ethics Board.

3.3.2 Measures

3.3.2.1 Prescription Drug Use

Patterns of non-prescribed medication use were assessed using a structured polysubstance use interview (Barrett, Gross et al., 2005; see Appendix B). To aid in recollection, participants viewed a series of cards depicting common anxiolytics, sedatives, and stimulants. These cards were adopted from the National Survey on Drug Use and Health (SAMHSA, 2008) and supplemented with images from the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, 2008). Participants reported on frequency and duration of non-prescribed use, routes of administration, and deliberate co-ingestion with other substances. Participants were asked to indicate all motives for use by selecting from a list derived from past research (Boyd et al., 2006). They were prompted to add other motives not included on the list. If participants endorsed multiple motives for a given medication class, they were asked to specify their primary motive. Participants also provided detailed descriptions of their most recent occasion of non-prescribed use. This form of guided recall has been

documented as reliable and valid in retrospective studies of substance use (Fals-Stewart, O'Farrell, Freitas, McFarlin & Rutigliano, 2000).

3.3.2.2 History of Substance Use

Participants were interviewed about their lifetime substance use with an adapted version of the Addiction Severity Index (McLellan et al., 1980; see Drug List Questionnaire, Appendix B). For each substance used, participants indicated their ages at first and last use, estimated total uses, and peak period of use. A variable indexing overall drug involvement (i.e., total number of substances used), was computed based on the use of alcohol, tobacco, cannabis, cocaine, amphetamines, opioids (e.g., heroin, opium, non-prescribed opioid analgesics), hallucinogens (e.g., lysergic acid diethylamide, psilocybin), MDMA/ecstasy, dissociatives (e.g., ketamine, phencyclidine), inhalants, and other illicit substances.

3.3.2.3 Personality

Participants completed the *Substance Use Risk Profile Scale* (SURPS; Conrod & Woicik, 2002; see Appendix C), a validated 28-item questionnaire measuring anxiety sensitivity (AS), hopelessness (H), impulsivity (IMP), and sensation seeking (SS). AS describes a pervasive fear that anxiety-related sensations of physiological arousal will lead to catastrophic consequences. H describes a tendency towards a pessimistic outlook. IMP describes a pattern of disinhibited behaviour. SS describes a tendency to seek out exciting or exhilarating experiences. Participants responded to each item using a Likert-type scale ranging from 1 (Strongly Disagree) to 4 (Strongly Agree). Cronbach's alpha coefficients for the AS, H, IMP, and SS subscales were 0.77, 0.92, 0.73 and 0.72,

respectively, indicating adequate or better internal consistency for the SURPS in the present sample.[11]

3.3.2.4 Non-Substance Psychopathology

The *Psychiatric Diagnostic Screening Questionnaire* (PDSQ; Zimmerman & Mattia, 2001; see Appendix D), a validated 126-item self-report, was employed to assess current symptoms of DSM-IV-TR (APA, 2000) Axis I disorders in the following domains: anxiety, mood, eating, psychosis, and somatoform. Participants responded to each item using a binary Yes/No format. Responses for each category were summed to determine if symptom thresholds were met. Participants also completed the *Assessment of Hyperactivity and Attention* (AHA; Mehringer et al., 2002; see Appendix E), a validated 18-item checklist based on inattentive and hyperactive/impulsive DSM-IV-TR criteria for ADHD. Participants rated the frequency at which they typically experienced each symptom using a Likert-type scale ranging from 1 (Never) to 4 (Always). Cronbach's alpha coefficients for the inattention, hyperactivity/impulsivity, and overall scales were 0.86, 0.79, and 0.90, respectively, indicating adequate or better internal consistency for the AHA.

3.3.3 Procedure

Confidential, face-to-face interviews were conducted in a single session lasting approximately two hours. Interviewers received extensive training and were supervised by a PhD-level clinical psychologist. Sessions proceeded in the following sequence:

[11] These values are based on 50 participants whose full SURPS questionnaires were available. For the remaining 22 participants, subscale summary scores were entered into the study database without the accompanying individual item responses, precluding an internal consistency analysis for these participants. The data analyses were repeated excluding any participants with missing SURPS data. No difference in any results was observed.

demographic details, prescription drug use interview, other substance use history, and self-report questionnaires.

3.3.4 Data Analytic Strategy

Consistent with previous research (Goodwin & Hasin, 2002; Hall, Howard & McCabe, 2010; Kokkevi et al., 2008; Pedersen & Lavik, 1991; see also Study 1, section 2.3.1), anxiolytics and sedatives were combined in the analysis. Specific motives for use were designated as therapeutic (i.e., corresponding to typical prescribed indications) or non-therapeutic. Use of anxiolytics or sedatives "To decrease anxiety" or "To help with sleep" and use of stimulants "To study or concentrate" was coded as therapeutic. Motives clearly intended to ameliorate aversive psychological or physical symptoms were also coded as therapeutic (e.g. "To alleviate depression," "To reduce pain"). All other motives were considered non-therapeutic. Use of anxiolytics or sedatives to induce sleep following use of psychostimulant drugs (e.g., cocaine, ecstasy) and use of stimulant medications to increase alertness following administration of depressant drugs (e.g. alcohol, opioids) were coded as non-therapeutic.

Participants were designated as therapeutic or non-therapeutic users based on their reported primary motive for non-prescribed use. Bivariate comparisons between primary motive and variables of interest were conducted using independent sample t-tests for continuous variables and chi-square tests for categorical variables. Subsequently, multiple logistic regressions were conducted to identify correlates of primary motives for non-prescribed anxiolytic/sedative and stimulant use. These analyses accounted for demographic factors that have been previously related to prescription drug misuse, including age, sex, education, and occupation (Huang et al., 2006; SAMHSA, 2011a).

For the purpose of analysis, occupation was defined as student or non-student, and education was defined as completed postsecondary or less than postsecondary. Any variables significant ($p<0.05$) or marginally significant ($0.05<p<0.06$) in bivariate analyses were included in the multivariate logistic regressions as potential predictors. Odds ratios (OR) and adjusted odds ratios (aOR) with 95% confidence intervals (CIs) are reported as indicators of effect size. All analyses were conducted using IBM SPSS Statistics 20.

3.4 Results

3.4.1 Sample Characteristics

Seventy-two participants were recruited for the study. One participant was excluded from the analyses due to providing incomplete data on the SURPS. The final sample was comprised of 71 participants (55% male), ranging in age from 18 to 48 years (M=24.8, SD=7.0). Ninety-four percent of participants identified as Caucasian, reflecting the distribution in the local community (Statistics Canada, 2007). Thirty-five percent had completed a postsecondary degree and 58% were current students. Twenty-five percent reported use of anxiolytics or sedatives, 28% reported use of stimulants, and 47% reported use of both classes of medication. Descriptive data for these medication classes are presented in Table 3.1.

3.4.2 Motives and Patterns of Non-Prescribed Anxiolytic/Sedative Use

Specific motives and patterns of non-prescribed anxiolytic and sedative use are presented in Table 3.2. Users were almost evenly split between primarily therapeutic motives (49%) and non-therapeutic motives (51%). Total number of uses did not differ

by motive. Men were significantly more likely than women to endorse primarily non-therapeutic motives for anxiolytic and sedative use, $\chi^2(1)=24.01$, $p<0.001$. Other demographic factors did not vary by primary anxiolytic and sedative motive.

Compared to therapeutic users, non-therapeutic users were more than eight times as likely to report ever co-administering the medication with another psychoactive substance, $\chi^2(1)=10.85$, $p=0.001$ and more than seven times as likely to report using multiple pills during a typical episode of use, $\chi^2(1)=10.70$, $p=0.001$. Alternate routes of anxiolytic and sedative administration were rare and did not differ significantly by motive group, $\chi^2(1)=0.67$, $p=0.41$.

Bivariate associations between primary motive for anxiolytic and sedative use and other variables of interest, including personality, psychopathology, and other substance use, are presented in Table 3.3. Non-therapeutic motives were associated with elevated levels of SS and with a number of substance use variables. A trend relating therapeutic motives to higher levels of AS was observed ($p=0.053$). There were no significant differences in psychopathology between therapeutic and non-therapeutic anxiolytic and sedative users in terms of their responses to the PDSQ[12] and AHA. While therapeutic anxiolytic/sedative users endorsed approximately five more anxiety-related symptoms on the PDSQ than non-therapeutic users, this difference was not statistically significant ($p=0.20$; Table 3.3).

Based on these bivariate analyses, the potential predictors included in the multivariate logistic regression for anxiolytic and sedative use motives in addition to demographic variables were the SURPS SS and AS subscales; lifetime use of

[12] Data for specific disorders not shown. Therapeutic and non-therapeutic users were compared in terms of anxiety disorders, depression, eating disorders, psychosis, somatoform disorders, and substance use disorders, as measured by the PDSQ.

amphetamines, opioids, hallucinogens, ecstasy, and dissociatives; and total number of substances used. Logistic regression confirmed that after adjusting for other factors, motive for anxiolytic and sedative use was related to sex (B=3.61, p<0.001), with men being significantly more likely than women to report non-therapeutic primary motives (aOR=37.00, 95% CI 5.69-240.42). Of the remaining variables, only lifetime opioid use retained a significant unique relationship with motive (B=2.51, p=0.029). Participants who reported ever using opioid drugs were significantly more likely to report non-therapeutic primary motives for non-prescribed anxiolytic/sedative use (aOR=12.32, 95% CI 1.30-117.06). The overall predictive power of the final logistic model was 84.3%.

3.4.3 Motives and Patterns of Non-Prescribed Stimulant Use

Specific motives and patterns of stimulant use are presented in Table 3.2. Overall, 45% of stimulant users reported primarily therapeutic motives and 55% reported primarily non-therapeutic motives. Number of uses of non-prescribed stimulants did not differ by primary motive. Non-therapeutic stimulant users were older (M=25.0 years, SD=7.0) than therapeutic users (M=22.0 years, SD=2.3), t(35.89)=2.20, p=0.034, and less likely to be current students, $\chi^2(1)=8.29$, p=0.004. Other demographic factors did not vary by primary stimulant motive. Non-therapeutic users were more than five times as likely to report ever co-administering a stimulant with another psychoactive substance, $\chi^2(1)=7.98$, p=0.005, almost four times as likely to report ever using an alternate route of administration, $\chi^2(1)=5.25$, p=0.022, and more than three times as likely to report taking multiple pills during a typical episode of use, $\chi^2(1)=3.89$, p=0.049.

Bivariate associations between primary motive for stimulant use and personality, psychopathology, and other substance use are presented in Table 3.4. Non-therapeutic

stimulant use was associated with a number of substance use variables. No significant differences between stimulant motive groups were found in the SURPS personality dimensions or the psychopathology measured by the PDSQ and AHA (Table 3.4).

Based on these bivariate analyses, the potential predictors included in the multivariate logistic regression for stimulant use motives in addition to demographic variables were lifetime use of cocaine, amphetamines, hallucinogens, ecstasy, and dissociatives, and total number of substances used. Logistic regression indicated that after adjusting for other factors, motive for non-prescribed stimulant use was related to lifetime number of substances used (B=0.31, p=0.008). For each additional substance ever used, the likelihood of reporting primarily non-therapeutic motives for stimulant use rose approximately 36% (aOR = 1.36, 95% CI 1.08-1.70). The overall predictive power of the final logistic model was 77.4%.

3.4.4 Consistency between Motives and Patterns of Use

Although non-therapeutic users appeared more likely to engage in high-risk patterns of anxiolytic, sedative and stimulant use, some therapeutic users also reported taking high doses of these drugs, co-administering other psychoactive substances, or using alternate routes of administration. To investigate whether self-reported motives were consistent with behavioural patterns during a specific episode of non-prescribed use, we examined details of participants' most recent episode of anxiolytic/sedative or stimulant use (Figure 3.1). While most relationships were in the expected directions, 14% of anxiolytic and sedative users and 19% of stimulant users reported a therapeutic motive but described patterns of use that were incongruent with typical therapeutic use. For example, users endorsing primarily therapeutic motives for stimulant use were as likely

as those endorsing primarily non-therapeutic motives to state that they used the stimulant in a social context (i.e., with other people using the same drug) and to report taking multiple doses of the drug during the session.

3.5 Discussion

The accurate characterization of non-prescribed psychiatric medication use has important research and clinical implications. This investigation expanded upon previous research by examining features associated with motives for use of anxiolytic, sedative and stimulant medications among community-recruited adult participants without prescriptions. The present results indicated that non-therapeutic motives for anxiolytic, sedative or stimulant medication use were associated with more hazardous patterns of substance use and with a more extensive history of other substance use. This is congruent with previous research (e.g., McCabe et al., 2009; see also Study 1, section 2.4.2) and provides further empirical support for distinct subtypes of prescription drug misuse that can be differentiated on the basis of motive (Boyd & McCabe, 2008).

Women were more likely than men to report therapeutic motives for non-prescribed anxiolytic or sedative use. The widespread use of these medications for the management of anxiety and insomnia among women (Simoni-Wastila, 2000) may have contributed to their diversion becoming a socially accepted practice (Petersen, Rasmussen, Daniel, Yazdy, & Honein, 2008). No sex difference in primary motive was observed among non-prescribed stimulant users. This finding is consistent with previous research suggesting that pathways to non-prescribed stimulant use may function in similar ways for men and women (Boyd, Young, Grey & McCabe, 2009; McCabe, Knight, Teter & Weschler, 2005).

Initial analyses demonstrated that non-therapeutic motives for anxiolytic and sedative use were associated with higher levels of SS, while therapeutic motives were associated at a trend level with higher levels of AS. These relationships correspond with the theoretical model linking motives and substance use vulnerability (Conrod, Pihl et al., 2000); however, the effects were no longer significant after adjusting for demographics and other factors in the multivariate model. Similarly, while therapeutically motivated anxiolytic and sedative users tended to self-report more symptoms of anxiety than non-therapeutically motivated users, this difference did not achieve statistical significance. These findings may be partially attributable to the limited sample size, although it is important to consider that therapeutic and non-therapeutic anxiolytic, sedative and stimulant users may share personality and psychopathological features. For example, individuals who administer anxiolytics or sedatives to decrease aversive side effects of psychostimulant drugs, such as cocaine or ecstasy, may have higher levels of AS and higher baseline levels of anxiety than users who are able to tolerate these effects. In future research, a more nuanced understanding could be achieved by broadening the sample size to allow for examination of specific motives for use.

Self-reported ADHD symptoms did not differ significantly based on primary motive for stimulant use. These findings are interesting in light of previous research linking non-prescribed stimulant use with untreated ADHD symptoms (Arria et al., 2011; Judson & Langdon, 2009). As ADHD symptom scores in the present sample are considerably lower than in a sample of prescribed stimulant users of comparable demographic composition (Darredeau et al., 2007), this finding is unlikely to be due to a ceiling effect (i.e., elevated ADHD symptoms across this entire sample of non-prescribed

users). Use of non-prescribed stimulants to enhance academic or occupational performance among those with normal cognition may be distinct from use to ameliorate difficulties with concentration or attention. In future, it would be beneficial to differentiate between true therapeutic motives for non-prescribed stimulant use and those associated with a desire for cognitive enhancement.

In a substantial minority of cases, participants reported therapeutic motives while describing patterns of medication use inconsistent with normal therapeutic guidelines, such as alcohol co-administration. This is consistent with previous research (e.g., Barrett, Darredeau et al., 2005) and suggests that although self-reported motives for non-prescribed medication use correspond predictably to patterns of use in most cases, more information would be useful in anticipating specific risks and harms from non-prescribed use. For example, some individuals may have comorbid substance use problems or other mental health concerns that prompt them to seek therapeutic effects from these medications, albeit in high-risk ways.

3.5.1 Clinical Implications

The findings of this investigation suggest a number of possible targets for the prevention and reduction of non-prescribed psychiatric medication use. As many users may fail to report non-prescribed psychiatric medication use to their health care providers, an increased awareness of the factors associated with non-prescribed use is essential for improving detection. Alcohol and illicit drug use represent important cues for clinicians to ask patients about their use of prescription drugs (Matzger & Weisner, 2007). Broader community-level initiatives could be beneficial in preventing non-prescribed use while encouraging users to seek formal assessment for difficulties with

anxiety, insomnia, or attention. Finally, the diversity of motives reported by non-prescribed medication users in this study suggests that the effectiveness of psychological interventions could be enhanced by targeting the intervention to the individual's primary motives for use (Boyd & McCabe, 2008; Rigg & Ibañez, 2010).

3.5.2 Limitations

Several methodological limitations of this investigation should be taken into account. Because the sample was recruited from a single geographic location over a relatively brief period of time, participants may not represent typical users of non-prescribed psychiatric medications. The use of maximum likelihood procedures such as logistic regression with a small sample can produce biased results, including an increased likelihood of Type I error and Type II error (Peduzzi et al., 1999). The modest sample size was necessitated by the time-intensive interview method employed. This approach has a number of advantages, including improved reporting veracity and collection of detailed information from respondents (Arria & Wish, 2006). In-depth interview studies represent a useful complement to the larger but less detailed survey-based studies that comprise the majority of the prescription drug misuse literature (Wilens et al., 2008). Furthermore, the behaviour of interest in this investigation occurs at a relatively low base rate in the general population. By specifically recruiting participants with histories of non-prescribed psychiatric medication use, we attained a sample size comparable to the proportion of participants reporting this behaviour in larger studies (e.g., Sharp & Rosén, 2007; Weyandt et al., 2009). Replication of the present findings in a larger sample would allow for increased confidence in the reliability and validity of these results.

The cross-sectional design precludes conclusions about causality, as it cannot adequately test the assumption that motives for non-prescribed medication use are causally antecedent to patterns of behaviour (Cooper, 1994). Likewise, although the motivational model of personality and substance use posits that personality dimensions function as relatively stable risk factors for problematic substance use (Krank et al., 2011), this does not rule out reciprocal relationships between personality and substance use (e.g., Hicks, Durbin, Blonigen, Iacono & McGue, 2012). Future studies utilizing prospective designs will be important for clarifying these relationships.

3.5.3 Conclusion

The present findings indicate that a unitary conceptualization of non-prescribed medication use is inadequate. Future research should employ clearly specified operational definitions that take into account users' motives and prescription status. Enhancing our understanding of heterogeneity among non-prescribed psychiatric medication users may prove crucial for predicting risk for specific consequences, detecting individuals in need of treatment, and developing targeted strategies for intervention.

Table 3.1. Characteristics of non-prescribed anxiolytic/sedative and stimulant medication use.

	Anxiolytics/Sedatives (*n*=51)	Stimulants (*n*=53)
	Mean (SD)	Mean (SD)
Age of first use (years)	20.4 (4.2)	17.8 (2.6)
Age of peak use (years)	22.3 (5.2)	19.3 (2.9)
Frequency of use during peak period (days per month)	6.0 (8.4)	7.3 (8.5)
Number of different non-prescribed medications used	2.2 (1.8)	1.9 (1.1)
Total lifetime uses	*n* (%)	*n* (%)
10 or fewer	27 (53)	23 (43)
11 to 50	12 (24)	13 (25)
51 to 100	7 (14)	7 (13)
More than 100	5 (10)	10 (19)

Table 3.2.

Specific motives and patterns of non-prescribed anxiolytic/sedative and stimulant medication use by overall primary motive (therapeutic or non-therapeutic) for use.

	Anxiolytics/Sedatives *n* (%)		Stimulants *n* (%)	
	Therapeutic (*n*=25)	Non-therapeutic (*n*=26)	Therapeutic (*n*=24)	Non-therapeutic (*n*=29)
Motives for non-prescribed use				
Curiosity	6 (24)	15 (58)	14 (54)	22 (76)
Get high/stoned/buzzed	4 (16)	19 (73)	7 (29)	27 (93)
Fit in with peers	1 (4)	0 (0)	3 (13)	5 (17)
Increase effects of another drug	3 (12)	6 (23)	3 (13)	6 (21)
Decrease effects of another drug	2 (8)	11 (42)	1 (4.2)	2 (6.9)
Study or concentrate	1 (4)	0 (0)	24 (100)	13 (45)
Stay awake	0 (0)	0 (0)	17 (71)	16 (55)
Give more energy	0 (0)	1 (3.8)	15 (63)	20 (69)
Reduce appetite/manage weight	0 (0)	0 (0)	3 (13)	4 (14)
Help with sleep	18 (72)	15 (58)	0 (0)	0 (0)
Reduce anxiety	20 (80)	10 (38)	0 (0)	2 (6.9)
Reduce physical pain	3 (12)	3 (12)	0 (0)	2 (6.9)
Avoid withdrawal	1 (4)	4 (15)	2 (8.3)	1 (3.4)
Safer than street drugs	0 (0)	0 (0)	0 (0)	0 (0)
Reduce depression	5 (19)	1 (3.8)	0 (0)	0 (0)
Reduce stress	2 (8)	1 (3.8)	0 (0)	1 (3.4)
Other [a]	1 (4)	3 (12)	0 (0)	2 (6.9)
Patterns of non-prescribed use				
Ever intentionally co-administered with other drug	10 (40)	22 (85)	11 (46)	24 (83)
Ever used by alternate route of administration	2 (8)	4 (15)	9 (38)	20 (69)
Number of pills administered in typical episode of use (M, SD)	1.2 (0.7)	2.4 (1.9)	1.8 (1.2)	3.5 (5.3)

[a] Other reported reasons for non-prescribed anxiolytic/sedative use included boredom, intoxication (while under the impression that the anxiolytic/sedative was another drug), and being given the anxiolytic/sedative without consent. Other reported reasons for non-prescribed stimulant use included enhancing creativity and mental clarity.

Table 3.3.
Univariate analyses comparing users of non-prescribed anxiolytic/sedative medications (*n*=51) by overall primary motive for use.

	Therapeutic (*n*=25)	Non-therapeutic (*n*=26)			
Lifetime substance use	*n* (%) reporting use of substance		χ^2	OR	95% CI
Alcohol	24 (96)	26 (100)	1.06	--	--
Tobacco (regular use)	12 (48)	17 (65)	1.57	2.05	0.66-6.31
Cannabis	22 (88)	26 (100)	3.32	--	--
Cocaine	13 (52)	20 (77)	3.47	3.08	0.92-10.25
Amphetamines[a]	6 (24)	15 (58)	5.97*	4.32	1.30-14.38
Opioids[b]	13 (52)	23 (88)	8.16**	7.08	1.68-29.76
Hallucinogens[c]	16 (64)	25 (96)	8.36**	14.06	1.62-121.84
Ecstasy	9 (36)	22 (85)	12.64***	9.78	2.55-37.43
Dissociatives[d]	4 (16)	17 (65)	12.83***	9.92	2.60-37.88
Inhalants[e]	4 (16)	9 (35)	2.33	2.78	0.73-10.62
	Mean (SD)		*t*	OR	95% CI
Lifetime number of substances used	4.7 (2.9)	8.7 (3.5)	4.59***	1.53	1.19-1.96
PDSQ number of anxiety items endorsed	20.4 (15.1)	15.3 (12.4)	1.24	0.97	0.93-1.02
AHA Inattention	8.4 (5.2)	8.8 (4.5)	0.33	1.02	0.91-1.14
AHA Hyperactive-Impulsive	9.6 (5.4)	10.5 (4.7)	0.61	1.04	0.93-1.16
AHA Overall Score	18.0 (10.1)	19.3 (8.6)	0.50	1.02	0.96-1.08
SURPS Anxiety Sensitivity	17.2 (3.1)	15.5 (3.0)	1.99§	0.83	0.68-1.01
SURPS Sensation-Seeking	16.0 (2.5)	19.1 (2.9)	3.97***	1.54	1.17-2.03
SURPS Impulsivity	16.1 (3.3)	17.1 (3.3)	1.03	1.10	0.92-1.31
SURPS Hopelessness	15.8 (4.3)	16.7 (4.9)	0.69	1.05	0.92-1.18

Note. 95% CI=95% Confidence Interval; AHA=Assessment of Hyperactivity and Attention; OR=Odds Ratio; PDSQ=Psychiatric Diagnostic Screening Questionnaire; SURPS=Substance Use Risk Profile Scale.

[a]Includes amphetamine and methamphetamine.

[b]Includes heroin, opium and opioid medications taken without a prescription.

[c]Includes lysergic acid diethylamide (LSD), psilocybin, *Salvia divinorum*, dimethyltryptamine (DMT), mescaline and peyote.
[d]Includes ketamine, phencyclidine (PCP) and dextromethorphan (DXM).
[e]Includes amyl nitrite and nitrous oxide.
**p*<0.05. ***p*<0.01. ****p*<0.001. [§]*p*=0.053.

Table 3.4.
Univariate analyses comparing users of non-prescribed stimulant medications (*n*=53) by overall primary motive for use.

	Therapeutic (*n*=24)	Non-therapeutic (*n*=29)			
Lifetime substance use	*n* (%) reporting use of substance		χ^2	OR	95% CI
Alcohol	24 (100)	29 (100)	--	1.00	--
Tobacco (regular use)	10 (42)	16 (55)	0.96	1.72	0.58-5.14
Cannabis	24 (100)	29 (100)	--	1.00	--
Cocaine	8 (33)	24 (83)	13.41***	9.60	2.66-34.67
Amphetamines[a]	6 (25)	19 (66)	8.65**	5.70	1.72-18.93
Opioids[b]	14 (58)	20 (69)	0.65	1.59	0.51-4.92
Hallucinogens[c]	16 (67)	28 (97)	8.32**	14.00	1.60-122.33
Ecstasy	12 (50)	24 (83)	6.47*	4.80	1.37-16.80
Dissociatives[d]	4 (17)	17 (59)	9.66*	7.08	1.92-26.08
Inhalants[e]	4 (17)	12 (41)	3.81	3.53	0.96-13.00
	Mean (SD)		*t*	OR	95% CI
Lifetime number of substances used	5.0 (3.4)	8.6 (3.2)	3.95***	1.41	1.14-1.73
PDSQ number of anxiety items endorsed	14.0 (12.1)	14.8 (12.4)	0.22	1.01	0.96-1.05
AHA Inattention	8.0 (3.4)	9.8 (4.9)	1.58	1.12	0.97-1.29
AHA Hyperactive-Impulsive	10.3 (3.4)	10.9 (4.9)	0.52	1.04	0.91-1.18
AHA Overall Score	18.2 (5.7)	20.7 (9.4)	1.18	1.04	0.97-1.12
SURPS Anxiety Sensitivity	15.6 (4.1)	16.0 (2.6)	0.47	1.04	0.88-1.23
SURPS Sensation-Seeking	18.3 (3.4)	18.6 (3.1)	0.24	1.02	0.86-1.21
SURPS Impulsivity	17.2 (3.5)	17.0 (3.2)	0.14	0.99	0.84-1.17
SURPS Hopelessness	15.5 (4.7)	15.2 (5.0)	0.22	0.99	0.88-1.11

Note. 95% CI=95% Confidence Interval; AHA=Assessment of Hyperactivity and Attention; OR=Odds Ratio; PDSQ=Psychiatric Diagnostic Screening Questionnaire; SURPS=Substance Use Risk Profile Scale.
[a] Includes amphetamine and methamphetamine.
[b] Includes heroin, opium and opioid medications taken without a prescription.
[c] Includes lysergic acid diethylamide (LSD), psilocybin, *Salvia divinorum*, dimethyltryptamine

(DMT), mescaline and peyote.
[d] Includes ketamine, phencyclidine (PCP) and dextromethorphan (DXM).
[e] Includes amyl nitrite and nitrous oxide.
*p<0.05. **p<0.01. ***p<0.001.

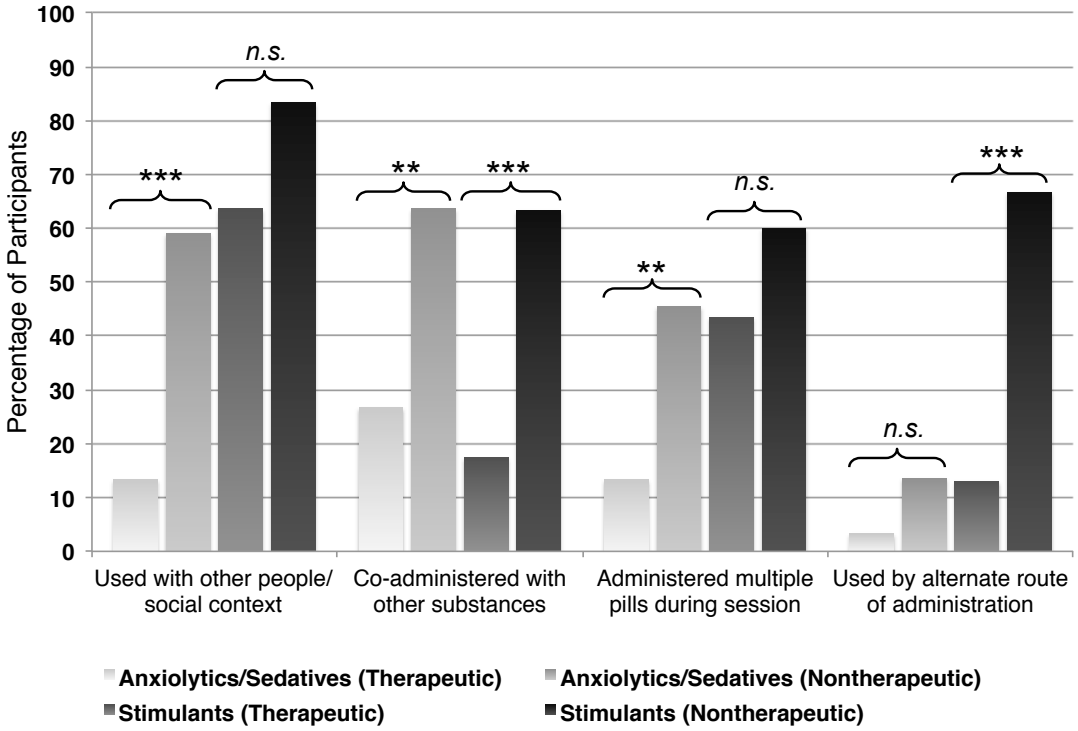

Figure 3.1. Patterns of most recent episode of non-prescribed anxiolytic/sedative and stimulant use by self-reported therapeutic or non-therapeutic motives. ***p*<0.01. ****p*<0.001. *n.s.*=nonsignificant.

3.6 Epilogue to Study 2: Sources of Non-Prescribed Medications

3.6.1 Previous Research on Sources of Anxiolytic and Sedative Medications

Just over half of the prescribed anxiolytic and sedative users in Study 1 had given away, sold, or traded their medication, indicating that diversion of anxiolytics and sedatives is a common phenomenon among community users. A few previous studies have examined sources of misused anxiolytics and sedatives among non-prescribed users. Using data from the NSDUH, Ford and Lacerenza (2011) found that the majority (55%) of misused anxiolytics were obtained from friends or relatives for free. However, a substantial proportion was purchased from a friend or relative (16%) or from a dealer or stranger (10%). Buying anxiolytics from a friend or relative, as opposed to obtaining them for free, was associated with more frequent misuse. Buying anxiolytics from a dealer or stranger was associated with a higher risk for meeting DSM-IV criteria for abuse or dependence. In a study of undergraduate students, McCabe and Boyd (2005) examined friends and relatives separately. In this study, obtaining anxiolytics or sedatives from peer sources was associated with a range of other risky substance use behaviours, including binge drinking, alcohol abuse, polysubstance use, and illicit drug use. In contrast, in almost all cases, obtaining anxiolytics or sedatives from family members showed no increased likelihood of alcohol and illicit drug misuse. In a sample of adolescents, Pedersen and Lavik (1991) found that almost all BZ users who obtained the medications from their parents reported therapeutic motives, while those who obtained BZs from their peers or illegally (e.g., from a drug dealer) were almost as likely to report intoxication as a motive as they were to report therapeutic use as a motive.

3.6.2 Supplementary Analyses of Sources of Non-Prescribed Medications in Study 2

Due to space limitations, analyses of sources of non-prescribed medications were omitted from the manuscript of Study 2 submitted for publication. These analyses were conducted to evaluate whether therapeutic and non-therapeutic users differed in their sources of non-prescribed medications. An overview of these findings is provided here.

The most common source of non-prescribed anxiolytic and sedative medications reported by therapeutic users was family members, who were the primary source for 46% of this group. Among non-therapeutic users, the most common source of non-prescribed anxiolytic and sedative medications was friends, who were the primary source for 65% of this group. Non-therapeutic users were almost nine times more likely to have obtained anxiolytic and sedative medication from a friend, $\chi^2(1)=8.31$, $p=0.009$, and over 11 times more likely to have obtained anxiolytic and sedative medication from a drug dealer, $\chi^2(1)=6.58$, $p=0.024$, compared to therapeutic users. No participant in either motive group reported obtaining anxiolytics or sedatives on the Internet.

The most commonly reported source of non-prescribed stimulant medications among all users was friends, who were the primary source for 88% of therapeutic users and 75% of non-therapeutic users. Eight (33%) of the therapeutic users and seven (24%) of the non-therapeutic users reported ever obtaining non-prescribed stimulant medication from a drug dealer. No participant in either motive group reported obtaining stimulant medications on the Internet. There were no statistically significant differences between motive groups in the likelihood of reporting any of the sources of non-prescribed stimulant medications.

3.6.3 Discussion of Supplementary Analyses of Sources of Non-Prescribed Medications

Among non-prescribed anxiolytic and sedative users in this study, those obtaining medications from family members were more likely to report therapeutic motives. Conversely, obtaining anxiolytics or sedatives from peers or drug dealers was strongly linked to non-therapeutic motives. While analyses revealed no relationships between motive groups and sources of non-prescribed stimulants, a large majority of both therapeutic and non-therapeutic users obtained stimulant medications from their peers, which may have limited the ability of this analysis to detect significant effects. That non-therapeutic users of all substance classes assessed (i.e., anxiolytics, sedatives and stimulants) tended to obtain these drugs from their peers suggests that non-therapeutic use may commonly take place in a social context. This finding is consistent with previous research associating peer sources of prescription drugs with high-risk forms of substance use that tend to take place in social settings, such as binge drinking and polysubstance use (McCabe & Boyd, 2005). Clinicians should be aware that motives and patterns of use of non-prescribed anxiolytics and sedatives, in particular, may differ depending on the user's typical source of these drugs. However, it is important to note that there are risks associated with non-prescribed medication use regardless of source and motive. Prescribing physicians can play a role in mitigating harms from non-prescribed medication use; for example, patient education and cautious prescription practices may assist in preventing diversion by prescribed users.

Despite concerns raised in the literature regarding the availability of prescription drugs on the Internet (Califano, 2004; Jena & Goldman, 2011), no participant in the present study reported obtaining a medication online. This finding parallels that of

Havens, Walker and Leukefeld (2010), who found that only 1.3% of a sample of benzodiazepine users had ever obtained the substance via the Internet, and that of McCabe and Boyd (2005), who found no evidence for the Internet as a source of prescription drugs among a large sample of undergraduate students. Although ongoing monitoring of online pharmacies appears warranted from a public health perspective (Jena & Goldman, 2011), the present findings suggest that addressing diversion of prescription drugs between peers and relatives represents a more important target for the reduction and prevention of prescription medication misuse.

3.7 Characteristics of Prescribed and Non-Prescribed Anxiolytic and Sedative Users

As noted in the introduction to this dissertation, in many prior investigations of anxiolytic and sedative misuse, researchers have grouped multiple forms of misuse under broad, comprehensive definitions, precluding the ability to distinguish between various specific forms of misuse and identify characteristics associated with various groups of anxiolytic and sedative users. Alternately, researchers have employed more circumscribed definitions (e.g., non-prescribed use only), potentially limiting the generalizability of findings to other forms of prescription anxiolytic and sedative misuse (Barrett et al., 2008). This dissertation addresses this gap within existing literature by considering misuse of anxiolytics and sedatives that occurs within both prescribed and non-prescribed contexts.

3.7.1 Supplementary Analyses of Prescribed and Non-Prescribed Anxiolytic and Sedative Users

3.7.1.1 Comparison of Study 1 and Study 2 Samples

Additional analyses were conducted to compare characteristics of prescribed and non-prescribed anxiolytic and sedative users who took part in Studies 1 and 2. The Study 1 sample included 67 participants (M=28.7 years, SD=10.9 years; 84% female) with current prescriptions for anxiolytics or sedatives. The Study 2 sample included 51 participants with histories of non-prescribed anxiolytic or sedative use (M=26.1 years, SD=7.9 years; 49% female). Controlling for age and sex, currently-prescribed anxiolytic and sedative users were compared to non-prescribed users across personality,[13] psychopathology, and substance use variables using univariate analysis of variance

[13] One non-prescribed participant had incomplete SURPS data and was thus excluded from these analyses.

(ANOVA) for continuous criterion variables and binary logistic regression for categorical criterion variables. An α level of $p<0.05$ was set as a threshold of statistical significance.

Analyses revealed trend-level group differences for the H, AS, and SS subscales of the SURPS. Mean scores on the H subscale were somewhat elevated among prescribed users (M=18.0, SD=4.4) as compared to non-prescribed users (M=16.2, SD=4.6), $F(1,113)=3.83$, $p=0.053$. Similarly, scores on the AS subscale were somewhat higher among prescribed users (M=18.1, SD=3.2) than among non-prescribed users (M=16.3, SD=3.1), $F(1,113)=3.67$, $p=0.058$. SS subscale scores were somewhat higher among non-prescribed users (M=17.6, SD=3.1) than among prescribed users (M=15.5, SD=3.7), $F(1,113)=3.63$, $p=0.059$. There were no significant differences in the IMP subscale between prescribed (M=16.2, SD=4.3) and non-prescribed (M=16.6, SD=3.3) users, $F(1,113)=0.28$, $p=0.598$.

Controlling for age and sex, prescribed users endorsed a significantly greater number of symptoms of psychopathology on the PDSQ (M=39.9, SD=18.9) than non-prescribed users (M=29.0, SD=20.6), $F(1,114)=6.25$, $p=0.014$. Considering anxiety disorders specifically, prescribed users also endorsed significantly more anxiety symptoms on the PDSQ (M=24.8, SD=14.1) than non-prescribed users (M=17.2, SD=13.9), $F(1,114)=5.97$, $p=0.016$. In particular, logistic regression analyses indicated that prescribed users were more likely than non-prescribed users to screen positive for social phobia (74% vs. 49%; $B=1.08$, $p=0.012$), somatization disorder (70% vs. 33%; $B=1.36$, $p=0.001$), and hypochondriasis (40% vs. 22%; $B=0.96$, $p=0.036$), and tended to be more likely to screen positive for agoraphobia (49% vs. 26%; $B=0.77$, $p=0.073$). Interestingly, prescribed and non-prescribed users were statistically equally likely to

screen positive for panic disorder (39% vs. 32%; *B*=0.18, *p*=0.673) and generalized anxiety disorder (55% vs. 41%; *B*=0.37, *p*=0.368). There were no significant differences between groups for any other disorders assessed on the PDSQ. On average, non-prescribed anxiolytic and sedative users had used a greater number of illicit substances in their lifetimes (M=6.7, SD=3.9) than prescribed users, (M=4.0, SD=3.0), $F(1,114)=7.97$, $p=0.006$.

3.7.1.2 Comparison of Exclusively Prescribed, Exclusively Non-Prescribed, and Mixed Anxiolytic and Sedative Users

There was substantial overlap between the samples of Study 1 and Study 2 in terms of participants' anxiolytic and sedative use history. Twenty-nine (43%) of the currently prescribed users in Study 1 reported having used an anxiolytic or sedative without a prescription at least once. None of the non-prescribed users in Study 2 held a current prescription for an anxiolytic or sedative, but 17 (33%) had done so in the past. Based on this overlap, an additional set of supplemental analyses was conducted to investigate potential group differences based on lifetime prescription status (i.e., between participants who reported exclusively using anxiolytics and sedatives with a prescription, those who reported exclusively using these medications without a prescription, and those who reported using them both with and without a prescription). The prescribed only group comprised 38 participants (M=29.1 years, SD=12.0 years; 84% female). The non-prescribed only group comprised 34 participants (M=23.4 years, SD=4.8 years; 38% female). The mixed group comprised 45 participants (M=27.6 years, SD=9.8 years; 78% female).

Controlling for age and sex, these three groups were compared in terms of personality, psychopathology, and substance use history using univariate ANOVA. An α

level of $p<0.05$ was set as a threshold of statistical significance for main effects. As these analyses involved a comparison of three groups, pairwise *post hoc* tests were conducted using a Bonferroni correction to adjust for multiple comparisons.

Results of these analyses are presented in Table 3.5. Analyses of the SURPS personality dimensions revealed a significant main effect for group in terms of SS. *Post hoc* pairwise comparisons indicated that the exclusively non-prescribed group had higher mean SS scores than the exclusively prescribed group, with the mixed group intermediate to, but not significantly different from, the other two groups. A trend was observed for the IMP scale, whereby mean IMP scores were the lowest among the prescribed only group, intermediate among the non-prescribed group, and highest among the mixed group. However, pairwise *post hoc* comparisons indicated no significant differences in terms of mean IMP scores. Analyses revealed no significant differences between the three groups in terms of H or AS; however, the pattern of results suggested somewhat higher scores on these dimensions among the mixed group relative to the other two groups. The exclusively non-prescribed group reported fewer symptoms of psychopathology on the PDSQ, and fewer anxiety-related symptoms in particular, than the other two groups, but these differences were not found to be statistically significant. In terms of substance use history, there was a significant main effect for group, with pairwise *post hoc* comparisons indicating that, on average, the exclusively non-prescribed and mixed groups had used a greater number of substances in their lifetimes than the exclusively prescribed group.

3.7.2 Discussion of Analyses Comparing Prescribed and Non-Prescribed Anxiolytic and Sedative Users

The above analyses demonstrate some interesting group differences between the prescribed and non-prescribed anxiolytic and sedative users who took part in Studies 1 and 2. In terms of SURPS personality dimensions, it is not surprising to find that the non-prescribed users tended to be higher in SS and that the currently prescribed users tended to be higher in AS and H. Individuals with more pronounced sensation-seeking characteristics may be more likely to disregard potential risks associated with non-prescribed use in favour of obtaining a desired effect from the drug. The AS and H dimensions have been linked to internalizing psychopathology (Conrod, Pihl et al., 2000) and elevations in these domains likely reflects the fact that these individuals were prescribed medication to manage ongoing symptoms of anxiety or disrupted sleep, which are highly comorbid with other internalizing disorders (Kessler et al., 2005). The elevated rates of psychopathology in general, and certain anxiety disorders in particular, among currently prescribed anxiolytic and sedative users is also not unexpected for the same reason. The higher rates of somatoform disorders among currently prescribed users is interesting, given their tendency towards higher levels of AS. This finding is consistent with previous research linking hypochondriacal concerns and somatization disorder with AS (Conrod, Pihl et al., 2000; Otto, Pollack, Sachs, & Rosenbaum, 1992) and suggests that these conditions may represent a target for increased clinical attention.

In addition, it is interesting to note that non-prescribed users also reported relatively high rates of anxiety-related symptomatology. In the cases of panic disorder and generalized anxiety disorder, non-prescribed users met diagnostic screening thresholds at rates comparable to currently prescribed users. This finding suggests the

possibility that non-prescribed users may be seeking out medications on their own to control these symptoms. Alternately, it may indicate that among users with current prescriptions, these symptoms are more effectively controlled by pharmaceuticals than those of other anxiety disorders. As the specific disorders and symptoms for which anxiolytics and sedatives were prescribed were not assessed in the present studies, additional research to explore these speculations would be warranted. In future investigations, it would be beneficial to include a control sample, thereby allowing for comparisons between prescribed and non-prescribed users with those with no history of anxiolytic or sedative use.

It is notable that there was substantial overlap between the two samples in terms of their anxiolytic and sedative use history, with over 40 percent of currently prescribed users also reporting non-prescribed use and over 30 percent of non-prescribed users also reporting past prescribed use. This is consistent with previous epidemiological research indicating a significant correlation between prescribed and non-prescribed use of anxiolytics and sedatives (Caces, Harford & Aitken, 1998). Additional analyses comparing participants based on lifetime prescription status for anxiolytics and sedatives (i.e., exclusively prescribed use, exclusively non-prescribed use, or both) revealed that exclusively non-prescribed users tended to have higher levels of SS than exclusively prescribed users and more extensive lifetime substance use histories than either of the other two groups. For the other SURPS personality risk variables, the results of these analyses were less clear. Although the mixed group tended to have higher levels of AS, H, and IMP than the other groups, these differences were not found to be statistically significant. The exclusively non-prescribed group tended to report fewer symptoms of

psychopathology on the PDSQ than the other two groups, but these differences were also not statistically significant. These findings may be related to decreased power resulting from splitting the sample into three smaller groups for this analysis. While SS appears to be linked to non-prescribed anxiolytic and sedative use, it appears that the sample reporting both prescribed and non-prescribed use may also present a high-risk picture in terms of personality risk dimensions. However, further research is needed to confirm this. Future prospective studies could focus on individual difference factors in relation to trajectories of prescribed and non-prescribed anxiolytic and sedative use. For example, it would be interesting to evaluate whether non-prescribed users with elevated levels of anxiety (or anxiety sensitivity) are more likely to subsequently seek medication to ameliorate distressing symptoms.

Table 3.5.
Comparisons of anxiolytic or sedative users, based on lifetime prescription status, in terms of personality, psychopathology, and substance use history.

	Prescribed Only (*n*=38)	Non-Prescribed Only (*n*=34)	Mixed (*n*=45)	Statistical Test
		Mean (SD)		*F* (*p* value)
SURPS personality dimension				
Anxiety Sensitivity	17.16 (3.26)	16.21 (3.41)	18.27 (3.04)	2.21 (0.115)
Hopelessness	17.18 (4.06)	16.62 (4.65)	17.76 (4.98)	0.30 (0.738)
Sensation-Seeking	14.87 (3.27)	18.18 (3.36)	16.31 (3.55)	3.23 (0.043)
Impulsivity	15.37 (4.29)	16.29 (3.29)	17.27 (3.91)	2.49 (0.087)
PDSQ psychiatric symptoms				
Total symptoms	36.87 (19.45)	28.32 (20.71)	39.22 (19.97)	1.83 (0.165)
Total anxiety symptoms [a]	23.50 (14.84)	16.82 (14.05)	23.62 (13.91)	1.46 (0.236)
Lifetime number of substances used	2.97 (2.11)	7.38 (3.69)	5.38 (3.58)	9.53 (<0.001)

[a] Includes symptoms of post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, agoraphobia, social phobia, and generalized anxiety disorder.

3.8 Comparison of Differing Versions of the Substance Use Risk Profile Scale

The Substance Use Risk Profile Scale (SURPS; Conrod & Woicik, 2002) was used to measure four personality dimensions in Studies 1 and 2 of this dissertation. The original version of this measure included 28 items grouped into four subscales: seven items for the anxiety sensitivity (AS) subscale, eight for the hopelessness (H) subscale, six for the sensation-seeking (SS) subscale, and seven for the impulsivity (IMP) subscale. In a later study (Woicik et al., 2009), the psychometric properties of the SURPS were further evaluated using exploratory factor analysis, which supported the same four-factor model. However, five items (one from the H subscale, two from the AS subscale, and two from the IMP subscale) overlapped significantly or detracted from overall model, and were thus excluded, yielding a 23-item version of the SURPS (Woicik et al., 2009). As the present investigation was initiated prior to the publication of the Woicik et al. study, prescribed and non-prescribed anxiolytic and sedative users in Studies 1 and 2 were administered the 28-item SURPS. To evaluate any potential differences in the present results if the 23-item measure had been employed instead, alternate subscale scores for the SURPS subscales were calculated using only the items from the original SURPS retained in the 23-item version.[14] These analyses included 117 prescribed and non-prescribed anxiolytic and sedative users from Studies 1 and 2.

[14] *Note.* The SS subscale contains the same six items in the 23-item and 28-item versions of the SURPS. Accordingly, the comparisons described in the following section focus on the AS, H, and IMP subscales.

3.8.1 Supplementary Analyses Comparing 28-item and 23-item Versions of the SURPS

Descriptive data for the two SURPS versions are presented in Table 3.6. Of note are highly similar internal consistency (alpha) reliabilities between the two sets of subscales. These values are consistent with or better than those obtained in previous research using the 28-item (e.g., Jaffee & Zurilla, 2009; Woicik et al., 2009) and 23-item (e.g., Conrod, Castellanos-Ryan & Strang, 2010; Woicik et al., 2009) versions of the SURPS.

Standardized scores for the AS, H, and IMP subscales were calculated for the 28-item and 23-item SURPS, then compared using bivariate correlation to evaluate the degree of relationship between the alternate versions of each subscale. Standardized subscale scores were extremely highly correlated for each of the AS (r=0.94), H (r=0.99), and IMP (r=0.93) subscales (all p-values less than 0.001), suggesting that the two versions of the SURPS were measuring almost identical constructs in this sample.

Subsequently, analyses replicating the bivariate and multivariate analyses from Studies 1 and 2 were conducted to evaluate relationships between the 23-item SURPS subscales and various forms of anxiolytic and sedative misuse and diversion in prescribed users, and between the 23-item SURPS subscales and motives for misuse in non-prescribed users. For the H subscale, all results for the 23-item measure were consistent with those obtained with the 28-item measure for both bivariate and multivariate tests. For the AS subscale, all results were consistent among prescribed users, with the exception of the bivariate relationship between AS and overall anxiolytic and sedative misuse, which trended towards significance (p=0.060) using the 28-item measure, but was not significantly related to AS using the 23-item measure (p=0.291). The bivariate

relationship between AS and non-therapeutic motives among non-prescribed anxiolytic and sedative users also differed slightly. This relationship was significant at a trend level (p=0.053) using the 28-item SURPS and significant (p=0.024) using the 23-item SURPS. For the IMP subscale, most results were also consistent across the two versions of the SURPS. The exceptions were misuse of prescribed anxiolytics and sedatives by co-administration, which was significantly related to IMP (p=0.004) using the 28-item measure and trending towards significance using the 23-item measure (p=0.056); misuse of prescribed anxiolytics and sedatives by using an alternate route of administration, which was significantly related to IMP (p=0.041) using the 28-item measure and non-significant (p=0.103) using the 23-item measure; and diversion of prescribed anxiolytics and sedatives, which was significantly related to IMP using the 28-item measure (p=0.016), and significant at a trend level using the 23-item measure (p=0.086). Similarly, the IMP subscale of the 28-item SURPS was significantly related to diversion in the multivariate model (p=0.020), but a trend towards significance was observed in the multivariate model when using the 23-item model (p=0.090). Despite these minor differences, the overall pattern of results obtained using the 23-item SURPS for both prescribed and non-prescribed anxiolytic and sedative users corresponded closely with that obtained using the 28-item version, suggesting that the relationships described between the SURPS personality dimensions and anxiolytic and sedative misuse among community-recruited adults in Studies 1 and 2 would have been largely the same had the alternate version of this measure been employed.

Table 3.6.
Means, standard deviations, alpha reliabilities, and ranges for the 28-item and 23-item versions of the Substance Use Risk Profile Scale among all anxiolytic and sedative users in Studies 1 and 2 (N=117).

	28-ITEM VERSION					23-ITEM VERSION				
SURPS Subscale	M	SD	α	Potential Range	Actual Range	M	SD	α	Potential Range	Actual Range
Hopelessness	17.2	4.7	0.90	8-32	8-29	14.7	4.0	0.90	7-28	7-25
Anxiety sensitivity	17.2	3.4	0.76	7-28	8-28	13.0	2.5	0.73	5-20	5-20
Sensation-seeking	16.4	3.7	0.79	6-24	7-24	16.4	3.7	0.79	6-24	7-24
Impulsivity	16.3	3.8	0.78	7-28	7-26	11.2	3.0	0.79	5-20	5-19

3.9 Linking Statement and Rationale for Study 3

The preceding chapters describe the misuse of anxiolytics and sedatives in prescribed and non-prescribed users recruited from the community. The results of Study 1 and Study 2 demonstrate heterogeneity in motives for misuse and complexity in patterns of misuse behaviours. Medication misuse among prescribed users and non-therapeutic motives for non-prescribed use were associated with various forms of other licit and illicit substance use and substance use problems. Analyses confirmed that non-therapeutic motives among non-prescribed users were associated with higher-risk patterns of misuse, including co-administration of anxiolytics or sedatives with other substances. Co-administration of other substances was also prevalent among prescribed users, with the concerning finding that alcohol was the most commonly co-administered substance, a combination which can result in serious harm to users (Longo & Johnson, 2000). These data substantiate calls in the literature for more detailed investigations of prescription drug misuse that take into account users' motives and patterns of use (e.g., Barrett et al., 2008; Boyd & McCabe, 2008).

In Study 2, correlates of non-prescribed medication use differed across prescription drug classes. For example, personality dimensions were differentially related to motives for anxiolytic and sedative use, but no such differences were found for stimulant use. These findings are consistent with previous literature supporting important differences in misuse patterns and correlates between different classes of prescription drugs (e.g., Hall et al., 2010; McCabe et al., 2009). To expand upon these findings, Study 3 involved a shift in focus from individual-level predictors towards exogenous, medication-related factors that may also be linked to anxiolytic and sedative misuse.

These external factors include classes of anxiolytics and sedatives and the manner in which these medications are prescribed to users. To carry out these analyses, all participants from Studies 1 and 2 reporting a history of prescribed anxiolytic or sedative use were combined into one sample. Participants who reported only non-prescribed use were excluded from this analysis.

CHAPTER 4 Study 3: Prescription Regimens and Misuse of Benzodiazepine and Non-Benzodiazepine Anxiolytics and Sedatives[15]

4.1 Abstract

Objective*:* To examine potential relationships between prescription regimen, drug class, and misuse of benzodiazepine (BZ) and non-benzodiazepine (non-BZ) anxiolytics and sedatives. ***Method:*** Eighty-five adults (aged 19 to 61 years; M=29.1, SD=10.7) with histories of prescribed anxiolytic or sedative medication use were recruited from the community. Participants completed a structured face-to-face interview assessing various forms of prescription drug misuse and diversion. ***Results:*** Prescription regimen (regularly scheduled vs. as-needed administration) was unrelated to any form of medication misuse or to diversion. Misuse was related to medication class, occurring more commonly with BZs than non-BZs. However, rates of non-BZ diversion were statistically equivalent to those of BZ diversion among participants who had used both medication classes. ***Conclusions:*** In addition to individual user characteristics (e.g., a patient's substance use history), medication characteristics are important considerations in the selection of a pharmacological treatment for anxiety or sleep disorders. The results of this investigation suggest that a non-BZ medication may be a preferable alternative to a BZ for individuals who are at risk for misuse of anxiolytics or sedatives.

[15] This manuscript has been submitted and is currently being considered for publication. This study involved a secondary analysis of the data collected in Studies 1 and 2. As first author, I contributed to study design, conducted statistical analyses, and wrote and revised the manuscript. Dr. Stewart and Dr. Barrett provided guidance in study design and statistical analysis and reviewed and provided feedback on the manuscript in preparation for submission for publication.

4.2 Introduction

The misuse of psychoactive prescription medications is a major public health issue and a pressing concern for health care providers (SAMHSA, 2008). Medications with CNS depressant effects, including those designed to treat anxiety and insomnia, have received substantial attention for their misuse potential. Benzodiazepine (BZ) anxiolytics and sedatives represent a widely prescribed class of medications with applications across a spectrum of clinical domains, including management of anxiety and sleep disorders (Hollister et al., 1993). In addition to having beneficial therapeutic effects for many patients, concerns with the use of BZs have been extensively documented (see Lader, 2011, for a review). Even when used according to therapeutic guidelines, BZs have a side effect profile that includes cognitive (Barker et al., 2004a; Buffett-Jerrott & Stewart, 2002) and psychomotor impairment (Lader, 1999) and development of physical dependence (Busto et al., 1986). Although clinical practice guidelines recommend short-term use (APA, 2006; CPA, 2006), and despite evidence for decreased efficacy over the long term (Lader, 1999), chronic BZ administration is common (Haw & Stubbs, 2007). Intentional misuse of BZs is also well documented (O'Brien, 2005). Overdose, especially when BZs are administered in combination with alcohol or other substances, is responsible for substantial morbidity and mortality among BZ users (Cai et al., 2010). Despite these concerns, BZs continue to be prescribed at a high rate (Lader, 2011).

While a number of alternative non-benzodiazepine (non-BZ) medications are indicated for the treatment of anxiety and insomnia (e.g., zolpidem, zopiclone, trazodone), concerns have also been raised following reports of their misuse (Cimolai,

2007; Hajak et al., 2003; Myrick et al., 1998), and empirical documentation of their abuse potential (Jaffe et al., 2004; Rush, Baker & Wright, 1999).

Optimizing anxiety and insomnia pharmacotherapy requires a comprehensive understanding of the factors related to the misuse of anxiolytic and sedative medications. Previous investigations of anxiolytic and sedative misuse have primarily focused on associations with individual user characteristics. Anxiolytic and sedative misuse has been linked to a history of other substance use (Becker et al., 2007; Fenton, Keyes, Martins & Hasin, 2010), psychiatric symptoms (Hajak et al., 2003), and personality characteristics (Hall et al., 2010). The manner in which these medications are prescribed to and administered by users is another important parameter, which has been largely neglected in previous research (Westra & Stewart, 2002). BZs and other anxiolytic and sedative medications can be prescribed according to a regular daily schedule or on an as-needed, or *p.r.n.*, basis. A large proportion of anxiety disorder patients with BZ prescriptions use them on a *p.r.n.* basis at least occasionally (Westra & Stewart, 2002). Advocates of *p.r.n.* use cite minimizing the amount of medication used, attenuating the development of dependence, facilitating discontinuation, and enhancing patients' perceived control over their symptoms as rationale for this manner of use (Kaplan & DuPont, 2005; Westra & Stewart, 2002). However, use of BZs in a symptom-contingent manner has been criticized for inducing conditioned drug tolerance (Dammen et al., 1994) and has been associated with poorer outcomes from cognitive-behavioural therapy for anxiety (Westra et al., 2002). While not yet empirically investigated, the greater flexibility inherent in *p.r.n.* use may facilitate use of anxiolytic and sedative medications in ways that are inconsistent with normal therapeutic guidelines. For example, users may save up

medications and administer in excess quantities on sporadic occasions or divert doses to other people.

The aim of the current investigation was to examine relationships between prescription regimens and the misuse and diversion of BZ and non-BZ anxiolytics and sedatives. First, we expected that misuse and diversion would occur more commonly when medications were prescribed on a *p.r.n.* basis than when prescribed according to a regular schedule (e.g., *b.i.d., t.i.d.*). Second, based on documented differences in the abuse liability of BZs relative to other forms of anxiolytics and sedatives (e.g., Jaffe et al., 2004), we predicted that rates of misuse and diversion would be higher for BZs than non-BZs.

4.3 Method

4.3.1 Study Participants

As part of a larger investigation of prescription drug use, adults (age 18 and up) with histories of prescribed anxiolytic or sedative use were recruited from the Halifax Regional Municipality, Canada. The recruitment strategy is described in detail elsewhere (see Study 1, section 2.3.1). Eligible medications included BZs and non-BZs with hypnotic, sedative, or anxiolytic effects. This criterion was based on the substances assessed by the National Survey of Drug Use and Health (SAMHSA, 2008). Because medications within these classes are often prescribed interchangeably for treating anxiety and insomnia (Brust, 2004), no differentiation was made at the time of recruitment. All participants provided written informed consent and were compensated for their time. The Dalhousie University Health Sciences Human Research Ethics Board approved this study.

4.3.2 Study Measures

Participants completed a structured face-to-face interview (Barrett, Gross et al., 2005; see Appendix B) focusing on lifetime substance use history. Participants provided demographic information and details of anxiolytic and sedative prescription medication use, including age at first prescription, reason for prescription, types of medications used, duration of prescription, and prescription regimen (i.e., *p.r.n.* or regular schedule). To capture various forms of anxiolytic and sedative misuse, participants were asked to report if they had ever taken their medication in excess of the prescribing clinician's guidelines (i.e., in greater quantities or more frequently than prescribed), used an alternate route of administration (e.g., intranasal or intravenous), or intentionally co-administered the medication with another substance. These yes/no responses were scored as 1 or 0 for each specific form of misuse. Responses to these queries were used to create binary composite variables for any misuse of BZs and/or non-BZs. Endorsing any specific form of BZ or non-BZ misuse resulted in a score of 1 for the composite variable indicating misuse of that substance class. Participants who denied all specific forms of misuse were given a score of 0 for the composite variable. Participants also reported on diversion, defined as giving away or selling their medication. Variables indicating diversion of BZs and non-BZs were similarly scored as 0 or 1.

A variable indexing overall non-prescription drug involvement (i.e., total number of substances used) was computed based on lifetime use of alcohol, tobacco, cannabis, cocaine, amphetamines, opioids (e.g., heroin, opium), hallucinogens (e.g., lysergic acid diethylamide, psilocybin), 3,4-methylenedioxymethamphetamine (MDMA/ecstasy), dissociatives (e.g., ketamine, phencyclidine), inhalants, and other illicit substances. Each

substance class was counted as one point, for a possible score range of 0 to 11 for this variable.

4.3.3 Study Procedures

Trained researchers administered the interview with each participant in a confidential setting in a single session of approximately two hours.

4.3.4 Statistical Analysis

For the purpose of analysis, prescription regimen was recorded in two ways. Participants were classified as either *p.r.n.* or regular users of BZs and/or non-BZs depending on their primary manner of administration of each medication category. Because it was common for participants to report receiving both *p.r.n.* and regularly scheduled prescriptions for a given drug category, a continuous variable was also created indexing the proportion of time (in months) each medication category was administered on a *p.r.n.* basis (Mueller et al., 2005). Bivariate analyses (i.e., independent sample *t* tests for continuous variables and chi-square tests for categorical variables) were conducted to investigate potential relationships between demographic variables and substance use history and BZ and non-BZ misuse and diversion. Subsequent analyses were conducted using bivariate logistic regression with BZ and non-BZ misuse and diversion variables as dichotomous outcome variables and prescription regimen variables as predictors. The α level to detect statistical significance was set at 0.05. All data were analyzed using IBM SPSS Statistics 20.

4.4 Results

Eighty-five adults (81% female) were included in the study. Participants ranged in age from 19 to 61 years (M=29.1, SD=10.7). The sample was 92% White, 2% Asian-Canadian, 1% African-Canadian, and 5% from other racial or ethnic groups. Sixty-four percent of participants were single. Fifty-four percent were current postsecondary students, while 37% had completed an undergraduate degree.

Seventy-seven participants (91%) reported at least one past or current BZ prescription and 38 (45%) reported at least one past or current non-BZ prescription. There was overlap between these groups, with 30 participants (35%) reporting at least one prescription from each category. A variety of medications were represented in each medication category. Table 4.1 lists the specific BZs and non-BZs that were most commonly reported by users of each medication class.

Participants received their first prescription at an average age of 21.7 years (SD=6.3). Characteristics of users' lifetime prescriptions for BZs and non-BZs and reasons for receiving these prescriptions are presented in Table 4.2. The majority of BZ users reported that the reason for the prescription was to reduce anxiety, while the majority of non-BZ users reported that their medication was prescribed to help with sleep. Among BZ users, 54 (70%) reported primarily being prescribed BZs on a *p.r.n.* basis, while the other 23 (30%) reported primarily being prescribed BZs according to a regular schedule. Among non-BZ users, 17 (45%) reported primarily prescribed non-BZs on a *p.r.n.* basis, while the other 21 (55%) were primarily prescribed non-BZs according to a regular schedule.

Frequencies of various forms of BZ and non-BZ misuse by users of each medication class are presented in Table 4.3. Demographic variables, age at first prescription, and total duration of medication use were not significantly related to misuse or diversion of BZs or non-BZs (data not shown). Among BZ users, participants reporting any form of misuse had used a significantly greater number of other psychoactive substances (M=5.8, SD=3.6) compared to those who had never misused a BZ (M=2.9, SD=2.2), $t(59.01)=4.27$, $p<0.001$. Among non-BZ users, those reporting any form of misuse had also used a significantly greater number of other substances (M=5.6, SD=3.0) compared to those who had never misused a non-BZ (M=3.0, SD=2.1), $t(17.75)=2.40$, $p=0.028$. Rates of BZ misuse did not differ depending on whether the medication was prescribed to treat anxiety, sleep, or for other reasons, $\chi^2(2)=2.86$, $p=0.239$. Similarly, rates of non-BZ misuse did not differ depending on the primary reason for which the medication was prescribed, $\chi^2(2)=2.90$, $p=0.234$.

To account for group differences in substance use history, lifetime number of psychoactive substances used was included as a covariate in subsequent regression analyses of medication regimen and misuse. Logistic regression indicated no difference between participants' dichotomized primary prescription regimens (*p.r.n.* vs. regularly scheduled) and any BZ misuse ($B=-0.51$, $p=0.362$) or BZ diversion ($B=0.44$, $p=0.429$). These results held when considering the proportion of time that BZs were administered on a *p.r.n.* basis. Proportion of time prescribed *p.r.n.* was unrelated to any BZ misuse ($B=-0.01$, $p=0.342$) or diversion ($B=0.003$, $p=0.570$). Similarly, no relationship was found between BZ regimen and any specific form of BZ misuse, including exceeding the

recommended dosage, co-administering with another substance, or using an alternate route of administration (data not shown).

Corresponding analyses conducted to examine non-BZ prescription regimens produced similar results. Dichotomized primary manner of non-BZ administration was unrelated to any non-BZ misuse (B=0.70, p=0.371) or diversion (B=0.98, p=0.180). The proportion of time non-BZs were administered *p.r.n.* was also unrelated to any non-BZ misuse (B=0.01, p=0.0312) or diversion (B=0.01, p=0.260). As with BZs, no relationship was found between non-BZ regimen and any specific form of non-BZ misuse (data not shown).

As Table 4.3 illustrates, all forms of misuse and diversion occurred more frequently among users of BZ medications than among non-BZ users. Because these comparisons included partially overlapping samples of participants, with some having prescriptions for only BZ or non-BZ medications and some having prescriptions for both, further analyses were performed among the subset of 30 participants with histories of using both categories of medication. These results are presented in Figure 4.1. Chi-square analyses revealed that each specific form of misuse was significantly more prevalent with BZs relative to non-BZs, including exceeding the recommended dosage, using the medication by an alternate route of administration, and intentionally co-administering the medication with other substances. However, rates of diversion of BZs and non-BZs did not differ significantly.

4.5 Discussion

Health care providers face a challenge in providing appropriate pharmacological interventions while simultaneously minimizing the potential for prescription drug misuse.

The results of this investigation have implications for the pharmaceutical management of anxiety and insomnia, which is often initiated in primary care settings (Lader, 2011). It is of concern that many participants in this study, especially BZ users, reported holding prescriptions for anxiolytics and sedatives for substantially longer than the typical recommended duration. This suggests many patients are using these drugs in a manner that puts them at higher risk for developing dependence.

This study extends previous research by examining prescription anxiolytic and sedative misuse in a framework that takes into account type of medication and manner of administration. The findings supported the hypothesis regarding medication type and misuse. Misuse was more common among BZ anxiolytics and sedatives than among non-BZs. This held true when restricting the analysis to participants with histories of both BZ and non-BZ use, suggesting that non-BZ anxiolytics and sedatives are less likely to be misused, even among individuals who are at risk to misuse BZs. This result is consistent with previous literature indicating an overall lower misuse liability of non-BZ anxiolytics and sedatives (Jaffe et al., 2004; Rush, Baker & Wright, 1999). Interestingly, frequency of non-BZ diversion did not differ significantly from frequency of BZ diversion among the subset of the sample that had held prescriptions for both classes of medication. As these findings indicate that differences between BZ and non-BZ medication classes in terms of misuse may not apply to diversion, prescribing physicians should advise patients of the risks associated with medication diversion regardless of type of anxiolytic or sedative being prescribed (BZ or non-BZ).

Clinicians should also consider that the efficacy of cognitive-behavioural therapy in the treatment of anxiety disorders and insomnia is well established (Butler, Chapman,

Forman & Beck, 2006; Smith, Huang & Manber 2005). Utilization of an empirically supported psychotherapy such as cognitive-behavioural therapy may be particularly important for improving treatment outcomes in patients at risk of engaging in anxiolytic or sedative misuse or diversion.

The data did not support the prediction that misuse and diversion of anxiolytics and sedatives would occur at higher frequencies when medications were prescribed in an as-needed manner. The lack of relationship between *p.r.n.* use and exceeding the recommended medication dosage was particularly surprising, since *p.r.n.* use has been criticized for inducing conditioned drug tolerance (Dammen et al., 1994). While these results may indeed indicate that prescription regimen is unrelated to risk for anxiolytic and sedative misuse, it is possible that the small proportion of regularly scheduled users in this sample, relative to *p.r.n.* users, limited the statistical power of this analysis.

Other possible explanations for this finding may arise from limitations in the way that prescription regimen was assessed. It would have been useful to obtain documentation of the original prescription rather than relying on participants' recall of the administration directions. Some individuals may have misunderstood the recommended prescription regimen and unintentionally deviated from it. Furthermore, participants reported on how the prescribing physician recommended that their medication be taken, but did not systematically report their compliance with their medication regimens over time. Some evidence suggests that patients using BZs over the long term tend to shift from scheduled to *p.r.n.* use (Romach et al., 1995). Within our sample, which included many long-term users, participants who reported initially being prescribed a medication according to a regular schedule may have ended up

administering it as needed. It is also possible that *p.r.n.* use may be associated with subtler indicators of misuse that were not assessed, such as context-specific escalations in use (e.g., administering the maximum daily dosage of medication within a brief time frame rather than spread throughout the day). While our results suggest that as-needed medication use is not associated with an increased risk for misuse or diversion, in light of previously documented concerns with *p.r.n.* use (Dammen et al., 1994; Westra & Stewart, 2002; Westra et al., 2002), further investigation of this issue appears warranted.

Several limitations of this study should be taken into account. Firstly, the sample was modest in size and largely female, White, and well educated. While the proportion of female participants reflects a gender imbalance in the prescription rate of anxiolytics and sedatives at the population level (Mant, Mattick, de Burgh, Donnelly & Hall, 1995), the sample size and demographic characteristics could restrict generalizability of the study findings. Secondly, variability in the pharmacodynamic and pharmacokinetic properties of substances within the BZ and non-BZ categories may contribute to differential liabilities for misuse (Griffiths & Johnson, 2005). Although the sample size did not permit sub-analyses of specific medications, this is a promising topic for future investigations. Finally, the cross-sectional design of this investigation restricts the ability to draw conclusions about temporal relations between variables.

4.5.1 Conclusions

Clinicians should be aware that individual user characteristics, particularly a history of substance use, have been empirically linked to misuse and diversion of anxiolytic and sedative drugs (Fenton et al., 2010). The findings of the current study indicate that likelihood of misuse is elevated among BZ medications as compared to non-

BZ medications. This difference may not apply to diversion, which occurred commonly among both medication classes. Enhancing assessment and detection of potential vulnerability factors prior to prescription of an anxiolytic or sedative offers the clinician the opportunity to select a medication with lower misuse liability or recommend a non-pharmacological intervention.

Table 4.1
Lifetime prescriptions for specific BZ and non-BZ medications.

	BZ users (*n*=77)
Benzodiazepines	*n* (%) of participants
Lorazepam	60 (78)
Clonazepam	38 (49)
Diazepam	18 (23)
Alprazolam	10 (13)
Temazepam	6 (8)
Triazolam	6 (8)
	Non-BZ users (*n*=38)
Non-benzodiazepines	*n* (%) of participants
Zopiclone	26 (68)
Trazodone	9 (24)
Cyclobenzaprine	7 (18)
Mirtazapine	4 (11)
Buspirone	4 (11)

Note. Percentages total more than 100 due to participants reporting multiple prescriptions. BZs and non-BZs that were reported by fewer than 5 percent of participants are not listed.

Table 4.2
Characteristics of lifetime BZ and non-BZ prescriptions.

	BZ users (*n*=77)	Non-BZ users (*n*=38)
	Mean (SD)	Mean (SD)
Lifetime number of medications prescribed	1.9 (1.5)	1.4 (0.8)
Total time prescribed (months)	45.3 (72.6)	21.3 (33.0)
Total time prescribed *p.r.n.* (months)	25.2 (46.0)	8.1 (18.0)
Total time prescribed regularly scheduled (months)	20.2 (49.9)	13.3 (30.9)
Proportion of time spent prescribed *p.r.n.* (%)	68.2 (42.4)	44.0 (47.8)
Primary reason for receiving prescription	*n* (%) of participants	*n* (%) of participants
To reduce anxiety	60 (77.9)	4 (11.8)
To help with sleep	14 (18.2)	28 (77.8)
Other [a]	3 (3.9)	4 (11.1)

[a] Other reasons for receiving prescriptions included managing withdrawal from alcohol or other drugs, pain, muscle tension, and feigning symptoms to obtain medication to be used for intoxication.

Table 4.3
Frequencies of various forms of BZ and non-BZ misuse by users of each medication class among the sample as a whole.

	BZ users (*n*=77)	Non-BZ users (*n*=38)
	n (%) of participants	*n* (%) of participants
Any medication misuse	37 (48.1)	14 (36.8)
Exceeded recommended medication dosage	33 (42.9)	11 (28.9)
Co-administered medication with another substance	28 (36.4)	11 (28.9)
Administered medication by alternate route	9 (11.7)	1 (2.6)
Medication diversion	37 (48.1)	14 (36.8)

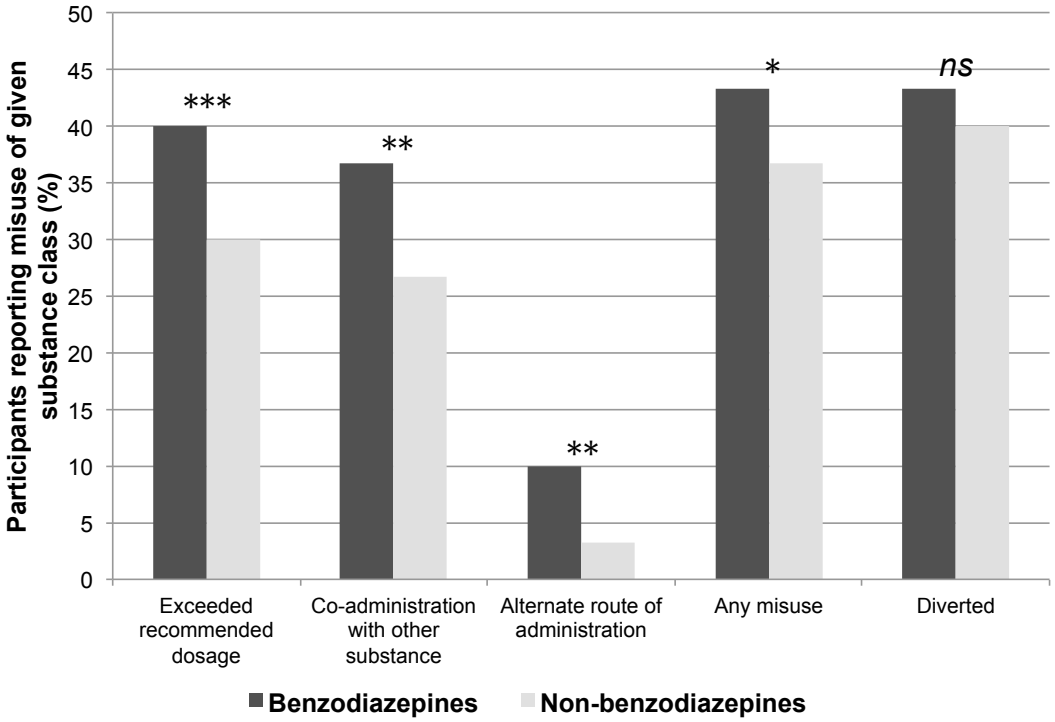

Figure 4.1. Prevalence of misuse and diversion by category of medication among participants with lifetime histories of both BZ and non-BZ use (n= 30). Significance values represent comparisons between proportions of the sample reporting forms of misuse conducted with chi-square tests. *p<0.05; **p<0.01; ***p<0.001; *ns* = non-significant.

4.6 Linking Statement and Rationale for Study 4

The findings of the preceding analysis correspond with existing literature demonstrating an increased likelihood of misuse of BZs relative to non-BZ anxiolytics and sedatives (Griffiths & Johnson, 2005). However, these results cannot be interpreted as indicating an absence of risk for misuse of non-BZ drugs. In Study 3, among a community-based sample, over 35 percent of participants reported misusing a prescribed non-BZ medication at least once, most commonly by exceeding the dosage recommended by their physician or by deliberately co-administering the non-BZ with another intoxicating substance. Misuse of non-BZs was associated with a more extensive substance use history.

This finding is interesting when considered in light of previous literature documenting an elevated risk of misuse of anxiolytics and sedatives among individuals with substance use disorders (Brunette et al., 2003). Users of opioid drugs, including methadone, are thought to be at high risk of misusing anxiolytics and sedatives, particularly benzodiazepines (Lintzeris & Nielsen, 2010). The concurrent misuse of benzodiazepines with methadone has been attributed to drug interactions that enhance the subjective effects of opioids (Lintzeris, Mitchell, Bond, Nestor & Strang, 2006). However, co-dependence on these drug classes can result in more severe withdrawal symptoms (de Wet et al., 2004). Prescribing clinicians are encouraged to consider alternatives to benzodiazepines for the management of anxiety and insomnia in high-risk substance-using populations, including opioid users, which include atypical antipsychotics with sedative and anxiolytic effects (Longo & Johnson, 2000). One such medication is quetiapine, which has become an increasingly common choice in the

treatment of insomnia and anxiety disorders (Wine, Sanda & Caballero, 2009; Wu et al., 2013). Accumulating data support its efficacy in treating these conditions (Carney, 2013; Wine et al., 2009).

As quetiapine can have serious side effects, even when used at low doses (Cates et al., 2009), a careful examination of the possible risks and benefits of its use is imperative for prescribing clinicians. Gaining a better understanding of the ways in which quetiapine may be misused is an important part of this process. In contrast to the perception of antipsychotics as "nonabusable" (Simoni-Wastila, 2000, p. 289), in a review of case reports, Fischer and Boggs (2010) found numerous examples of quetiapine misuse, abuse, and dependence. Deaths related to quetiapine overuse have been reported among both prescribed and non-prescribed users (Fernandes & Marcil, 2002; Pilgrim & Drummer, 2013). This literature indicates that those at risk for quetiapine misuse tend to have concurrent mental health and substance use issues as well as significant psychosocial challenges (e.g., incarceration; Fischer & Boggs, 2010). Quetapine has been reported to increase plasma levels of methadone (Uehlinger et al., 2007). Although no signs of overmedication or intoxication have been attributed to this effect (Uehlinger et al., 2007), this suggests some vulnerability for misuse of quetiapine among methadone users.

A large proportion of the prescription drug misuse literature is comprised of population-based epidemiological studies (e.g., those based on NSDUH or NESARC data) and more detailed studies on limited demographic groups (e.g., U.S. college students). Individuals with substance use disorders, including those in treatment, have received relatively little attention from researchers. Although findings from specialized

clinical samples may not generalize to the overall population, research in this area is essential as these individuals are likely to be at elevated risk of harmful consequences resulting from misuse of prescription drugs. Furthermore, such high-risk groups often utilize a wide variety of health services. Understanding more about the unique health care needs of these populations offers the opportunity to develop targeted and empirically based strategies for intervention. The following chapter, Study 4, examines misuse of quetiapine among clients of a low-threshold, community-based methadone maintenance program.

CHAPTER 5 Study 4: Characteristics of Quetiapine Misuse Among Clients of a Community-Based Methadone Maintenance Program[16]

5.1 Abstract

The atypical antipsychotic quetiapine has sedating properties and is increasingly being used to treat insomnia and anxiety. Deliberate misuse of this medication has been documented in a series of recent case reports. The objective of this study was to systematically investigate potential quetiapine misuse among a sample of high-risk substance users. Seventy-four clients of a methadone maintenance treatment program in Halifax, Nova Scotia completed a structured interview focusing on lifetime substance use, including misuse of prescription drugs. Participants were asked to report on specific instances of quetiapine misuse and diversion. Demographic and substance use variables were examined to identify possible predictors of quetiapine misuse. Bivariate relationships between various forms of quetiapine misuse and these variables were examined using *t* tests and χ^2 tests. Over 80% of participants had used quetiapine, with three-quarters of this group reporting at least one form of quetiapine misuse. Certain forms of quetiapine misuse were reported frequently, including use without a

[16] This chapter was published in an abbreviated form as McLarnon, M.E., Fulton, H. F., MacIsaac, C. & Barrett, S. P. (2012). Characteristics of quetiapine misuse among clients of a community-based methadone maintenance program. *Journal of Clinical Psychopharmacology, 32,* 721-723 (see Appendix G). Copyright (2012), Lippincott Williams & Wilkins. Reproduced with permission (see Appendix H). As first author of this article, I contributed to the design of the study, participated in training of research assistants, recruited participants on-site at the methadone clinic, conducted interviews with participants, managed data collection, entered data, conducted analyses, wrote the manuscript, and revised the manuscript in accordance with suggestions from my co-authors, peer reviewers, and journal editor. This study was funded by a grant from the Canadian Institutes of Heath Research. Acknowledgements go to Ms. Lacey Peters for contributing to the data collection and the staff and clients of Direction 180 for their support of this study.

prescription, deliberate co-administration with other substances, and administering in excess of prescribed dosages. Use of quetiapine by an alternate route of administration was much less common. Half of prescribed quetiapine users reported diverting their medication to others. Participants' quetiapine misuse and diversion was most typically motivated by a desire to achieve a therapeutic effect. Past misuse of prescription anxiolytics or sedatives was associated with an increased likelihood of reporting quetiapine misuse. Quetiapine misuse and diversion were found to occur frequently within this high-risk substance-using population. Users' primary motives for engaging in these activities appear to be related to quetiapine's sedating or calming effects. Among patients at risk, enhanced education to prevent or reduce potential harms associated with quetiapine misuse and diversion may be warranted.

5.2 Introduction

Quetiapine is an atypical antipsychotic medication approved for treatment of schizophrenia and bipolar disorder. It has documented effectiveness in treating these conditions and is reportedly better tolerated than other atypical antipsychotics (Adityanjee & Schulz, 2002). Relatively low doses of quetiapine have demonstrated efficacy in improving sleep induction and continuity (Cohrs et al., 2004) and emerging evidence supports its efficacy in treating various anxiety disorders (Adityanjee & Schulz, 2002; Ravindran, Al-Subaie, & Abraham, 2010). Correspondingly, quetiapine has become an increasingly popular pharmacotherapy for anxiety and insomnia, often in place of traditional BZ anxiolytics or sedatives (Murphy, Bailey, Stone, & Wirshing, 2008). Quetiapine acts on dopaminergic, serotonergic, histaminic, and alpha-adrenergic systems (Gugger & Cassagnol, 2008). Although its specific mechanisms of action are not fully understood, quetiapine has been described as having subjective effects similar to central nervous system (CNS) depressants, such as drowsiness and sedation (Tcheremissine, 2008).

Similar to other prescription medications with sedative effects, there have been reports of quetiapine misuse, including use in excessive amounts (Chen, Shiah et al., 2009; Murphy et al., 2008; Pais & Ayvazian, 2001; Paparrigopoulos, Karaiskos, & Liappas, 2008; Reeves & Brister, 2007), in combination with other substances (Harrison, Dilley, Loeb, & Nelson, 2006; Paparrigopoulos et al., 2008; Waters & Joshi, 2007) and by alternative routes of administration (Hussain, Waheed, & Hussain, 2005; Morin, 2007; Pierre, Shnayder, Wirshing, & Wirshing, 2004; Waters & Joshi, 2007). Some users have been described as exhibiting drug-seeking behaviour and impairment of social

functioning consistent with DSM-IV-TR (APA, 2000) substance dependence (Chen, Shiah et al., 2009; Fischer & Boggs, 2010; Murphy et al., 2008; Pinta & Taylor, 2007). Several reports have described users embellishing or fabricating symptoms to obtain quetiapine (Fischer & Boggs, 2010; Murphy et al., 2008; Pierre et al., 2004; Reeves & Brister, 2007). Instances of quetiapine being acquired or sold through illegitimate channels have also been reported (Murphy et al., 2008; Pierre et al., 2004; Pinta & Taylor, 2007; Reeves & Brister, 2007).

In most cases, the reported motive for quetiapine misuse appears to be self-medication for insomnia (Reeves & Brister, 2007), anxiety (Chen, Shiah et al., 2009; Morin, 2007; Reeves & Brister, 2007), or depressed mood (Chen, Shiah et al., 2009), rather than for its "mind-altering effects" (Keltner & Vance, 2008). However, because quetiapine misuse has yet to be systematically investigated in a larger sample, little is known about the ways in which it may be misused. In the current study, we investigated patterns of quetiapine misuse among clients of a methadone treatment program with histories of prescription opioid dependence. Study 1 of this dissertation suggests that individuals with an extensive history of substance use are at increased risk for misusing prescription sedative or anxiolytic medications (see Chapter 2), which may put users at risk for misusing quetiapine specifically (Fischer & Boggs, 2010, Sansone & Sansone, 2010). Quetiapine has been reported to increase plasma concentrations of methadone (Uehlinger et al., 2007), suggesting another possible motive for its misuse among individuals receiving methadone treatment.

5.3 Method

5.3.1 Participants

Seventy-four participants (68.9% men) were recruited as part of a larger study from a low-threshold community-based methadone maintenance program in Halifax, Canada. Recruitment took place via word of mouth at the methadone program with the assistance of clinic staff. All clients enrolled in the program were advised of their eligibility to take part in the study. They were informed that participation was voluntary, their responses would be confidential, and that their status within the methadone program would be unaffected regardless of whether they elected to take part in this research.

Participants ranged in age from 18 to 64 years (M 41.2, SD 10.6). The sample was 77.0% Caucasian, 9.5% Aboriginal, 4.1% African-Canadian, and 9.5% from other racial or ethnic groups. 71.6% of participants reported an annual income of less than $10,000 Canadian per year. 45.9% had completed less than a high school level of education. Participants were receiving mean daily methadone doses of 108.3 mg (SD 45.6 mg) to treat prescription opioid dependence. All participants provided written informed consent prior to participating and were compensated for their time. The Capital District Health Authority research ethics board in Halifax approved the study.

5.3.2 Procedure

Each participant completed a confidential face-to-face interview with a member of the research team. Interviews took place at the methadone clinic and lasted one to two hours. Participants completed a modified version of a polysubstance use interview (Barrett, Gross et al., 2005), adapted from the Addiction Severity Index (McLellan et al., 1980). Participants reported on lifetime use of alcohol, tobacco, illicit drugs, and other

substances, including prescription drugs (see Drug List Questionnaire, Appendix B, and Quetiapine Use Interview, Appendix G). To assist with recollection, participants were prompted with a card depicting various forms and dosages of quetiapine. This card was created for this study with images from the *Compendium of Pharmaceuticals and Specialties* (e-CPS, 2009). Those who had used quetiapine were asked when the medication was prescribed to them and which conditions it was intended to treat. Participants reported on any instances of quetiapine misuse, defined as use via alternate routes of administration, deliberate co-administration with other substances, intentionally exceeding the recommended dosage, or use without a valid prescription. They also reported on instances of quetiapine diversion, defined as selling, trading, or giving away their medication. Participants were presented with a list of motives and asked to select those corresponding to their reasons for misusing or diverting quetiapine. This list was based on previous investigations of prescription drug misuse (Boyd et al., 2006). Participants had the option of supplying a different motive for use if theirs was not included in the existing list.

5.3.3 Data Analytic Strategy

Prescription drug use, misuse and diversion were coded as dichotomous variables. Frequencies were used to describe proportions of participants who had used and misused quetiapine. Bivariate analyses (independent sample *t* tests for continuous variables and χ^2 tests for categorical variables) were conducted to examine relationships between demographic and substance use variables. An α level of $p<0.05$ was set as a threshold of statistical significance. Statistical analyses were performed using Predictive Analytics SoftWare (PASW 18.0; SPSS, Inc. Chicago, IL).

5.4 Results

Participants had used an average of 9.0 illicit drugs (SD=4.1) in their lifetimes. Sixty-three participants (85%) reported a history of misuse of anxiolytic or sedative medications. Quetiapine usage was common, with 57 participants (80%) reporting lifetime use. Of these, 21 (37%) reported only taking quetiapine with a valid prescription, 12 (21%) reported only taking quetiapine without a prescription, and 24 (42%) reported using quetiapine both with and without a prescription. Overall, 43 participants (75% of all quetiapine users) had engaged in at least one form of quetiapine misuse. Sixteen participants (28% of all quetiapine users) reported intentionally administering quetiapine concurrently with another substance. The substance class most commonly co-administered with quetiapine was prescription anxiolytics and sedatives (8 participants [11%]), primarily benzodiazepines. Two participants (3.5% of all quetiapine users) reported using quetiapine by an alternate route of administration; in both cases, it was used intranasally.

Participants' sex, race/ethnicity, income, and level of education were unrelated to likelihood of reporting quetiapine misuse. Participants who reported any form of quetiapine misuse were significantly younger than those who did not, $t(55)=2.41$, $p=0.02$. Individuals with a history of prescription anxiolytic/sedative misuse were over 8 times more likely to report having misused quetiapine, as compared to those who had never misused anxiolytics or sedatives, $\chi^2(1)=6.42$, $p=0.03$. Of 41 participants who had misused both quetiapine and anxiolytics or sedatives, in all but 3 cases (93%), the onset of anxiolytic or sedative misuse preceded the onset of quetiapine misuse. Participants' total

number of illicit drugs used was unrelated to the likelihood of engaging in quetiapine misuse, $t(55)=0.88$, $p=0.38$.

Of those who had ever held a prescription for quetiapine ($n=45$), 39 participants (87%) reported that the medication was prescribed to help with sleep or to reduce anxiety, three (4.1%) reported receiving quetiapine to assist with withdrawal from other substances, and two (2.7%) reported receiving it for treatment of psychosis or bipolar disorder. Seventeen (38%) of the prescribed users admitted to intentionally taking quetiapine in excess of its prescribed dosage on at least one occasion, while 23 (51%) reported diverting the medication to others at least once. All but one of the prescribed users who reported taking quetiapine in excess amounts (94%) stated that the primary reason for doing so was to increase its therapeutic effect. More than three-quarters (76%) of those who had diverted quetiapine stated that they provided the medication to another individual who intended to use it to induce sleep. Similarly, 32 (89%) of the participants who had ever used quetiapine without a prescription reported that their primary reason for taking it in that context was to help with sleep.

5.5 Discussion

This study examined misuse of the atypical antipsychotic quetiapine among clients of a methadone maintenance program. Quetiapine use was extremely common within our sample, with over 80% of participants reporting some experience with it. Overwhelmingly, participants who had received prescriptions for quetiapine were prescribed the medication for the treatment of insomnia or anxiety. Despite concerns raised in the literature about the potential for intranasal or intravenous misuse of quetiapine (e.g., Pierre et al., 2004; Waters & Joshi, 2007), these high-risk forms of

misuse were rare or nonexistent among this sample. However, other forms of misuse, such as administering quetiapine in excess amounts, concurrently with alcohol or other drugs, or without a valid prescription, were prevalent. Interestingly, most participants who reported misusing the medication stated that their intent was to increase its therapeutic effect, to reduce anxiety or induce sleep. The same motive was commonly reported among those who reported diverting quetiapine to others (i.e., the recipients' motives were also therapeutic). The total number of illicit drugs participants had used was unrelated to quetiapine misuse; however, this finding may represent a ceiling effect, as most participants within the sample had used numerous illicit substances. Quetiapine misuse was more frequent among participants who had misused anxiolytic or sedative medications in the past, suggesting that individuals with a history of CNS depressant drug use may be at elevated risk to misuse quetiapine.

The present results should be considered in light of the following methodological considerations. Participants were recruited from a low threshold methadone maintenance program and it is likely that the relative rates of misuse would be lower in non-drug abusing populations. It is also possible that participants may have underreported misuse due to a desire to minimize their apparent participation in illegal or socially undesirable activities. However, structured interviews similar to those employed in this study are generally considered to be a valid and reliable means of collecting self-report data on substance use (Fals-Stewart et al., 2000). Furthermore, participants in this study were assured of confidentiality and readily provided details about a broad spectrum of substance use experiences.

Future research is needed to more fully elucidate the factors relating to quetiapine misuse and assist in developing strategies by which the safe and effective use of this medication may be maximized. Prevention efforts should also be directed towards better screening for individuals at risk for quetiapine misuse. A review of the published reports of quetiapine misuse demonstrated comorbid mental illness among many of the cases (Fischer & Boggs, 2010). Assessing the relationship between mental health symptoms and risk for quetiapine misuse represents a promising avenue for future investigations.

5.5.1 Conclusion

This study provides insight into patterns of quetiapine misuse among methadone clients and is, to our knowledge, the first systematic investigation on this topic. The high rates of diversion and of non-prescribed quetiapine use in the current study suggest that better education is needed regarding the risks of taking psychoactive medications without a clinician's supervision, particularly among high-risk, substance-using populations.

CHAPTER 6 Discussion

6.1 Discussion Overview

This dissertation examined misuse of prescription anxiolytic and sedative medications among adults recruited from the community and from a methadone maintenance program in Halifax, Nova Scotia. The primary objectives of this research were to characterize patterns of misuse among prescribed and non-prescribed users of these drugs; to investigate putative individual-level correlates of misuse, including motives, personality characteristics, other substance use, and non-substance psychopathology; and to examine medication-related factors that may relate to misuse. The specific hypotheses, methods, and results of the four studies that make up this dissertation are detailed in the preceding chapters. This discussion chapter will integrate these findings across studies and review the contributions of this program of research to the broader literature on anxiolytic and sedative misuse. This chapter will also review strengths, limitations, promising areas for further investigation, and clinical implications of this work as a whole.

6.2 Summary and Integration of Findings

6.2.1 Support for a Heterogeneous Conceptualization of Anxiolytic and Sedative Misuse

Despite having different research questions and sample characteristics, some common themes emerged across the four studies making up this thesis. Results consistently demonstrated heterogeneity within prescription anxiolytic and sedative misuse. This was congruent with theoretical predictions (Boyd & McCabe, 2008), and

provides further evidence for the existence of subtypes of prescription anxiolytic and sedative misuse that can be differentiated on the basis of motives for use and behavioural patterns. Studies 1 and 2 documented a variety of forms of misuse among prescribed and non-prescribed users of anxiolytics and sedatives. Over half of the prescribed users in Study 1 reported misusing their medication at least once, with the most common form of misuse involving deliberately exceeding the dosage recommended by their physician. In this sample, many participants reported that their motive in doing so was to achieve a therapeutic effect; however, half of those who had administered their medication in excess reported doing so with non-therapeutic motives on at least one occasion. Although taking more of a medication than recommended could not be assessed in those without valid prescriptions, among the non-prescribed anxiolytic and sedative users in Study 2, many reported taking multiple pills during a typical episode of use. This behaviour was associated with non-therapeutic motives for use, indicating that non-therapeutic users are likely to ingest dosages of anxiolytics and sedatives that put them at increased risk for adverse consequences.

Another common form of misuse involved intentionally administering anxiolytics and sedatives with other substances, which was reported by 41 percent of prescribed users in Study 1 and 63 percent of non-prescribed users in Study 2. Consistent with expectations, non-therapeutic motives were associated with concurrent administration of anxiolytics and sedatives with other substances. Participants reported multiple patterns of co-administration, indicative of variability even within this particular form of misuse. One pattern involved the use of anxiolytics and sedatives to augment the effects of other psychoactive substances. It is notable that the substance most frequently co-administered

with anxiolytics and sedatives among prescribed users was alcohol, which acts synergistically with these medications and increases the risk of overdose (Longo & Johnson, 2000). Interestingly, among the 28 percent of quetiapine users in Study 4 who had deliberately taken quetiapine concurrently with another psychoactive substance, the most commonly co-administered substances were anxiolytics and sedatives (primarily benzodiazepines), which may indicate an attempt to obtain an augmented effect from these depressant drugs. This finding is concerning in light of a recent study of fatal pharmaceutical overdoses involving quetiapine, which demonstrated that the most commonly co-administered drug with quetiapine was diazepam (Pilgrim & Drummer, 2013).

A different variation of anxiolytic and sedative co-administration, reported by approximately 10 percent of prescribed users in Study 1 and a quarter of the non-prescribed users in Study 2, involved the use of anxiolytics and sedatives with illicit stimulant drugs, including cocaine, amphetamine, and MDMA/ecstasy. Participants typically reported engaging in this behaviour to induce sleep following stimulant use. Use of anxiolytics and sedatives to ameliorate withdrawal symptoms from cocaine and other stimulants has been previously reported (e.g., O'Brien, 2005); however, participants in the present studies were reporting on the use of anxiolytics and sedatives to mitigate the adverse effects of stimulants while still under the influence of these drugs. This pattern is of concern, as users may increase their consumption of stimulant drugs to hazardous levels with the belief that anxiolytics or sedatives can be used to moderate their effects. Collectively, these results indicate that anxiolytic and sedative misuse often takes place within a high-risk polysubstance context.

The use of anxiolytics or sedatives by alternate routes of administration was found to be less frequent than other forms of misuse, with 7.5 percent of prescribed users in Study 1 and 12 percent of non-prescribed users in Study 2 reporting ever engaging in this behaviour. Among participants who had used an alternate route of administration, most reported using the medication intranasally, rather than by injection or smoking. Previous literature indicates that misuse of anxiolytics and sedatives typically takes place via oral administration of these drugs (Griffiths & Weerts, 1997; Sajan et al., 1998). Although the present data support this, it is interesting to find evidence that non-oral administration can occur with some regularity among a community-based sample. As alternate routes of administration can put users at increased risk of harm, including development of substance use disorders (Compton & Volkow, 2006), further attention to this phenomenon is warranted.

6.2.2 Relationships between Anxiolytic and Sedative Misuse and Other Substance Use

A second common theme emerging from these studies is a robust association between anxiolytic and sedative misuse and other substance use. In previous investigations, a more extensive substance use history and substance-related problems have differentiated individuals who misused anxiolytics and sedatives from non-users (Becker et al., 2007; McCabe, 2005; McCabe et al., 2009). The present research builds on this literature by providing evidence that patterns of other drug use vary among groups of anxiolytic and sedative users. In Study 1, misuse of anxiolytics and sedatives among prescribed users was associated with the use of a number of illicit drugs and with problematic consequences as a result of drug use. The number of illicit drugs an

individual had used was found to be the strongest predictor of misusing one's own medication. Among non-prescribed users in Study 2, non-therapeutic motives for anxiolytic and sedative use were associated with a variety of substance-related variables. Results demonstrated a particularly strong relationship with opioid use. It is notable that high rates of anxiolytic and sedative misuse were reported by the participants of Study 4, all of whom were receiving methadone to manage prescription opioid dependence. Overall, these results may be reflective of a general tendency towards the misuse of drugs with depressant effects (e.g., among individuals seeking relief from aversive affective states).

6.2.3 Individual Differences and Anxiolytic and Sedative Misuse

The studies comprising this dissertation advance the understanding of individual difference factors relating to anxiolytic and sedative misuse. Studies 1 and 2 are the first to examine the applicability of a personality and motivational model of substance use (Conrod, Pihl et al., 2000; Conrod & Woicik, 2002) to the misuse of anxiolytics and sedatives among prescribed and non-prescribed users. The results of these analyses were largely consistent with hypotheses based on this theoretical model. Studies 1 and 2 demonstrated differential links between the four dimensions of personality presented in Conrod, Pihl et al.'s model and varying motives and forms of anxiolytic and sedative misuse. Among prescribed users, the personality dimension H was associated with misuse of anxiolytics and sedatives by intentionally exceeding the prescribed dosage, possibly indicating use of anxiolytics or sedatives to avoid aversive affective experiences. IMP was associated with co-administration of anxiolytics or sedatives with other substances, consistent with previous research demonstrating links IMP and polysubstance

use (Balodis, Potenza & Olmstead, 2010). IMP was also linked with an increased risk for diverting one's own medication. A SS personality style was associated with use of an anxiolytic or sedative by an alternate route of administration, consistent with the conceptualization of SS as indicating a predisposition for thrill-seeking experiences (Conrod, Pihl et al., 2000). Among non-prescribed users, higher levels of SS were associated with the use of anxiolytics and sedatives for non-therapeutic purposes. In the same sample, higher levels of the personality dimension AS were associated with therapeutic motives at a trend level. Although this result did not attain statistical significance (potentially due to small sample size and resultant low statistical power), it suggests that individuals who experience distress as a result of the physiological symptoms of anxiety may be prone to use anxiolytic or sedative medications to avoid these feelings (in this case, despite not having valid prescriptions for these drugs). Among prescribed users, AS was not associated with any of the specific forms of misuse assessed. This finding corresponds with that of Krank et al. (2011), who found H, SS and IMP to be the strongest and most consistent predictors of substance use and misuse variables in an adolescent sample. AS may be related to indicators of problematic prescription drug use not assessed using the present methodology, such as lack of adherence to a regular prescription regimen (Westra & Stewart, 2002). Alternately, the lack of relationship between AS and misuse among prescribed anxiolytic and sedative users may reflect relatively high levels of AS among this entire sample, regardless of whether they had ever engaged in misuse of their medication. This explanation is consistent with the observed tendency towards higher AS scores among the prescribed

anxiolytic and sedative users in Study 1 as compared to the non-prescribed users in Study 2.

This also suggests a possible explanation for the lack of relationship between psychiatric symptoms and misuse in Study 1, and between psychiatric symptoms and motives for use of non-prescribed medication in Study 2. Among non-prescribed users in Study 2, those reporting use of these medications to reduce anxiety or induce sleep endorsed more anxiety symptoms than those reporting non-therapeutic motives; however, this result was not statistically significant. Previous literature has shown that non-prescribed anxiolytic and sedative use is associated with mental health difficulties, particularly symptoms of anxiety disorders (Fulton, Barrett, MacIsaac & Stewart, 2011; Goodwin & Hasin, 2002; Hajak et al., 2003), suggesting that elevated levels of symptomatology may have been present in both motive groups.

Another possible explanation for the lack of relationship between motives for misuse and non-substance psychopathology relates to the ways in which these factors were assessed. The PDSQ measures current psychiatric symptoms based on a timeline consistent with the DSM-IV (e.g., depressive symptoms are assessed over the previous two weeks, generalized anxiety symptoms are assessed over the previous six months). In contrast, the prescription drug interview asks participants to report on lifetime instances of misuse. As psychiatric symptoms can fluctuate over time, participants' self-reports at the time of their participation in the study may be incongruent with their symptoms at the time of misuse, especially if misuse happened in the remote past. Further investigation in this area is essential to better understand how non-substance psychopathology may relate to motives for anxiolytic and sedative misuse.

6.2.4 Medication-Related Factors

In Study 3, responses from participants from Studies 1 and 2 who had ever held prescriptions for anxiolytics and sedatives were analyzed to investigate putative relationships between prescription regimen, medication class and misuse. Based on the greater flexibility inherent in as-needed use, it was expected that higher rates of misuse and diversion would be found among those with as-needed prescriptions compared to those who were prescribed according to a regular schedule. Contrary to this prediction, medication regimen was found to be unrelated to misuse. This finding could be interpreted in a number of ways. Although participants reported on how their medications were prescribed, the extent to which they adhered to the recommended regimen in practice is unknown. It is possible that participants who reported being prescribed an anxiolytic or sedative according to a regular schedule ended up administering it on an as-needed basis (Romach et al., 1995), thereby negating putative differences between these prescription regimens. It is also possible that medication regimen may have a relatively weak relationship to misuse compared to individual-level characteristics. Griffiths and Weerts (1997) reviewed several potential determinants of BZ misuse liability, including characteristics of the user, pharmacokinetic properties of the drug, and the behavioural context in which the drug is used. Based on the results of over two dozen studies, these authors concluded that individual-level characteristics represent the most important determinants of misuse, with the most significant of these being the individual's substance use history. Although a diagnosis of substance abuse or dependence appears to confer the greatest risk, individuals with histories of moderate alcohol use also appear to be at increased vulnerability for BZ misuse as compared to light drinkers (Griffiths &

Weerts, 1997). The results of the current research are consistent with this finding, in that that use of multiple illicit drugs, even in the absence of drug-related problems, was found to be a significant predictor of anxiolytic and sedative misuse.

In Study 3, all forms of anxiolytic and sedative misuse were more prevalent with BZ medications than non-BZs. This finding corresponds with hypotheses and previous literature (Griffiths & Johnson, 2005; Rush, Baker & Wright, 1999), suggesting that among individuals who are at risk to misuse anxiolytics and sedatives, the likelihood of misuse may be mitigated somewhat by prescribing a non-BZ medication. A novel finding of the present analysis, however, was that this relationship did not extend to medication diversion, with participants who had used both BZ and non-BZ medications diverting these drugs to others at equivalent rates. Patterns of prescription drug diversion, and the potential harms that can arise from this activity, are inadequately understood and in need of further systematic study (Inciardi et al., 2009).

Study 4 built upon the results of Study 3 by examining the misuse of a specific non-BZ medication, quetiapine, among clients of a low-threshold methadone maintenance program. As the first study to systematically investigate quetiapine misuse, this investigation represents a novel contribution to the literature. In this sample, the prescribed and non-prescribed use of quetiapine as a sedative and anxiolytic was widespread. Misuse of quetiapine by exceeding its recommended dosage or co-administering with another substance was relatively frequent, while alternate routes of administration were rare. Interestingly, quetiapine misuse was associated with previous misuse of other anxiolytic and sedative medications. Motives for the misuse and diversion of quetiapine were largely therapeutic. These data are notable in light of recent

evidence indicating that the risk of quetiapine-associated fatality is elevated when quetiapine is used in excess or concurrently with interacting drugs, such as anxiolytics or sedatives (Pilgrim & Drummer, 2013). Furthermore, although the safety and tolerability profile of quetiapine is favourable compared to many other antipsychotic medications (Miodownik & Lerner, 2006), excess use can increase the risk of serious extrapyramidal and metabolic side effects (Asmal et al., 2013; Carney, 2013). Although non-substance psychopathology was not assessed in Study 4, comorbid psychiatric symptoms, which are highly prevalent in this population and largely undiagnosed and untreated (Fulton et al., 2011), may be related to the misuse of quetiapine.

Considering the results of Studies 3 and 4 together, non-BZ medications appear to be favourable to BZs in terms of misuse potential; however, extrapolating this finding to clients with extensive histories of substance use should be viewed with caution.

6.3 Strengths, Limitations, and Future Research Directions

As the preceding chapters discuss the strengths and limitations of each of the individual studies making up this dissertation, this section will focus on a few key commonalities. One important feature of the present research is the use of in-depth structured interviews, which provided a unique opportunity of collecting detailed information from respondents about motives and patterns of prescription anxiolytic and sedative misuse (Colliver & Gfroerer, 2008). Gathering this information allowed for empirical demonstration of diverse motives for anxiolytic and sedative misuse and for parsing of factors associated with therapeutic and non-therapeutic motives. A further advantage of this approach is that it allows for the development of rapport between interviewer and participant, which can improve reporting veracity (Arria & Wish, 2006).

Although there are advantages of in-depth interviews over self-report surveys and questionnaires, it is important to note that there are limitations inherent in the use of retrospective self-report regardless of methodology. In the area of substance use, there has been considerable controversy over the use of self-reports and discussion of the factors that can influence response veracity, including characteristics of the respondent, the task, and the social context in which the research is carried out (Del Boca & Darkes, 2003). In the case of substance use motives, self-report data rest on the assumption that participants are aware of their reasons for using substances. Evidence suggests, however, that substance use behaviours can be driven by implicit mechanisms, such as conditioning processes, that are outside of conscious awareness (Curtin, McCarthy, Piper & Baker, 2006). The nature of such mechanisms within these samples of anxiolytic and sedative users, and the extent to which implicit processes could have affected the present results, is unknown. Consideration of the role implicit motivations may play in prescription drug misuse represents a potentially fruitful avenue for future study.

Throughout these studies, efforts were made to minimize the potential for intentional distortion (e.g., by assuring participants during the consent process of the confidentiality of their responses and by informing them that disclosure of illicit activities would put them at no risk of legal consequences). Similarly, efforts were made to improve accuracy of prescription misuse self-report data by anchoring recall to specific salient instances of use (Barrett, Darredeau & Pihl, 2006). However, as anxiolytics and sedatives can detrimentally affect episodic memory (Buffett-Jerrott & Stewart, 2002), it is possible that participants' memories of the events they reported were incorrectly encoded at the time of occurrence or inaccurately recalled. The co-administration of

alcohol and other substances reported by many participants in these studies may have exacerbated possible difficulties in memory retrieval. In future investigations, the use of experience sampling techniques (e.g., electronic or written diary; Shiffman, Stone & Hufford, 2008) or biochemical assays to corroborate self-report data (e.g., urinalysis) would allow for increased confidence in the accuracy of participants' reports.

An additional drawback of in-depth interviews is their time-intensive nature, limiting the sample size of each study in the present dissertation to a modest number of participants. This may have negatively impacted the ability to detect significant relationships between the variables of interest. Nonetheless, the present studies advance existing knowledge regarding heterogeneity in misuse of anxiolytics and sedatives and may be used to inform future investigations in this area that take into account motives and varying forms of misuse. Interestingly, the most recent iteration of the Canadian Alcohol and Drug Use Monitoring Survey (CADUM) introduced additional questions assessing motives for misuse of prescription opioids and stimulants (Health Canada, 2012). Previous versions of this survey simply asked respondents to indicate if they had used psychoactive pharmaceuticals for "the experience, the feeling they cause or to get high." The most recent edition asked past-year users of opioid analgesics whether they had used these pain relievers "to feel better, to cope with stress or problems or for any other reason." Past-year users of stimulants were asked if they ever used stimulants "for other reasons, such as, to study, stay alert or decrease appetite" (Health Canada, 2012). The modification to the CADUM is promising in that it reflects recognition of research documenting varying motives for misuse of prescription opioids and stimulants (e.g., Boyd et al., 2006; Judson & Langdon, 2009; McCabe, Cranford et al., 2007) and calls for

an increased acknowledgement of these variables in population-based studies (Colliver & Gfroerer, 2008; Zacny & Lichtor, 2008). However, no additional motives were included for anxiolytics or sedatives, suggesting that this survey fails to capture motives for the misuse of anxiolytics or sedatives other than use to achieve an intoxicating effect. It is hoped that the findings of the current studies may assist in the refinement of instruments such as the CADUM, leading to a better understanding of anxiolytic and sedative misuse in the broader population.

Another limitation of the present studies is the use of categorical definitions to classify predictors and outcomes of prescription anxiolytic and sedative misuse. Using "lifetime" reports of prescription drug misuse groups respondents together irrespective of the frequency of misuse. Although such categorical classifications are used frequently within the substance use literature (Feingold, Tiberio & Capaldi, 2013), this approach has been criticized for producing inflationary results in favour of the problem behaviour of interest (Fischer & Rehm, 2007). Analyses comparing therapeutic and non-therapeutic motives were also conducted by grouping specific motives under the general categorizations of therapeutic and non-therapeutic motives. This resulted in a loss of detail for those participants who reported a variety of motives and prevented the examination of the features associated with specific therapeutic and non-therapeutic motives. In addition to the potential salience of specific misuse motives, having a higher number of motives has itself been previously related to risk for anxiolytic and sedative misuse (Nattala et al., 2012). By defining drug and alcohol abuse and dependence according to DSM-IV (APA, 1994) thresholds, designations of severity among affected individuals were omitted. Furthermore, individuals with detectable subthreshold

symptoms were classified as unaffected, despite potentially experiencing clinically significant substance use problems (Grekin et al., 2006). While this approach resulted in some unavoidable loss of detail in the data, it is unlikely to have negated clinically relevant findings, such as the links between personality dimensions and specific forms of misuse. The extent to which personality, psychiatric, and substance use symptoms are differentially related to specific motives and to quantifiable indicators of misuse are important prospective topics for future investigations.

The use of cross-sectional designs is a limitation relevant to each study in this dissertation. Most significantly, this approach precludes drawing conclusions about causality. Although the model of personality and substance use vulnerability employed posits that the personality dimensions function as risk factors for problematic substance use (Conrod et al., 2000), other research has demonstrated reciprocal and interactive relationships between personality and substance use (e.g., Caspi et al., 2005; Hicks et al., 2012). The personality characteristics measured in this study have been shown to be relatively stable over a one-year interval (Krank et al., 2011); however, because these traits were not measured longitudinally in the current sample, the directionality of the links between personality and patterns of use cannot be conclusively determined. Likewise, cross-sectional data cannot adequately test the assumption that motives for use are causally antecedent to substance use behaviours (Cooper, 1994). Furthermore, motives are unlikely to be static over time. An indicator of this phenomenon was observed in the present studies, as many participants anecdotally reported curiosity as a motive for initial episodes of prescription drug misuse, with other motives becoming predominant in subsequent episodes. In a qualitative analysis of prescription misuse

motives, Rigg and Ibañez (2010) reported that in many cases, individuals' motives evolved from intoxication to avoidance of withdrawal symptoms. Past research investigating trajectories of alcohol and illicit drug use has consistently identified variations in substance consumption over time, in terms of frequency (e.g., persistent regular use or occasional use), age of initiation (e.g., early- or late-onset), and discontinuation of use (Sloboda et al., 2012). The present studies do not differentiate between those who misuse anxiolytics and sedatives on a low-frequency basis from those who go on to more chronic problematic use. Future research using prospective designs are essential to test the potential pathways into prescription anxiolytic and sedative misuse described in this research.

In the current analysis, support for relationships between medication-related factors and anxiolytic and sedative misuse was mixed. Other exogenous variables represent promising targets for future investigation. For example, external factors include characteristics of the social and environmental context in which prescription drugs are used and misused (Ballantyne & LaForge, 2007). Social learning is thought to play an important role in prescription drug misuse (Compton & Volkow, 2006; Ford, 2008). Among adolescents, peer groups, community characteristics, and media exposure have been linked to attitudes towards prescription drug misuse (Twombly & Holtz, 2008) and school enrollment and family structure have been shown to relate to risk for misuse (Havens, Young & Havens, 2011). Although detailed consideration of social and contextual factors was beyond the scope of the current research, these are important variables that should be more fully investigated in the future. Particularly intriguing is the

manner in which individual and environmental characteristics may interact in the development and maintenance of problematic substance use (Sloboda et al., 2012).

6.4 Clinical Implications

Physicians face a difficult challenge in delivering appropriate pharmaceutical treatment for anxiety and sleep disorders while minimizing the potential for misuse of these drugs. Most patients who receive anxiolytic and sedative prescriptions do not misuse them, and overly stringent prescription practices can have the effect of limiting access to therapeutically useful drugs for patients in need (Brust, 2004). However, injudicious prescribing of anxiolytics and sedatives may put users at risk for misuse-related harms. Strategies to address misuse of prescription drugs necessarily differ from those aimed at illicit drug use, as any attempt to prevent or reduce prescription misuse must be balanced with the need to maintain availability of such pharmaceuticals for appropriate therapeutic uses (Sproule, Brands, Li & Catz-Biro, 2009). Assessment, prevention, and intervention are made more complex by the observation that some individuals who misuse prescription medications may also have a physical or psychological condition for which the medication is indicated (Sproule et al., 2009). By identifying individual-level characteristics that are linked to prescription anxiolytic and sedative misuse and diversion, including substance use history, motives for use, and personality traits, the findings of the present studies suggest some possible targets for preventing and treating anxiolytic and sedative misuse.

Prescribing physicians can play a crucial role in preventing prescription drug misuse by identifying patients at risk for misuse or diversion (SAMHSA, 2011a; Wilens et al., 2008). Despite knowledge of the links between anxiolytic and sedative misuse and

other substance use, these medications are still commonly prescribed to individuals who are at high risk for misuse (Brunette et al., 2003). For a primary care physician, conducting lengthy interviews or assessing personality characteristics is unlikely to be feasible, given the limited time allotted for patient visits. However, the results of the present research suggest that use of illicit drugs and substance use-related problems are linked to misuse and diversion of anxiolytics and sedatives. It is reasonable that a physician considering medication options for treating anxiety or sleep disorders could ask several brief questions regarding patients' substance use histories and use any positive responses as cues to inquire further about misuse of prescription drugs (Matzger & Weisner, 2007; SAMHSA, 2011a). For patients who have used multiple substances, or who report past or current symptoms of substance use disorders, prescribing clinicians may wish to provide additional information about the safe use of anxiolytics and sedatives, monitor these patients more closely, or consider selecting medications with lower misuse liability (Griffiths & Johnson, 2005; Kollins, 2007). Clinicians should also consider effective non-pharmacological treatments, such as cognitive-behavioural therapy, as a front-line treatment for management of anxiety and sleep disorders (Butler et al., 2006; Smith et al., 2005).

Paralleling previous research (e.g., Cicero, Shores, Paradis & Ellis, 2008; McCabe & Boyd, 2005), the majority of participants in Study 2 who had used anxiolytics or sedatives without a prescription reported obtaining these medications from friends or relatives. This ready access to controlled prescription drugs for non-prescribed use provides evidence for the necessity of developing better strategies for reducing diversion among prescribed users. Such approaches could include enhancing clinician-patient

communication to improve compliance with treatment regimens, to educate about the risks of medication diversion, and to encourage patients to dispose of leftover medication appropriately (SAMHSA, 2011a).

Although improved communication between clients and clinicians holds promise for reducing prescription drug misuse and diversion, many physicians appear to be uncomfortable discussing prescription drug misuse with their patients (Boyd et al., 2007). To mitigate this, medical programs or continuing education courses could incorporate strategies to facilitate dialogue on these topics. Resources exist for the prevention of misuse of prescription pain medication (e.g., American College of Preventive Medicine, 2011) and could be readily adapted for patients receiving prescribed anxiolytics or sedatives. A motivational interviewing approach (Miller & Rollnick, 2013) may be particularly useful for working with clients with multiple motives for problematic anxiolytic and sedative use (Nattala et al., 2012). The extent to which clinician intervention may reduce prescription drug misuse and diversion, particularly among at-risk individuals, is an interesting empirical question which future research could investigate.

Due to the widespread occurrence of non-prescribed psychiatric medication use and the likelihood that non-prescribed users may not have the opportunity of receiving information from a health care professional, broader prevention initiatives may also be warranted. For instance, targeted interventions for individuals with other substance use issues could be beneficial in reducing high-risk non-therapeutic use while encouraging therapeutic users to seek formal assessment and treatment for difficulties with anxiety or insomnia.

The findings of this research also have important implications for treatment planning and service delivery within substance use treatment programs. Given the common co-occurrence of anxiolytic and sedative misuse with other substance use, screening for anxiolytic and sedative misuse is important even when clients present with other substance use difficulties. This can provide a more comprehensive picture of clients' treatment needs and assist with supporting their recovery (SAMHSA, 2011a). It is essential that intervention efforts take into account individual differences in motivations for misuse of anxiolytic and sedative drugs, as the present research demonstrates that the patterns and correlates of misuse tend to vary depending on whether a medication is self-administered for therapeutic or nontherapeutic reasons. Moreover, the effectiveness of psychological interventions could be enhanced by tailoring the intervention to the individual's primary motives for use (Boyd & McCabe, 2008; Rigg & Ibañez, 2010) and to their personality risk profile (Conrod et al., 2010; Conrod, Stewart et al., 2000).

6.5 Conclusion

This dissertation presented the results of four studies examining misuse of prescription anxiolytic and sedative medications. This research provides strong evidence that a unitary conceptualization of prescription anxiolytic and sedative misuse inadequately captures the complexity of this phenomenon and is unlikely to provide insight into the potential harms associated with specific forms of misuse. Furthermore, the findings of this series of studies support an association between specific patterns of anxiolytic and sedative misuse and individual difference factors, including therapeutic and non-therapeutic motives for use, substance use history, and personality dimensions. It

is essential that future research in this field adequately consider this diversity, employing appropriate terminology and clearly specified operational definitions. In clinical contexts, approaches to the prevention and treatment of prescription anxiolytic and sedative misuse may be improved by considering users' motives and other individual-level characteristics.

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APPENDIX A. Prescription Drug Misuse Across the Lifespan: A Developmental Perspective

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Prescription Drug Misuse Across the Lifespan: A Developmental Perspective

16

Megan E. McLarnon, Sean P. Barrett, Tracy L. Monaghan, and Sherry H. Stewart

Abstract

The misuse of psychoactive prescription drugs, including opioids, sedatives, anxiolytics, and stimulants, is an issue of growing concern. Factors contributing to the increasing prevalence of prescription drug misuse are thought to include rising prescription rates, social acceptability of use, and lack of perceived harm from use. Prescription drug misuse is associated with a number of direct and indirect costs. Risks to the user include development of substance use disorders, overdose, and other adverse medical consequences. Medication misuse is also responsible for a sizable burden on the health care system. Despite the indications of a growing trend, the literature is far from conclusive regarding the correlates of prescription drug misuse. Existing research is characterized by inconsistency in how prescription drug misuse is operationalized. Depending on how *misuse* is defined, it may encompass a heterogeneous group of motivations for use with varying associated behavioral patterns. Another impediment to understanding prescription drug misuse is the tendency for this phenomenon to manifest in different ways across the lifespan. Studies have documented patterns of misuse in young people that differ strikingly from those in older adults. This chapter considers the misuse of psychoactive prescription medications using a developmental framework, focusing separately on adolescence and early, middle, and late adulthood. The implications for detection, prevention, and treatment of prescription drug misuse are discussed for each age group.

Learning Objectives

- Inconsistencies in the operational definition of prescription drug misuse employed in the research literature have made it difficult to compare findings across studies.
- Age-specific patterns and correlates of prescription drug misuse can be identified by focusing separately on adolescence, young adulthood, middle adulthood, and later adulthood.
- Treatment and prevention implications differ by age group.

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Issues that Need to Be Addressed by Future Research

- Standardized terminology for describing and referring to the various forms of prescription drug misuse will facilitate cross-study comparisons.
- Future inquiries will benefit from examining individuals' contexts of use and motivations for misuse of prescription medications.
- Researchers should increase their focus on middle adulthood, a demographic group that has received little attention in the literature on prescription drug misuse.

Prescription Drug Misuse Across the Lifespan: A Developmental Perspective

Psychoactive prescription medications, including opioid analgesics, anxiolytics, sedatives, and stimulants, have important therapeutic applications in pain management, relief from insomnia, and the treatment of psychiatric conditions, such as attention-deficit hyperactivity disorder (ADHD) and anxiety disorders [1–4]. Although medications from these four classes play a crucial role in alleviating distress and discomfort in those who suffer from these conditions, many also have psychoactive effects that render them liable to be misused. In recent years, the misuse of prescription medications has garnered a substantial amount of attention in the scientific literature and the popular media. A growing body of research has documented increases in the prevalence of prescription drug misuse [3, 5, 6]. Epidemiological data collected in the USA indicate that of all individuals initiating use of an intoxicating substance illicitly in the past year, nearly one-third reported nonmedical use of a prescription psychotherapeutic medication [7]. Rates of substance use disorders involving psychoactive prescription drugs, as categorized according to *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) [8] criteria have also shown an increase [9]. Correspondingly, concern over nonmedical use of prescription medications has grown, with the issue being labeled an "epidemic" and a problem of "staggering" proportions [10].

The rising popularity of these types of prescription medications for nonmedical reasons has been linked both to an increase in their availability and to a general perception that they are relatively less harmful than illicit drugs [10, 11]. Pharmaceuticals may be misused for a multitude of reasons, including enhancing the effects of other drugs, achieving an intoxicating effect, and managing symptoms of withdrawal. They may also be used with the intent of self-medicating psychiatric or medical symptoms [12–14]. The potential for abuse of and dependence on each of these classes of substances has been noted as a major focus of concern [4, 10, 15, 16]. Although much of the epidemiological data concerning prescription drug misuse has been collected in the USA [7] emerging data suggest that this phenomenon is increasing worldwide [17, 18]. Expenditures for psychoactive prescription drugs continue to increase [19], and despite concerns about their misuse, opioid analgesics, anxiolytics, sedatives, and stimulants remain among the most frequently prescribed classes of prescription medications [20].

What Do Researchers Mean by "Misuse"?

A major problem in the existing prescription drug literature is a lack of a universally accepted definition of misuse [21], an issue that has long been identified as a major impediment to making cross-study comparisons [22]. This issue impedes conducting comprehensive evaluations of the literature, including those related to the epidemiology of prescription drug misuse, the factors associated with misuse, and the possible negative consequences of misuse. Unfortunately, a wide range of operational criteria continues to persist in this field, resulting in the grouping of a heterogeneous collection of behaviors and motivations under the same descriptive term [21, 23].

One common way of characterizing prescription drug misuse is on the basis of prescription status. Numerous existing studies have defined misuse as any prescription drug use without a physician's prescription [24–31]. By definition, all forms of nonprescribed use may be considered to be misuse, as they take place without a physician's oversight and are inherently risky. These individuals do not receive clinical assessments, follow-up, or medical information from a health care provider [29]. However, equating misuse with nonprescribed use fails to take into account individuals' motives for use of prescription drugs [21]. Understanding motives for substance use is crucial for predicting risk for problematic consequences [32]. Griffiths and Johnson describe two forms of prescription drug self-administration that differ in motive and associated patterns of use [33]. Recreational use, or use for the purposes of experimentation or intoxication, is thought to be distinct from self-administration with quasi-therapeutic intent, which is generally an attempt to self-medicate undiagnosed or undertreated physical (e.g., pain) or psychiatric (e.g., anxiety) symptoms [33, 34].

Another limitation to this definition of misuse is that it excludes individuals who possess a valid prescription but use their medication in unsanctioned ways. Examples include increasing the dosage or frequency of administration, coadministering with other substances (licit and illicit), and altering the route of administration by injecting, smoking, or inhaling the prescription drug [21]. Furthermore, defining misuse as use without a prescription does not take into account individuals who procure prescriptions for unsanctioned reasons; for example, with the intent of using them recreationally or diverting to others.

Characterizing prescription drug misuse by evaluating symptoms of problematic prescription drug use based on formal DSM-IV [8] diagnostic criteria is another method which has been employed [9, 15, 35, 36]. Although this approach may yield information that aids in treatment planning for some individuals [35], it is problematic for several reasons. Hazardous use of prescription drugs may occur even when diagnostic criteria for a substance use disorder are not met. Conversely, symptoms of dependence, such as physiological tolerance to a drug's effects and symptoms of withdrawal following its cessation, have long been observed to develop as a consequence of long-term use of certain medications, even when used according to a physician's instructions [15]. In this situation, the patient and physician may decide that the risk of this occurrence is outweighed by the benefit that the medication provides in controlling the symptoms for which it was prescribed. Studies that classify prescription drug misuse based on symptoms of substance use disorders may describe a heterogeneous group of individuals and therefore be of limited predictive value [21].

Several large-scale epidemiological studies have been conducted in the USA examining patterns of substance use, including misuse of prescription drugs, at a population-based level. The National Survey on Drug Use and Health (NSDUH) is one such ongoing investigation [7]. The NSDUH assesses nonmedical use of prescription psychotherapeutics, defined as use without a prescription, for the experience, or for the feeling that the substance caused [7]. This definition of prescription drug misuse is congruent with the definition currently recommended by Canada's national public health agency [37]. As this characterization has been adopted by numerous recent studies focusing on prescription drug misuse [9, 16, 38–44], the term "misuse" in the current chapter will be employed to correspond with this definition.

It should be noted that the NSDUH definition presents some inherent limitations. By capturing a wide range of behaviors, respondents may potentially be required to recall multiple instances of substance use in order to provide an accurate response to a single survey item [23]. For researchers, it is impossible to tease apart the specific factors associated with risk for different forms of prescription misuse; for instance, that engaged by prescribed users versus nonprescribed users. Despite the inclusiveness of the NSDUH definition, some forms of misuse may nevertheless be underreported. For example, using a prescribed sedative to minimize the negative side effects of stimulant drugs [45] corresponds to none of the behaviors described in the definition.

Numerous researchers have identified the need to adopt a standard definition of prescription drug misuse in order to coordinate the efforts to better understand the nature, extent, and complexity of this issue [10, 21]. This avenue of research represents an important area for future investigations.

Risks and Consequences Associated with Prescription Drug Misuse

There are a number of reasons why prescription drug misuse is of critical concern to health care professionals, policymakers, and the general public [9]. Misuse of prescription drugs may reportedly transition to use of illicit drugs over time [46]. Misuse has also been reported as a risk factor for subsequent onset of prescription drug abuse and dependence [47] and may also play a role in exacerbating existing substance use disorders involving other substances [48]. This may result in direct costs to the user, such as poor health and diminished quality of life, as well as indirect societal costs, such as lost productivity and increased demands upon the health care and criminal justice systems [49]. In addition to increased risk of developing a prescription drug use disorder, adverse medical sequelae of misuse can include cardiac arrhythmia, respiratory depression, and overdose [3, 33]. Use of prescription medications in ways that are not in accordance with physician recommendations has also been associated with a host of other factors, including psychiatric symptoms [15, 16] and risk for accidents and injury [33].

Prescription Drug Misuse Across the Lifespan

The use and misuse of psychoactive substances are closely related to age, developing and varying in correspondence with the life cycle [50]. Forms of prescription medication misuse have been reported in all age groups from early adolescence [42, 51] to late adulthood [52–54]. Epidemiological data indicate that prevalence rates tend to vary by age, with the highest rates reported in the late teens and early twenties [7]. Other studies have found that older adults are also at elevated risk for prescription drug misuse [53, 54]. Despite the indications of a growing trend of misuse, existing research is far from conclusive as to the demographic features or other characteristics associated with increased risk for misuse of prescription drugs [10].

Another rarely acknowledged issue in the literature is that prescription drug misuse appears to manifest in different ways across development, suggesting that studies that investigate misuse in a given age group are unlikely to generalize to other populations. The remainder of this chapter will employ a developmental framework to describe the heterogeneity of prescription drug misuse across the lifespan. Specifically, patterns of use, correlates, and treatment

considerations will be examined in various age groups, including adolescents, young adults, middle age, and older adults.

Prescription Drug Misuse in Adolescence

Adolescence, defined chronologically as the period between approximately age 12 and 17 and socially as a transitional period between childhood and adulthood [55], is a time of rapid development, growth, and change—physically, emotionally, and intellectually. For many adolescents, it is also a time of experimentation with substance use. Initiation of the use of many types of substances, including alcohol, tobacco, and illicit drugs, is commonly documented to occur in the teen years [43, 56]. Prevention and treatment initiatives have long been employed to educate teens about the harms associated with substance use, and encouragingly, rates of tobacco and alcohol use in teens are at historically low levels [51]. However, the issue of prescription drug misuse in adolescent populations has increasingly drawn the attention of health professionals, educators, policymakers, and the general public [57]. The alarm this issue has prompted is exemplified by phrases such as "Generation Rx," coined to refer to teenagers in North America in the twenty-first century [58].

Although research documenting prescription drug misuse in adolescent populations suggests that there is cause for concern, researchers are far from reaching a consensus about the nature and extent of this issue [57]. Results from several large-scale epidemiological surveys have detailed widespread misuse of prescription psychoactive medications among teens [7, 51]. However, as described previously, comparisons between different studies are complicated by varying operational definitions of "misuse" employed by different researchers [21, 42]. Considerable variation is evident even in the findings of studies purporting to study the same phenomenon [59]. For example, depending on the definition used, prevalence estimates among adolescents for having engaged in misuse use of any of the most commonly misused psychoactive prescription drug classes, including sedatives, tranquilizers, stimulants, and opioids, range from 1.1% [59] to 20% [60, 61]. Although specific prevalence estimates are difficult to agree upon, there are a number of trends indicative of a growing problem. In contrast to the declining prevalence of alcohol and illicit drug use documented among adolescents in recent years, most studies indicate that rates of misuse of prescription medications have grown [51, 55]. Recent reports from the USA indicate that in relation to other drug use, the prevalence of prescription drug misuse among teens is second only to that of marijuana. Teens represent the fastest-growing segment of new misusers of prescription drugs [7]. Though diagnosable prescription medication-related substance use disorders were thought to manifest infrequently during adolescence as recently as a decade ago [59], more current data suggest that symptoms of prescription medication abuse and dependence may also be increasing [40]. One large, population-based study found that over 17% of adolescents who reported misusing a prescription medication in the previous year met diagnostic criteria for substance abuse or dependence, with nearly two-thirds of those cases relating solely to opioid analgesics [41].

In addition to signs that adolescent prescription medication misuse is becoming more widespread, a number of other considerations make this a particularly vital issue. Adolescent substance use is associated with increased likelihood of injury, fights, declining school performance, unwanted sexual activity, peer conflict, property damage, and trouble with police [55]. The risk of accident or injury may be particularly heightened with the use of sedatives and opioids, which can affect cognition and motor skills even at low doses [62]. Another reason for the concern surrounding adolescent prescription drug misuse is that brain development progresses through critical stages during the teenage years. In fact, changing connectivity, neurotransmitter activity, and neurocognitive function are thought to be some of the factors underlying the increase in high-risk and disinhibitory behavior seen in adolescents [63]. Exposure to psychoactive prescription drugs at this time has the potential to induce lasting neurobiological changes in the brain [10, 62]. Although the behavioral consequences are unknown, research does indicate that early onset of prescription misuse also appears to be associated with increased risk of substance use disorders in adulthood [64]. McCabe et al. found that for each year prescription drug misuse was delayed, risk for subsequent abuse of or dependence on a prescription medication declined by 5% [47]. With a growing body of evidence documenting the potential for negative outcomes of prescription drug misuse in adolescence, it is critical that more efforts be directed to increasing our understanding of this phenomenon, to developing ways to prevent its occurrence, and to providing appropriate intervention when problems are identified.

Patterns of Prescription Drug Misuse in Adolescence

Although the media has often portrayed adolescent prescription drug misuse as a unitary construct, a review of the existing literature suggests that the nature of the issue is far more complex. Although misuse of all forms of psychoactive prescription medications has been documented in adolescents, the highest rates have been found for opioid painkillers, followed, in decreasing order of prevalence, by sleeping, sedative/anxiety, and stimulant medications [13, 61, 65, 66]. Patterns of use are thought to vary by class of medication used [13, 42, 61].

Further complicating these investigations is the diversity of pharmaceutical products and drug formulations within a

given class of medications [57]. For example, misuse of stimulant medications, such as methylphenidate and dextroamphetamine, is well documented [27, 40, 67]. However, this class of medications includes a number of substances that are chemically distinct from one another, have different functions in the brain, and that are produced in a variety of formulations. Some of the sustained-release formulations are specifically designed to decrease the likelihood of their being administered through an altered route of administration [68]. Patterns of misuse observed with short-acting stimulant medications may not generalize to the extended-release formulations; unfortunately, existing studies often fail to make this distinction [69].

As noted, increases in prescription drug misuse have been partially attributed to availability of abusable prescription drugs [13, 51]. Children and adolescents under the age of 19 receive, per capita, the highest proportion of stimulant medications for treatment of Attention-Deficit Hyperactivity Disorder (ADHD) of any age group [20]. These drugs may be misused by the individuals they were intended to treat or diverted to users without a prescription [60]. Indeed, diversion, including "borrowing" or "sharing" of all types of prescription drugs, is particularly prevalent among teens [60, 70]. Several North American studies report that between one-quarter and one-third of middle- and high-school students with prescriptions for stimulant medications have been approached to sell, trade, or give away their prescription [27, 71, 72]. Additionally, adolescents have ready access to prescription drugs in their own homes, often attaining prescription painkillers and anti-anxiety medications from family members or friends, both with their permission and via theft [60].

Although friends and family with prescriptions appear to be the primary sources from which adolescents obtain diverted prescription medications [7, 40, 60, 73], the recent proliferation of online pharmacies has raised the concern that teens may be illicitly obtaining prescription drugs over the Internet [18, 74]. As yet, data do not support Internet pharmacies as a major source, perhaps due to the ready availability of medications from other sources [60, 70]. One large survey asked American teens to estimate the time it would take them to attain prescription drugs for the purposes of intoxication. More than one-third of these participants reported being able to attain illicit prescription drugs within a day's time, with the vast majority listing parents, other family members, and friends as the sources of these drugs [75].

Coupled with easier access to prescription medications is the issue of lower perceived harm, which is also thought to be a major contributing factor to this growing problem [62]. One study found that 40% of teens believed prescription drugs to be "much safer" than illegal drugs, while 25% believed that painkillers were not addictive [76]. Societal shifts in attitudes toward medications and drugs and their perceived negative effects may be reflected in changing patterns of substance use [51]. In the context of widespread medical use and direct-to-consumer advertising, it is not surprising to find that many adolescents perceive prescription drug use to be acceptable and consider the hazards associated with their use to be minimal compared to the use of illicit street drugs [10, 51, 62].

In addition to the influences of society, community, and culture on teens' substance use, when exploring how prescription drug misuse in adolescence may be differentiated from other age groups, it is also important to take into account more proximal environments and contexts in which the misuse takes place [42]. The attitudes, beliefs, and customs of adolescents' peer groups are thought to have a profound effect on teens' patterns of substance use. Peer group approval has been shown to be associated with increased misuse of medications [51], and having friends who use illicit drugs is associated with increased risk for prescription drug misuse in teens [66, 77]. Parental expectations and modeling are also important predictors of substance use [10]. Permissive attitudes toward the use of alcohol and marijuana among parents are associated with greater use of these substances by teens; although not yet evaluated empirically, this relationship may also apply to prescription drugs [75].

Intrinsic to the current review is the idea that considering motives for use of prescription medications is crucial to making sense of the heterogeneity within the group of behaviors broadly classified as prescription medication misuse. Contrary to representations in the popular media which suggest that most adolescents using prescription drugs nonmedically are doing so for recreational purposes, empirical results suggest that adolescent prescription drug misuse is more frequently in keeping with the accepted therapeutic purpose of the medications [13, 62]. For instance, teens have reported self-medication with tranquilizers to help with sleep or decrease stress, with stimulants to enhance their level of concentration while studying, and with analgesics to manage pain [13, 60]. As these individuals may be unaware of the side effects or drug interactions, this is far from being a risk-free activity; yet, the potential harms associated with this type of therapeutically motivated misuse are likely to differ from purely recreational use. Boyd et al. examined motives for use of prescription sedatives, anxiolytics, stimulants, and painkillers in an adolescent student sample and found that motives varied by substance used [13]. While three-quarters of nonmedical sedative use was reported as being solely for the purpose of helping with sleep, motives for use of analgesic and stimulant medications were much more diverse, with many students reporting multiple concurrent motives. These researchers found that as the number of motives for use of prescription drugs increased, so too did the risk for other substance use problems [13]. Adolescents reporting purely self-medication motives for prescription drug misuse demonstrated no increased risk of other substance problems.

Correlates of Prescription Drug Misuse in Adolescent Populations

Investigations of prescription drug misuse in adolescence have emphasized quantifying the extent of the problem, rather than characterizing it. Existing research has tended to focus on misuse of opioid analgesics and stimulants, with sedatives and tranquilizers receiving relatively less attention [41]. Although evidence for correlates of prescription misuse in adolescents is just beginning to accumulate, these studies have identified a number of factors associated with the misuse of prescription medications in this age group. The most commonly replicated finding is a strong association between prescription drug misuse and increased likelihood of engaging in all other forms of substance use, including alcohol, tobacco, and illicit drugs [27, 41, 43, 60, 66, 67, 72, 77]. For instance, one study found that adolescent non-medical prescription drug users were seven times more likely to smoke cigarettes, five times more likely to drink alcohol and smoke marijuana, almost four times more likely to binge drink, and eight times more likely to have used several other illicit drugs [60]. This association holds across the various categories of abusable prescription drugs. Additionally, adolescent prescription drug misuse appears to often take place in a polysubstance context [41]. Teens who misuse prescription stimulants [43] and analgesics [77] have reported a high level of coadministration with other drugs, putting them at risk for adverse consequences from drug interactions.

A general tendency toward risk-taking behavior among adolescents has also been found to be predictive of misuse of all categories of commonly misused prescription drugs [41]. For example, teens who reported stimulant misuse were more likely to have been a passenger in a car driven by someone who had consumed alcohol [27]. McCabe, Boyd, and Teter found that opioid painkiller misuse was associated with a range of "problem behaviors," including having been suspended or expelled from school, skipping school in the past month, buying illegal drugs at school, and frequently using drugs to get high [77].

Several studies have examined relationships between demographic variables and prescription drug misuse. Rates of prescription drug misuse have been shown to increase consistently from early to late adolescence [27, 51, 60, 67]. The association between gender and medication misuse appears to vary between drug classes. Studies of prescription stimulant misuse typically report similar rates in adolescent males and females [40, 43], or slightly higher rates in males [27, 72]. In contrast, females appear to be more likely than males to misuse opioids and tranquilizers [13, 60, 66]. This may reflect either the higher frequency with which females receive prescriptions for these medications and/or self-medication of disorders such as depression or anxiety, which occur more often in females. Prescription misuse also appears to differ across racial and ethnic groups. Most studies report the highest prevalence of misuse among Caucasian adolescents [27, 40, 67]. However, Boyd and colleagues found equal rates of prescription opioid misuse among Caucasian and African-American students in an ethnically diverse school district in the USA [13], and Sung et al. found that African-American teens were actually at higher risk for opioid misuse compared to other racial groups [66].

The likelihood of methylphenidate misuse appears to be greater among students with poorer academic performance [41, 66, 67, 72]. Adolescent stimulant misuse has also been found to be more common in low-income families and families receiving government assistance [40, 66].

Only a few studies have looked at the relationship between mental health and prescription misuse in adolescents. Poulin found that high school students with elevated levels of depressive symptoms, as well as those screening positive for ADHD, had a higher likelihood of having used stimulant medication without a prescription [72]. Schepis and Krishnan-Sarin reported a positive association between misuse of any prescription drug and experiencing a major depressive episode or receiving mental health treatment in the preceding year [41]. Further examining these relationships, as well as identifying associations with any other psychiatric conditions (e.g., anxiety disorders), represents an important area for future investigations.

Implications for Prevention and Treatment in Adolescents

The recent escalation in prescription medication misuse among adolescents and the increasingly well-documented risks of such misuse make it essential to develop initiatives to minimize the negative effects to teens. The body of literature described above indicates that adolescents involved in prescription drug misuse are a heterogeneous group. Individual differences in the particular prescription medications used, patterns of use, and motives for use, are all essential to consider when developing prevention or treatment interventions [37].

As mentioned, motivations for prescription drug misuse are commonly reported to be therapeutic; thus, traditional anti-drug campaigns may be inappropriate for addressing prescription misuse in teens [13]. Effective treatment programs will need to consider the motivations and perceptions that may have encouraged adolescents to initially misuse medications [40, 42]. One of the most important prevention strategies may be education programs targeted at adolescents that highlight the dangers and risks of misusing prescription medications [60] while at the same time taking care not to downplay their legitimate use [42].

Considering the frequency of self-medication motives for prescription drug misuse, it is also important that adolescents receive appropriate treatment for relevant

psychological conditions [13]. Poulin found that less than 10% of those with symptoms of ADHD or depression were actually receiving appropriate medication; the presence of these psychiatric symptoms was linked to taking stimulant medications illicitly [72]. Better screening programs are needed to detect and address adolescent mental health conditions that may be linked to prescription drug misuse [72].

For adolescents, family involvement may prove to be a key to prevention in a number of important ways. Parents can limit their teens' access to abusable prescription drugs in the home by monitoring and securing any medications that are present, as well as appropriately disposing of expired or unused medications. Schinke et al. found that female teens in families with better parent–child communication and clear anti-drug views were less likely to have misused prescription drugs [78]. Higher parental involvement in teens' lives has also been associated with lower rates of opioid misuse [66]. More favorable outcomes may be achieved if parents participate in prevention programs along with their children [42].

Other potential targets for intervention programs to reduce prescription drug misuse in adolescents include schools and the health care system. Educators can discuss potential harms of prescription misuse and diversion with teens, focusing on the specific hazards of each drug class [51, 62]. Because of the high occurrence of polysubstance use among adolescents misusing prescription drugs, preventative efforts should educate adolescents about the risks for adverse drug interactions [77]. Given the frequency of diversion from peer sources [60] especially in schools [73], strict school policy and monitoring of legitimate prescription drug use is also crucial.

Clinicians and service providers who work with adolescents, including doctors, nurses, social workers, and pharmacists, can act as "gatekeepers," monitoring teens' prescription use in order to detect signs of diversion and being mindful of the risk factors for misuse, particularly given the relationship with other substance use [27, 41]. Although it is important to be able to identify specific risk factors to minimize access to medications that may be harmful if used inappropriately, clinicians face a challenge in balancing the effective delivery of care with the risk for misuse of certain medications.

Prescription Drug Misuse in Young Adults

Like adolescence, early adulthood is a time of transition. During this period of life, defined approximately as ages 18 to 25 [79], individuals begin to assume adult responsibilities and pursue new educational and vocational goals [79]. This age group comprises the largest proportion of students at postsecondary educational institutions in North America [80, 81]. Enrollment in colleges and universities has grown over recent decades, with current data indicating that nearly 40% of 18- to 25-year-olds are current postsecondary students [82]. This population has been the recipient of much attention in the literature, due to the prevalence of substance use among college and university students [51, 79] as well as their proximity to academic researchers. Accordingly, this section on prescription drug misuse in young adults will focus primarily on postsecondary students.

Culturally, the college years are perceived as a time of experimentation and risk taking [83], in which substance use is often viewed as normative [79, 84]. In addition to reporting the highest rates of illicit drug use of any age group, 18- to 25-year-olds in North America report the highest rates of prescription drug misuse [7], with evidence suggesting that prevalence rates are increasing [85]. Although representing only 13% of the US population [7], recent epidemiological investigations found that this age group accounted for 32% of all opioid pain reliever misuse [86], 35% of prescription stimulant misuse [40], and 21% of prescription tranquilizer misuse [7]. Although much of the existing research has been conducted in the US and Canada, worldwide data appear to corroborate this trend [59, 87].

As with other age groups, methodological differences between studies and variations in the operationalization of misuse make it difficult to determine definitive estimates of the extent of prescription drug misuse in college- and university-age populations. However, particular attention has been paid to the misuse of stimulant medications [32, 57, 88–92]. The lifetime prevalence of prescription stimulant misuse in college and university students has been reported to range from 7% [88] to 43% [93], greatly exceeding the lifetime prevalence of between 2 and 5% reported in the general population [3, 40]. Hall et al. found the rate of nonprescribed use of prescription stimulants in a college sample to be second only to marijuana, with nearly half of the respondents stating that they knew a fellow student who had misused these drugs [90]. Far fewer studies have been conducted examining rates of opioid, anxiolytic, and sedative medication misuse in postsecondary students, but preliminary data have reported prevalence rates of approximately 15% for opioids [38, 94, 95] and 8% for anxiolytics and sedatives [25].

There are a number of reasons why prescription medication misuse in young adult populations is of particular concern. Misuse is frequently reported to occur in the context of simultaneous polysubstance use [92, 95–98], putting users at risk for adverse drug interactions. Co-administration of stimulants [92, 96], opioids [83], and tranquilizers [83] with alcohol has been reported among university students. In a study focusing on prescription stimulants, Barrett et al. found that co-administration of other substances was common even when students reported using stimulants exclusively when studying [97].

One study that examined students' perceptions of nonprescribed stimulant use found that 79% of the students who engaged in this behavior reported no concerns about potential negative consequences, suggesting many may

underestimate the potency and adverse health effects of stimulant misuse [91]. Quintero, Peterson, and Young found that college students tended to describe the use of prescription drugs as more socially and legally acceptable and less hazardous than illicit drugs [83]. Many college students do not appear aware that one of the risks of prescription drug misuse is the development of medication-related substance abuse or dependence [47]. In fact, one large population-based study found that the mean age of onset for medication-related substance use disorders was in the early 20s [3]. Kroutil et al. reported that young adults who had misused prescription drugs in the past year were at higher risk for dependence on and abuse of prescription medications, as compared to older age groups [40].

Patterns of Prescription Drug Misuse in Young Adult Populations

As with adolescents, young adults' motives for misuse of prescription medications are essential to consider [14]. Within individual classes of medication, multiple motives for use have been reported. The majority of research on prescription drug misuse in young adult populations has focused on the misuse of stimulant medications, including various forms of methylphenidate (Ritalin, Concerta), dextroamphetamine (Dexedrine), and mixed-salts amphetamine (Adderall). Given the high level of demands in college environments, students may seek out stimulant medications to assist in staying awake and focused while studying [32, 57, 90], a form of misuse which is somewhat congruent with these medications' intended therapeutic purpose [14]. This supposition is borne out by a series of studies reporting that students' primary motives for taking a stimulant medication without a prescription were to concentrate and increase alertness [32, 38, 92, 93, 99, 100]. Judson and Langdon also found that individuals who had self-diagnosed themselves as having ADHD were more likely to use stimulant medications without a prescription [100]. Although some reports suggest that many students believe that stimulant medications will improve their academic performance [93, 100], interestingly, one study found that only 14% of nonprescribed stimulant users agreed that using these drugs had had a positive long-term effect on their academic achievements [90].

Given that stimulant medications act in similar ways in the brain to illicit stimulant drugs, they may also be used for recreational purposes [101]. Although recreational use of prescription stimulants has been found to be prevalent, evidence suggests that it is less commonly students' primary motive for use [92, 99, 100]. Emerging evidence suggests that these two motives, self-medication and recreation, may describe distinct subtypes of prescription drug misuse among college students [14].

Less evidence has documented differing motives for use in other prescription drug classes in university and college students. One study found that the primary purpose for nonprescribed use of opioids was to relieve pain, with 63% of students endorsing this motive. However, other motives were common, with 32% reporting having taken prescription opioids to get high and 29% reporting use for experimentation [94]. Although engaging in prescription drug misuse for any reason has the potential to escalate into problematic patterns of use [101], gaining a better understanding of young adults' motives for use will help provide insights into the potential short- and long-term consequences of this behavior [32].

Another important avenue of investigation concerns misuse among individuals with prescriptions for psychoactive drugs. Several studies have examined prescription drug misuse in college students with prescriptions to treat ADHD [90, 91, 99]. Arria et al. found that 27% of the students reported overuse of their own medication and 16% reported nonprescribed stimulant use [99]. Teter et al. found similar rates of stimulant misuse in students with and without past prescriptions for stimulant medications [32], while Judson and Langdon found that students with current prescriptions for stimulants were more likely to report misuse [100]. These results suggest that medication misuse among students with prescriptions is also a concern.

Studies assessing patterns of diversion among prescribed young adult users of psychoactive medications are equally important. The literature indicates that most nonprescribed medication administered by individuals in this age range originates from peers with prescriptions [11, 86, 91, 94, 95, 99, 102]. In a sample of students with prescriptions for stimulant medications to treat ADHD, Advokat et al. found that 83% had been asked to give their medications away and 54% had been asked to sell their medications [93]. Undergraduate men have been found to be more likely than women to have been approached to divert their opioid medication [95]. As compared to other sources, students who obtained prescription drugs from peers reported more frequent heavy episodic alcohol use, higher rates of drug use, and a greater tendency to engage in polysubstance use [102]. These students were also more likely to report symptoms of drug and alcohol use disorders [94]. One study reported that opioids diverted from peers were commonly co-administered with alcohol, while those diverted from family members were exclusively used for pain management [95]. Several studies have found gender differences in sources for diverted prescription drugs, with females more likely than males to have received sedative, anxiolytic, and pain medications from familial sources [94, 95, 102]. Obtaining medications using methods such as pharmacy theft, prescription fraud, online pharmacies, or seeking prescriptions from multiple doctors is thought to be rare among young adults [11, 86, 94, 99].

A further consideration when examining patterns of misuse of prescription drugs in young adult populations is the drug formulation and route of administration used. Extended-release formulations appear to have lower misuse liability; however, tampering with medications may allow faster drug delivery, alternate routes of administration, and separation and purification of active drug ingredients [68]. Not surprisingly, most stimulant medication misuse appears to involve short-acting methylphenidate and dextroamphetamine, but misuse of long-acting forms has also been reported [40].

The most common route of administration for misused prescription stimulants among young adults appears to be oral, followed by intranasal [91, 97]. Likewise, the most common route of administration for opioids appears to be oral [94], with other routes reported much less frequently. Interestingly, the route of administration for opioids has been shown to vary depending on prescription source and motive for use. McCabe et al. found that less than 1% of the students reporting pain management as their motive for opioid misuse reported intranasal use [94]. No student who obtained prescription opioids from a parent reported intranasal administration, while more than 16% of the students obtaining these drugs from non-parent sources (predominantly friends) reported intranasal use [94], Eighty percent of the group of intranasal users was composed of students who reported using the medications to get high [94]. Overall, those students reporting non-oral routes of administration had increased odds of experiencing drug-related problems [94].

Correlates of Prescription Drug Misuse in Young Adult Populations

As with adolescent populations, studies focusing on young adults have consistently found a relationship between prescription drug misuse and increased prevalence and frequency of other substance use [11, 32, 93, 102], as well as problems associated with alcohol and other drugs [28, 30, 103]. These studies have overwhelmingly concentrated on nonprescribed stimulant use, which has been associated with higher rates of binge drinking [26, 32, 88, 89, 104, 105], tobacco use [32, 88, 104], marijuana use [88, 89, 97, 105], ecstasy use [26, 88, 89, 97], cocaine use [26, 88, 97], and other illicit drug use [26, 97, 105]. Nonprescribed stimulant medication users are more likely to report adverse consequences related to substance use, including missing classes, developing a hangover, and being injured while under the influence of alcohol or drugs [89]; risky activities such as having unplanned sex and driving while intoxicated [88, 89]; and antisocial behaviors such as being arrested, stealing, and selling drugs [105]. Interestingly, some studies have found that compared to nonusers, college students who had engaged in nonprescribed stimulant use reported more extensive alcohol and other drug use histories regardless of whether their primary motive for using the medication was to help concentrate or for recreation [32, 97]. Teter et al. argue that this finding runs contrary to the notion that students who use stimulant medications without a prescription to study are engaging in relatively less hazardous behaviors [32]. Although most studies have investigated the correlates of nonprescribed stimulant use, higher rates of substance use, as well as increased risk for alcohol and marijuana dependence, have also been observed in prescribed stimulant users who report overuse of their own medications [99].

As noted, considerably fewer studies have examined opioid, sedative, and anxiolytic misuse in young adult populations. Existing evidence supports a link between misuse of these medications and other substance use in this age range [11]; however, the patterns appear to differ somewhat from those observed with young adults' stimulant misuse. For instance, other substance use has been found to differ among nonprescribed opioid users depending on their motives for use [94] and on the source of the medication [95]. Students who reported using opioids exclusively to manage pain did not differ from nonusers in terms of binge drinking and alcohol use disorders, while those reporting nontherapeutic motives for use had elevated rates of these problems [94]. As compared to nonusers, higher rates of tobacco use, illicit drug use, and binge drinking were observed in nonprescribed opioid users who obtained the medication from their peers, while no such elevations were found among those who obtained opioids from familial sources [95].

Multiple studies have examined demographic correlates of prescription drug misuse in an attempt to better understand the risk factors for misuse [16]. Findings relating to gender are inconsistent across studies. Several investigations have demonstrated similar overall prevalence of prescription drug misuse in male and female young adults [89, 91, 105, 106], while others have found higher rates in males [11, 26, 32, 90, 92, 95]. Less commonly, higher rates in females have also been reported [59]. The reason for this lack of clarity may stem from variations between studies in how prescription misuse was operationalized. Some evidence suggests that an interaction between gender and motives for use may be present, such that young women may be more likely to misuse prescription drugs for medical reasons, while young men may be more likely to report nonmedical motives [77, 94]. One study [11] found that although young women were prescribed anti-anxiety and pain medications at higher rates than young men, men reported more misuse of these substances, defined in this study as use without a prescription.

Studies analyzing use in different racial or ethnic groups have found the highest rates of misuse of prescription stimulants, opioids, and anxiolytics among Caucasian postsecondary students [11, 25, 26, 94, 105, 107]. One study [32], however, reported similarly high levels of stimulant misuse

among Hispanic students. Typically, African-American and Asian young adults have been reported to be at lower risk.

A number of other socio-demographic factors appear to be correlated with prescription drug misuse in young adults. Having a higher family income [89] and having attended a private high school [91] have been associated with increased use of stimulant medications without a prescription, suggesting a relationship between higher socio-economic status (SES) and stimulant misuse in postsecondary students, a pattern which differs from that observed in high school students. Interestingly, colleges with more competitive entrance requirements have been found to have higher rates of stimulant misuse [88]. The authors of this study suggest that competitive entrance requirements may be serving as a proxy for SES. In addition, although this study did not measure students' motivations for prescription stimulant misuse, it suggests that misuse of these medications may be more common in environments that place a high degree of emphasis on academic achievement. More research is needed to examine this pattern and explore the potential reasons (developmental and otherwise) for the differing relationships between stimulant misuse observed in adolescent and young adult populations.

Several studies have found that postsecondary students with lower grade point averages are more likely to report prescription drug misuse [107]. In particular, this relationship has been noted for both opioids [95] and stimulants [26, 88]. Arria et al. found that nonmedical users of stimulants and analgesics skipped more classes, spent more time socializing and less time studying, and had lower GPAs. These authors suggest that students engaging in prescription drug misuse represent a high-risk group for academic problems in college [38].

Further investigations of individual differences in this area have suggested relationships between misuse of prescription drugs and physical health, mental health, and personality. Poorer health has been found to be correlated with increased risk for misuse [107], while involvement in athletics appears to be a protective factor for sedative, anxiolytic, and painkiller misuse, especially among females [108]. Surprisingly, few studies have examined the role of mental health in young adults' prescription drug misuse. Herman-Stahl et al. found that higher scores on a broad measure of psychological distress were associated with vulnerability to engage in prescription misuse [105]. Consistent with past studies finding a robust association between sensation seeking and drinking behavior in postsecondary students [79], high sensation seeking appears to be associated with greater risk for stimulant medication misuse [92, 109]. This relationship was found to be especially pronounced among students with high perfectionism scores, leading the authors to speculate that perfectionism appears to function synergistically with sensation seeking to predict misuse of prescription stimulants [92].

Implications for Prevention and Treatment in Young Adults

College and university environments present unique challenges to implementing intervention strategies to minimize the diversion and misuse of prescription medications [88]. Institutions need to act proactively to address substance-related problems experienced by their students [110], which may include developing educational initiatives targeted at students, their parents, and health care providers. Treatment programs could be designed to address the specific demands intrinsic to college life, especially regarding the intensity of the social environment and academic pressures [110].

At the health care provider level, clinicians may be able to make use of some of the demonstrated correlates of prescription drug misuse, particularly the strong relationship between alcohol and illicit drug use and prescription drug misuse. In all cases, there is a need to strike a balance between the delivery of essential medications and the need to reduce misuse of these drugs [95]. As evidence suggests that malingering of symptoms of ADHD in order to obtain medications for misuse is becoming more common [111], it is essential that patients be given a thorough and comprehensive assessment before medications with known misuse liability are prescribed. Because most college students who misuse prescription medications obtain them from their peers, clinicians need to appropriately monitor students with prescriptions for abusable prescription drugs, not only to improve clinical outcomes, but also to help prevent the misuse of these medications [40]. When treating students with ADHD who may be at risk for misuse or diversion, physicians may wish to consider nonstimulant alternatives [112] or pharmaceutical delivery systems that are less prone to misuse [88].

Assessing young adults' motives for use of prescription drugs is critical, as the correlates of different motives appear to vary by drug class. As noted, studies indicate that for those endorsing pain relief as the sole reason for nonprescribed opioid use, there was no increase in risk for substance use problems [94], while both academic and recreational stimulant misusers reported higher rates of such problems. Health care professionals should also inquire about the routes of administration used and the sources of medications, as the associated risks also appear to vary considerably depending on these factors.

Prescription Drug Misuse in Middle Adulthood

The period of life defined herein as middle adulthood extends roughly from the early 30s to the early 60s. Some of the key developmental challenges encountered by individuals in this age group involve establishing a career, maintaining stable

marital and family relationships, and parenting [113]. Despite comprising the largest proportion of the population, research examining prescription drug misuse in middle adulthood is by far the sparsest. The investigations of adolescents and postsecondary students described previously in this review portray distinct patterns of use (e.g., stimulant misuse in academic contexts) that are unlikely to generalize to individuals in middle adulthood. Perhaps in recognition of the unique characteristics of adolescent and college-age populations, epidemiological studies often report prevalence rates and demographic correlates of prescription drug misuse in adults separately from those in younger groups [35, 40]. However, grouping individuals in middle adulthood together with older adults fails to take into account that patterns and correlates of prescription drug misuse are dynamic and likely to continue changing over the lifespan. In addition, many of the studies that do include participants in this age range focus on specific subpopulations, such as street drug users [114], hospital inpatients [115], military veterans [116], and chronic pain patients [117, 118], precluding extrapolation of their findings to the broader adult population.

Patterns of Prescription Drug Misuse in Middle Adulthood

After peaking in late adolescence and early adulthood, the evidence suggests that prescription drug misuse in the general population begins to decline steadily [7]. In a large population-based study, Blanco et al. found past-year prevalence of prescription drug misuse and prescription drug use disorders in middle adulthood were intermediate between young adults and those over age 55 [9]. In another epidemiological study, the prevalence of prescription drug misuse in adults aged 30–64 was found to be similar to those aged 18–29, but significantly more frequent than in those aged 65 and above [3]. No significant differences were found in the prevalence of misuse between sedatives, tranquilizers, opioids, and stimulants. Using the nationally representative NSDUH dataset, Blazer and Wu found that the rates of opioid pain reliever misuse were significantly greater in middle-aged adults as compared to those over age 65 [39]. Interestingly, the majority of opioid misusers in this study reported that they initiated misuse in adulthood, with more than 20% of these individuals reporting initiation at age 50 or above.

Anxiolytics, sedatives, and opioid painkillers are prescribed more frequently for adults in middle age as compared to younger age groups [20]. As noted previously, symptoms of substance dependence, particularly physiological dependence, tolerance, and withdrawal, are known to occur routinely following long-term use of these medications, even when used according to a physician's prescription [45]. Many of these users may be unaware of this dependence until they attempt to discontinue taking the medication [15]. Although this form of prescription drug use is not encompassed by the definition of prescription drug misuse employed by many studies, it represents a problematic consequence of medication use that is nevertheless an important target for research and clinical attention.

Correlates of Prescription Drug Misuse in Middle Adulthood

Studies examining prescription drug misuse in middle adulthood have focused on a disparate set of subpopulations. Although the findings from these investigations cannot be extrapolated directly to the general population, they provide important contributions to our understanding of the heterogeneity and diversity of individuals engaging in misuse of prescription drugs.

Among an urban sample of street drug users, prescription opioid misuse was most commonly reported for the purposes of pain reduction and withdrawal management [114]. Only 37% of this sample reported misuse of opioids for their euphoric effects; these individuals were more likely to report administering the drugs intranasally or by injecting. Conversely, in a study of rural illicit stimulant users, prescription opioid misuse was associated with comorbid anxiety and illicit drug use, but not with higher levels of chronic pain [119]. Although these samples differ considerably, self-medication of physical or psychological symptoms may have contributed to opioid misuse in both cases.

Studies in the alcohol literature have suggested that failure to master the typical developmental goals of adulthood is associated with increased risk for alcohol use problems [113]. Although research in the prescription drug misuse literature has yet to address this topic directly, some evidence suggests a similar association with prescription drug use problems. An association between prescription drug misuse and unemployment has been reported in studies involving participants ranging from US military veterans, hospital inpatients [115], and a general community-based sample [120]. In a large sample of military veterans in the USA, Becker et al. found that prescription drug misuse was associated with being unmarried and experiencing financial difficulties [116]. In this study, misuse of prescription drugs was also associated with smoking, illicit drug use, chronic pain, and depression.

The role of gender in prescription drug misuse and dependence has long been a focus of attention. Women receive prescriptions for psychotropic medications at higher rates than men, particularly those with the potential for misuse [121]. Several factors have been proposed to contribute to this difference, including higher rates of mood, anxiety, and pain-related problems, an increased willingness to seek treatment, and a tendency of physicians to interpret symptoms as indicative of psychiatric complaints [122]. Green et al. reported

that the strongest risk factor for opioid misuse was recent use of prescribed opioid medication; unsurprisingly, they also found that women were 50% more likely to report recent opioid misuse [123]. Simoni-Wastila, Ritter, and Strickler found that being female increased the odds of reporting problem use of opioid analgesics, including symptoms of dependence [124]. In a sample of general hospital patients, prescription drug dependence was more prevalent in females, and was found to be commonly associated with comorbid mood, anxiety, and other substance use disorders [115].

Implications for Prevention and Treatment in Middle Adulthood

Although onset of prescription drug misuse typically occurs during adolescence or early adulthood, a substantial number of older adults have reported engaging in misuse for the first time after age 50 [39], indicating that prevention efforts for this age group are still warranted. One investigation found that patients with comorbid substance use disorders actually had an increased likelihood of receiving a prescription medication with misuse potential as compared to those with no comorbid substance use disorder [125]. Primary care physicians can play an important role in minimizing psychoactive prescription drug misuse in adults by recognizing factors associated with risk for misuse, such as a history of alcohol or illicit drug problems. However, as demonstrated with gender, it is important to be aware that the relationships between prescription drug misuse and factors correlating with misuse may be indirect or moderated by other variables, such as prescription rates.

Physicians have an ethical responsibility to balance the provision of safe and effective care with the risks associated with various prescription drugs [125]. Based on the potential for abuse of and dependence on opioid analgesics and benzodiazepine anxiolytics, many researchers have argued that the use of these medications should be restricted as much as possible to the treatment of short-term pain, anxiety, and insomnia [20, 45]. If the symptoms are likely to persist for a longer duration, an alternative treatment may be indicated. In cases where no viable alternative is available, more careful monitoring by health care providers is warranted.

Prescription Drug Misuse in Older Adults

As described previously, the highest prevalence of substance use across the lifespan has been reported to occur in late adolescence and early adulthood. Correspondingly, clinical and research attention has focused primarily on these younger populations, with relatively less attention paid to examining substance use and misuse in older adults [50]. Illicit drug use in adults over age 60 is relatively rare, yet the misuse of alcohol and prescription drugs among this population has been identified as a substantial public health concern [54, 126, 127]. Prescription medication misuse has been described as the most widespread pattern of problematic substance use among senior populations [50]. Although the epidemiology and treatment of alcohol abuse in older adults has been relatively well described, comparable data on prescription drug misuse are lacking [54]. Investigations into the causes, correlates, and sequelae of prescription misuse in this population are few [128], and, surprisingly, no validated screening or assessment tools for identifying this phenomenon among older adults have been developed [129].

Adults over 60 years of age are the fastest growing segment of the population. As life expectancy continues to rise and the average overall age of the population increases, the consumption of psychoactive prescription medications has been predicted to grow [50]. This has the potential to profoundly affect all sectors of the health care system, including addiction-related services [130]. Compared to younger individuals, seniors are prescribed more medications and tend to take them more frequently [50]. It is estimated that in the USA, at least one in four older adults has a prescription for a psychoactive medication with the potential for misuse [54]. In North America, adults over 60 years of age represent just 13% of the population, yet they are the consumers of an estimated 50% of all psychoactive prescription medications [130, 131]. This disproportionate share is thought to occur, at least in part, because older individuals tend to experience a relatively greater number of illnesses for which these medications are typically prescribed [50]. Some of the most commonly reported health issues in old age are insomnia and mental health issues; correspondingly, the medications most frequently prescribed to this population include sedatives and anxiolytics [132]. Older adults are also more likely to continue use of these psychoactive medications for longer periods of time than younger individuals [126]. In particular, benzodiazepine anxiolytics and opioid analgesics are prescribed on a long-term basis more frequently for elderly patients than for any other age group [128].

Despite data indicating a growing population of older individuals with exposure to prescription medications with misuse potential, there is considerably less information available about the actual prevalence rates of medication misuse in this age group. In the general population, researchers have argued that observed increases in the rates of prescription drug misuse may be attributed to increased medication availability and social acceptance surrounding the use of sedatives, anxiolytics, and analgesics [6, 53]. The lack of empirical data specific to older adults is thought to be related to a number of issues, including undersampling of older adults in population-based studies, inconsistent definitions of substance abuse and dependence, and prevalence

estimates based on subpopulations such as emergency department patients and residents of long-term care facilities that may not accurately represent older prescribed medication users in general [54, 133, 134].

Patterns of Prescription Drug Misuse in Older Adult Populations

Researchers have reported a number of ways in which prescription drug misuse may differ qualitatively and quantitatively in older adults as compared to those earlier in life [129]. Older adults use fewer classes of prescription drugs, most commonly sedatives, opioids, and anxiolytics [133]. Most older adults obtain medications from a physician by means of a legitimate prescription [128]. Use of medications obtained from illicit sources is thought to be much rarer than in younger populations, although risky behaviors such as seeking prescriptions from multiple doctors, taking pills from family or friends, or stockpiling medications over time have been reported in older prescription drug users [129]. Existing research suggests that the use of prescription medications for recreational purposes or in the context of polysubstance use occurs less frequently in older adults than their younger counterparts [129]. More typically, the motivation for use of prescription medications is therapeutic. As mentioned previously, however, problems with psychoactive prescription drug use can manifest even when medications are used with therapeutic intent. For instance, Busto et al. reported that older adults tended to take benzodiazepines for longer periods of time and have more problems with withdrawal than younger adults, both signs of physiological dependence [135].

Raffoul described several different patterns of medication misuse in older adult populations [136]. One form of misuse may result from the use of medications following incorrect instructions or from misunderstanding the directions for appropriate medication administration. Older individuals with cognitive impairments may be particularly at risk for adverse consequences resulting from this type of unintended noncompliance with prescription regimens. Another form of unintentional misuse may result from the simultaneous use of multiple medications. For many older adults, polypharmacy is the norm. In a sample of older adults accessing a community-based mental health clinic, Jinks and Raschko found that 92% of these participants had current prescriptions for three or more medications [134]. Finlayson and Davis reported an average of approximately 2.9 psychoactive drugs per person administered concurrently within a geriatric inpatient population, in addition to an average of 2.8 nonpsychoactive medications per person [133]. Older adults may also supplement prescribed medications with over-the-counter preparations, which have the potential to interact and produce harmful side effects [137].

Although use of prescription medications for recreational purposes in older adults is thought to be rare, different forms of intentional misuse of prescription medications have been reported, ranging from deficient to excessive use [50]. Medication noncompliance and underutilization may be associated with health risks, such as failure to adequately treat a health condition. Overuse of medications such as anxiolytics and opioid analgesics can increase the risk for accidents (e.g., falls), injury, or overdose, particularly if used in combination with alcohol or other drugs [33].

Correlates of Prescription Drug Misuse in Older Adult Populations

Problematic substance use in older adults has been described as a "hidden epidemic" [138]. One reason that this population has received less attention than younger individuals may be due to the differing manifestations of prescription drug misuse in older adults. Zimberg noted that family members or friends often do not identify alcohol problems in seniors, as there may be fewer consequences in social, legal, occupational, and interpersonal domains in older people [137]. Prescription drug misuse in older adults may be underreported for similar reasons.

Another important consideration in older adult populations is the role of biological factors. Physiological sensitivity to some medications increases with age, which can result in negative side effects even at previously tolerated dosages [50]. For example, benzodiazepine anxiolytics, which are widely prescribed in older adults, may cause multiple cognitive side effects, including sedation, memory problems, and attentional impairments [139]. Changes in body composition, including less body water, more fat stores, and changes in organ function may also affect how a given medication acts in older adults [138].

Researchers have suggested a wide variety of factors that may increase vulnerability for prescription drug misuse in seniors. Despite the widespread utilization of medications with misuse potential in older adults, intentional misuse in those without a history of other substance use problems is relatively uncommon [54, 129]. High rates of psychiatric comorbidity are common in elderly patients with prescription drug dependence [133]. In one investigation of individuals with prescription drug dependence, a diagnosable psychiatric illness was present in 85% of elderly patients but in only 36% of younger patients [140]. In this sample, older patients were more likely to have a history of memory loss, sleep disturbance, irritability, delusions, and inability to conduct daily activities without assistance. Younger patients, in contrast, were more likely to have experienced blackouts and to report that prescription medication misuse had negatively affected their relationships and careers. Unintentional misuse in older adults may be more likely to occur when individuals

suffer from more health problems, lack knowledge about the medications and their effects, visit a greater number of physicians and pharmacists, and live further from the medical clinic at which treatment is received [141].

A number of psychosocial factors unique to older populations have been associated with the risk for prescription drug misuse [50]. Elderly individuals are likely to encounter a range of difficult life circumstances, including loss of status following retirement, diminished social support and self-esteem, financial hardship, reduced mobility and social isolation, compromised physical health, or loneliness following the death of a spouse or close friends [138]. The use of psychoactive prescription medications has been suggested as a means of coping with these difficulties [50]. Of these negative factors, depression and social isolation are thought to be some of the most potent risk factors for prescription medication misuse [138]. For individuals with a history of using substances to cope with negative life events, the stresses associated with aging may be compounded by an exacerbation of existing substance-related problems [142].

Implications for Prevention and Treatment in Older Adults

A number of barriers have been identified that may impede the detection of problematic prescription drug use in older adults [128]. In addition to the lack of formal diagnostic tools [129], the negative consequences of misuse may be subtle and thus more difficult for health care providers to discern [138]. Potential warning signs of prescription misuse, such as concurrent alcohol or illicit drug use, prescription forgery, acquisition from nonmedical sources, or dose escalation may be less commonly observed in older adults as compared to their younger counterparts [128]. Consequences of misuse, including cognitive or psychomotor impairment or exacerbation of depression or anxiety, may be overlooked or attributed to the effects of aging. It may be difficult to determine whether an individual's difficulties are due to the effects of a medication, related withdrawal symptoms, the underlying condition the medication is prescribed to treat, or an interaction of these and other factors [128]. Complicating matters further, evidence suggests that elderly patients may underreport their medication usage [143] and that health care workers tend to display a low index of suspicion regarding substance misuse in older patients [137].

Access to appropriate treatment services presents another important consideration regarding older prescription drug misusers. Increased awareness of the problem of prescription drug misuse in older adults has provided some impetus for the development of intervention programs [50]. Zimberg argues for an aging-specific approach to treatment that aims to decrease problem substance use in the context of the other stresses associated with aging [137]. Treatments aimed at increasing social support and self-esteem may be more acceptable for older adults than interventions aimed solely at decreasing problem prescription drug use. Additionally, promoting the involvement of family members in the treatment process may produce better outcomes [50].

General Conclusions

Although the many definitions of prescription drug misuse used within the literature make it difficult to arrive at specific estimates of prevalence, existing research portrays a growing problem which, thus far, has been inadequately characterized and addressed [42, 66]. Distinct patterns of prescription drug misuse are evident in the various age groups covered in this review.

Patterns of prescription drug misuse are strikingly different across developmental stages and demographic classifications. More research is needed on socio-cultural factors relating to prescription drug misuse, as well as personality correlates and psychiatric comorbidities [83]. One consistent finding across age groups is the association between prescription drug misuse and increased use of alcohol and illicit drugs, a finding that has implications for the detection, assessment, and treatment of prescription drug misuse, abuse, and dependence. It is essential that prevention and intervention efforts take into account individual differences in motivations for misuse of prescription drugs, as the patterns and correlates of use tend to vary depending on whether a medication is self-administered for therapeutic or nontherapeutic reasons.

The body of research examining prescription drug misuse focuses on the extremities of the age continuum, a problem that is shared with the alcohol use literature [113]. Although many studies have examined the patterns and predictors of prescription drug misuse in young adulthood and older age, information about the intervening period is scarce and little is known about transitions between developmental stages.

Methodological considerations for future research include employing standardized definitions of prescription drug misuse, abuse, and dependence. Additionally, agreement on standard age ranges would facilitate comparisons across studies [113]. It should be noted that most existing research in this area is cross-sectional and should not be interpreted as implying causal relationships. For example, young adults may engage in prescription drug misuse to cope with negative feelings associated with poor academic performance. Alternately, prescription misuse may impair functioning, resulting in poorer grades. Either, or both, of these relationships may be true. The cross-sectional nature of these data also renders it difficult to track trends in prescription drug misuse over time [86]. Cohort differences could imply that

as these individuals age, higher rates of misuse now observed in younger age groups will manifest as increased prevalence in older age groups in the future. It is also possible that the findings reported here demonstrate age-specific correlates of prescription drug misuse that reflect changing life circumstances [86], suggesting that the observed patterns of prescription drug misuse should remain relatively constant over time. Further longitudinal investigations are needed to clarify these relationships.

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APPENDIX B. Polysubstance and Prescription Drug Use Interview

INFORMATION SHEET

Date: _____ *(mm/dd/yy)* Date of Birth: _____ *(mm/dd/yy)* Age: ____years

Gender: M / F Ethnicity: _____ Handedness: Right / Left *(circle one)*

Occupation: _____ University student? Y / N *(circle one)*

1. What city(ies)/town(s)/community(ies) have you lived in during your life? Please be as detailed as possible and provide age ranges.

2. Highest Level of Education Completed
(tick only one; provide additional details if necessary)

____ Elementary School
____ Junior High School
____ High School
____ Trade School
____ Community College
____ University
____ Other

3. Marital Status
(tick only one)

____ Single (never married)
____ Married/Cohabitating
____ Separated/Divorced
____ Widowed

4. Annual Family Income *(tick only one)*

____ < $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
____ > $80,000

5. Living Status *(tick only one)*

_____ Renting
_____ Own your own home
_____ Living with friends (not paying rent)
_____ Living with family (not paying rent)
_____ Living in community shelter/ transitional housing
_____ Living on streets
_____ Other (please describe:_____)

6. Have you ever smoked cigarettes? Yes / No *(If No, skip to next section)*
7. At what age did you first try smoking? _____
8. Have you ever smoked cigarettes regularly? Yes / No
If yes, for how long? _____ *(Range of ages that you smoked for)*
If yes, how much did you, or do you, typically smoke? _____ *(Average # cigs/day)*
9. Have you smoked any cigarettes in the last 30 days? Yes / No
If yes, how many days? _____ How many did you smoke per day on average? __
10. When was the last time you smoked cigarettes? _____*(Age is sufficient if not used in past 12 months)*
11. About how many days do you think you have smoked cigarettes in your entire life?
(Show scale card)
___1-5 ___6-10 ___11-20 ___21-50 ___51-100 ___101-500 ___>500
12. When have you smoked cigarettes the most in your life? Age: _____
13. What is the maximum number of days over any consecutive 30 day period that you smoked cigarettes? (*Rephrase:* **What is the greatest # of days out of 30 that you have ever smoked cigarettes?) _____**days/30

PRESCRIPTION DRUG USE INTERVIEW

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

1. Are you <u>currently</u> taking any medication prescribed by a doctor for any behavioural, emotional or personal difficulties you may have experienced; for example, anxiety, mood, sleep or attention?
Yes ____ No ____

2. Please list the medications that are currently being prescribed to you for these reasons. *(Just list medication names here; do not get details about dosage, formulation, reason for prescription etc.)*

____
____
____

3. You mentioned that you have a prescription for xxxx *(list medications reported in previous question)*. **In addition to xxxx, have you ever had a prescription for any of the following substances in your lifetime?**
(Go through categories one by one, i.e. ask about anti-anxiety medications, then stimulants, then analgesics)

☐ Tranquilizers/Anti-anxiety medications or Sedatives/Sleeping pills

☐ Stimulants

☐ Analgesics/Painkillers

Now I'm going to show you some pictures of these types of medications. *[Prompt with pill card].* **Some of the medications come in different forms. Can you tell me if you recognize the ones you were prescribed? Are there any other pills on these pages that you remember having a prescription for, that you didn't already mention?**

List all prescriptions named by the participant:

____
____
____

For <u>analgesics</u> only, ask the following: **Did you ever used the medication not as prescribed – did you ever take it for recreation, to get high, or mix it with alcohol or other drugs? Did you ever give away or sell the medication to someone else?**
If any analgesic was misused (i.e. used NOT just for controlling pain), make a note of it and transcribe it to a *Prescription Drug Use Interview Schedule* page.

Transcribe each other substance named onto a separate *<u>Prescription Drug Use Interview Schedule</u>* page.
Ask about current prescription first, then continue with next most recent etc.

NON-PRESCRIBED DRUG USE AND POLYSUBSTANCE USE INTERVIEW

Please list all prescription medications you have used throughout your life *without a prescription*. Next, rank the drugs by putting a 1 next to the drug you have used most often, a 2 next to the drug you have used second most, a 3 next to the drug you have used third most etc.

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)
_____ Trazodone
_____ Triazolam (Halcion, Novodorm, Songar)
_____ Secobarbital (Seconal)
_____ Secobarbital sodium/amobarbital sodium (Tuinal)
_____ Zopiclone (Imovane)
_____ Zolpidem (Ambien)

Other tranquilizer/sedative medications?

_____

_____

Stimulants

_____ Methamphetamine (Desoxyn, Methedrine)
_____ Amphetamine (Benzedrine, Biphetamine, Adderall)
_____ Phentermine (Fastin, Ionamin)
_____ Methylphenidate (Ritalin, Concerta, Methylin, Vitamin R)
_____ Pemoline (Cylert)
_____ Dextroamphetamine (Dexedrine, Eskatrol)
_____ Benzphetamine (Didrex)
_____ Mazindol (Mazanor, Sanorex)
_____ Phendimetrazine (Plegine)
_____ Phenmetrazine (Preludin)
_____ Diethylpropion (Tenuate)

Other stimulant medications?

_____

_____

Pain Relievers

_____ Dextropropoxyphene (Darvocet-N)
_____ Propoxyphene (Darvon, Dolene, SK-65)
_____ Co-codamol (Tylenol with Codeine, Tylenol 3, Phenaphen with Codeine)
_____ Oxycodone (Percocet, Tylox, Percodan, Percolone, OxyContin)
_____ Hydrocodone (Vicodin, Lortab, Lorcet/ Lorcet Plus)
_____ Codeine
_____ Meperidine (Demerol)
_____ Hydromorphone (Dilaudid)
_____ Butalbital (Fioricet, Fiorinal)
_____ Methadone (Dolophine, Methadose)
_____ Morphine
_____ Butorphanol tartrate (Stadol)
_____ Pentazocine (Talacen, Talwin, Talwin NX)
_____ Tramadol (Ultracet, Ultram)

Other pain relief medications?

_____

_____

PRESCRIPTION DRUG USE INTERVIEW SCHEDULE

Specify drug name:	
1. Why did you receive this prescription?	
2. How old were you when the medication was initially prescribed?	Age: _____
3. When was this prescription last filled? *If they cannot recall specific date, ask for an approximation.*	Age: _____ or _____/_____/_____ day / month / year
4. Did your doctor recommend that you take this prescription according to a particular schedule, or is/was it just taken as needed? *Get details of specific schedule (dosage, # times per day).*	
5. Is/was your prescription a normal formulation, or sustained/extended release formulation etc.?	
6. In total, for how many months/years have you been prescribed xxxx throughout your lifetime?	_____Years _____Months What age(s) were you? _____
7. Have you been taking xxxx consecutively throughout this time period, or have you gone on and off of it?	
8. If currently prescribed (regularly scheduled): On how many of days in the past 30 days have you used xxxx exactly as prescribed?	Number of days:_____
9. **Have you ever, even once, shared or given away your prescription?** **What about trading it with someone? Have you ever sold your prescription?** *If 'yes' to any of the above:* What was the purpose of sharing/giving away? Trading? Selling? How many times (i.e., on how many days) have you shared/given away, traded and/or sold your prescription? When did you do this?	*Circle:* Yes / No **Shared/Given Away**: ☐ Frequency:_____ Purpose:_____ When:_____ **Traded**: ☐ Frequency:_____ Purpose:_____ When:_____ **Sold**: ☐ Frequency:_____ Purpose:_____ When:_____
10 a. **Have you ever used xxxx in greater amounts or more often than prescribed?** *If yes:* In what ways? How many times have you used xxxx in this/these way(s) since initially prescribed? When was this?	*Circle:* Yes / No Specify change(s) in amount/frequency:_____ # occasions since first prescription:_____ When: _____

10 b. *If yes to above question,* **What was the reason(s) for taking xxxx in greater amounts or more often than prescribed?** *Show Motives for Use card. Check all motives that apply; indicate most frequently adopted motive with a ★.*	☐ 1. Out of curiosity ☐ 2. To get high/stoned/drunk/buzzed ☐ 3. To fit in with peers ☐ 4. To increase the effects of another drug ☐ 5. To decrease the effects of another drug ☐ 6. To study/concentrate ☐ 7. To stay awake ☐ 8. To give you more energy ☐ 9. To reduce appetite/manage weight ☐ 10. To help with sleep ☐ 11. To reduce anxiety ☐ 12. To reduce pain ☐ 13. To avoid withdrawal ☐ Other(s): _____
11. **Have you ever taken xxxx without having a prescription for it?** Estimate total number of lifetime uses *(Prompt with Lifetime Uses Scale card)* What were the reasons for using xxxx not as prescribed? *(Prompt with same reasons from previous question using Motives for Use card)* How was the substance obtained? *(Place a ★ to indicate most frequent source of medication)*	*Circle*: Yes / No Age of first non-prescribed use: _____ Age of most recent non-prescribed use: _____ # of days used in past 30 days:_____ # lifetime non-prescribed uses:_____ _____ _____ _____ Most frequent reason: _____ ☐ **Bought (From who:____ When:____)** ☐ **Given (From who:____ When:____)** ☐ **Stolen (From who:____ When:____)** ☐ **Other methods:** _____ **(From who:____ When:____)**
11. **Have you ever taken xxxx through a route of administration that was not recommended? For example, have you ever snorted, injected, smoked it, or used any other route?** If xxxx is normally taken orally, have you ever taken it this way for reasons other than those recommended? How many times have you used xxxx through this/these non- recommended route(s)? What were the reason(s) for using it in that/those way(s)? *Prompt with Motives for Use card if participant does not answer spontaneously.* *Check all that apply. Frequency = approximate number of days [use scale card]* When was this?	*Circle:* Yes / No ☐ **Snort** Frequency:_____ Purpose:_____ ☐ **Inject** Frequency:_____ Purpose:_____ ☐ **Smoke** Frequency:_____ Purpose:_____ **Other**(s): Specify:___Frequency:_____ Purpose:_____ ***For each of the above, indicate whether use was prescribed or not with a "P" or "NP"***

12. **Have you ever taken xxxx orally** (i.e, by its normal route) **for reasons other than those recommended?** *(Prompt with appropriate examples if needed, e.g. Have you taken it to get high, recreationally etc.)*	*Circle:* Yes / No ***Indicate whether P or NP.*** Purpose:______________________________ When:________________________________ Frequency:____________________________
13. **Have you ever deliberately used any other drugs or alcohol together with xxxx?** *(Clarify this if necessary: you want to get at <u>purposeful</u> mixing of two or more substances)* *Only check off the box if the person is using one drug while still experiencing the effects of the other; e.g. using Ativan while under the influence of alcohol OR drinking alcohol while under the influence of Ativan. The person must be experiencing the effects of both drugs at the same time.* *If yes:* **Please tell me all the substances you've taken together with xxxx. Are you sure you're not missing anything?** **What about energy drinks? What about any other prescription medications, like stimulants, tranquilizers, sedatives, or painkillers?** *Check all that apply; specify "other" drugs in space provided.* (S) = specify drug **What was the reason for deliberately mixing xxxx with this/these substance(s)?** *Prompt with Motives for Use card if participant does not answer spontaneously.* **How many times have you mixed xxxx with this/these substance(s)?** *Prompt with Lifetime Uses Scale card if necessary.* **When was this?** *Enter participant's age if occurrence was not in the past year.*	*Circle*: Yes / No ***Indicate whether use was P or NP.*** ***Drug*** ***Purpose of using with xxx / Freq. / When*** ☐ Alcohol __________ ☐ Cannabis __________ ☐ Mushrooms __________ ☐ LSD __________ ☐ Cocaine __________ ☐ Ecstasy __________ ☐ Mescaline __________ ☐ Amphetamine __________ ☐ Methamphetamine __________ ☐ PCP __________ ☐ GHB __________ ☐ Ketamine __________ ☐ Heroin __________ ☐ Salvia __________ ☐ Inhalants __________ ☐ Energy Drinks __________ ☐ Stimulants (S) __________ __________ __________ ☐ Tranquilizers (S) __________ __________ __________ ☐ Sedatives (S) __________ __________ __________ ☐ Pain Relievers (S) __________ __________ __________ Others:______ __________ __________ __________

14-15. **Think about the very first / last time you used xxx in a way that wasn't prescribed** [insert one of the forms of misuse mentioned above]. *(If details cannot be recalled, ask about the earliest recalled time the substance was used)* **When was this?** **Do you remember where you were?** **Who were you with?** *Estimate number of people present and number of people using substance.* **What was the purpose for using xxx during this session?** *(Prompt with Motives for Use card if they do not respond spontaneously)* **Was it the only substance you were using or were you also using and/or experiencing effects from other substances at the same time?** *(List prescription medication and all substances used with xxx; no need to list tobacco)* **How much of each substance did you consume in total on that occasion?** **In what order?** *(Amount: specify units; Order: specify # in sequence).* *Use ® to indicated a repeated pattern of use (e.g. alcohol, cannabis, alcohol, cannabis, alcohol …)* **What routes of administration** (oral, iv, snort, smoke)? **Were you also smoking tobacco? More, less, or the same as usual?**	Was the medication prescribed or non-prescribed? **P / NP** When: _____ Where:_____ With Who:_____ Only person using drug? _____ Purpose of using xxx: _____ _____ Other Substances: Yes / No Medication/Drug Amount Order Route _____ Tobacco: None____ More____ Less____ Same____

IMPORTANT: If the participant has BOTH misused a given prescribed medication AND taken it without a prescription, go through the first and last use questions TWICE. That is, ask them about the first and last times they misused their own prescription, plus their first and last non-prescribed use.

NON-PRESCRIBED AND POLYSUBSTANCE USE INTERVIEW SCHEDULE

Specify Drug Name:	
1. Age of first use:	
2. Age of last use:	
3. Number of days in the past 30 days (if any)	
4. Typical amount consumed per day in the past 30 days	
5. *Peak period of use (date, frequency, amount)* **At what point in your life were you using xxxx the most heavily?** **How often were you using it at this time?** **What was the typical amount per session you were consuming at this time?**	*Start Date* _____ (mm/yy) → *End date* _____ (mm/yy) Age: _____ Frequency: _____ Amount: _____
6. **Estimated total number of lifetime uses** *(Check appropriate box; prompt with Lifetime Uses Scale card)*	☐ 1-5 ☐ 21-50 ☐ >500 ☐ 6-10 ☐ 50-100 ☐ 11-20 ☐ 100-500
7. **Have you ever used xxxx for any of the following reasons?** *(Prompt with Motives for Use card. Check all that apply.)* *Note <u>most frequent</u> reason (★)*	☐ 1. Out of curiosity ☐ 2. To get high/stoned/drunk/buzzed ☐ 3. To fit in with peers ☐ 4. To increase the effects of another drug ☐ 5. To decrease the effects of another drug ☐ 6. To study/concentrate ☐ 7. To stay awake ☐ 8. To give you more energy ☐ 9. To reduce appetite/manage weight ☐ 10. To help with sleep ☐ 11. To reduce anxiety ☐ 12. To reduce pain ☐ 13. To avoid withdrawal ☐ Other(s): _____
8. Route of administration *(Check all that apply; indicate frequency)* **When using xxxx, how have you used it?** **What was/were the purpose(s) for using xxxx through this/these routes of administration?** *Prompt with Motives for Use card if participant does not answer spontaneously.* **What is the estimated amount of times you have used xxxx in this/these way(s)?** Use *Lifetime Uses Scale Card* **When was this?**	☐ **Oral** Purpose: _____ Frequency: _____ When: _____ ☐ **Snort** Purpose: _____ Frequency: _____ When: _____ ☐ **Inject** Purpose: _____ Frequency: _____ When: _____ ☐ **Smoke** Purpose: _____ Frequency: _____ When: _____ ☐ **Other** (Specify: _____) Purpose: _____ Frequency: _____ When: _____

9. **How was the substance ever obtained?** *List off all options, check all that apply, and indicate specific source.* *Note <u>most frequent</u> source (★)*	☐ **Bought** From who (friend, dealer, internet)? _____ When: _____ ☐ **Given** From who (friend, colleague)? _____ When: _____ ☐ **Stolen** From who (friend, family)? _____ When: _____ ☐ **Other methods** (Specify: _____ When: _____
10. **Have you ever deliberately used any other drugs or alcohol together with xxx?** *(Clarify this if necessary: you want to get at purposeful mixing of two or more substances)* *Only check off the box if the person is using one drug while still experiencing the effects of the other; e.g. using Ativan while under the influence of alcohol OR drinking alcohol while under the influence of Ativan. The person must be experiencing the effects of both drugs at the same time.* *If yes:* **Please tell me all the substances you've taken together with xxx. Are you sure you're not missing anything?** **What about energy drinks? What about any other prescription medications, like stimulants, tranquilizers, sedatives, or painkillers?** *Check all that apply; specify "other" drugs in space provided.* *(S) = specify drug* **What was the reason for deliberately mixing xxx with this/these substance(s)?** *Prompt with Motives for Use card if participant does not answer spontaneously.* **How many times have you mixed xxxx with this/these substance(s)?** *Prompt with Lifetime Uses Scale card if necessary.* **When was this?** *Enter participant's age if occurrence was not in the past year.*	Circle: Yes / No ***Drug*** ***Purpose of mixing*** ***When*** ***Freq.*** ☐ Alcohol _____ ☐ Cannabis _____ ☐ Mushrooms _____ ☐ LSD _____ ☐ Cocaine _____ ☐ Ecstasy _____ ☐ Mescaline _____ ☐ Amphetamine _____ ☐ Methamphetamine _____ ☐ PCP _____ ☐ GHB _____ ☐ Ketamine _____ ☐ Heroin _____ ☐ Salvia _____ ☐ Inhalants _____ ☐ Energy drinks _____ ☐ Stimulants (S): _____ _____ _____ ☐ Tranquilizers (S): _____ _____ ☐ Sedatives (S): _____ _____ _____ ☐ Pain Relievers (S): _____ _____ Others: _____ _____ _____

11-12. **Think about the last / first time you used xxxx.** *(If details cannot be recalled, ask about the most recent recalled time that the substance was used)* **When was this?** **Do you remember where you were?** *(City or town; type of event)* **Who were you with?** *Estimate number of people present and number of people using substance.* **What was the purpose for using xxx during this session***? (Prompt with Motives for Use card if they do not respond spontaneously)* **Was it the only substance you were using or were you also using and/or experiencing effects from other substances at the same time?** *(List prescription medication and all substances used with xxx; no need to list tobacco)* **How much of each substance did you consume in total on that occasion?** **In what order?** *(Amount: specify units; Order: specify # in sequence).* *Use ® to indicated a repeated pattern of use (e.g. alcohol, cannabis, alcohol, cannabis, alcohol…)* **What routes of administration** (oral, iv, snort, smoke)? **Were you also smoking tobacco? More, less, or the same as usual?**	When:________________________________ Where:______________________________ With Who:____________________________ Only person using drug?__________________ Purpose of using xxx: ____________________________ Other Substances: Yes / No Medication/Drug Amount Order Route __________ _______ ______ ______ __________ _______ ______ ______ __________ _______ ______ ______ __________ _______ ______ ______ __________ _______ ______ ______ __________ _______ ______ ______ __________ _______ ______ ______ __________ _______ ______ ______ Tobacco: None____ More____ Less____ Same____

MOTIVES FOR USE CARD AND LIFETIME USES SCALE CARD[17]

Motives for Use Card

1. Out of curiosity
2. To get high/stoned/buzzed
3. To fit in with peers
4. To increase the effects of another drug
5. To decrease the effects of another drug
6. To study/concentrate
7. To stay awake
8. To give you more energy
9. To reduce appetite/manage weight
10. To help with sleep
11. To reduce anxiety
12. To reduce pain
13. To avoid withdrawal
14. Because it was safer than street drugs
15. Other(s): _____

Lifetime Uses Scale Card

1-5 6-10 11-20 21-50 51-100 101-500 >500

[17] These cards were presented to participants during the polysubstance and prescription drug use interview to prompt them to identify motives for use and estimate the total number of lifetime uses of various substances.

DRUG LIST QUESTIONNAIRE

Substance	Ever used xxx? Y(✓) N(×)	How old were you the first time you used xxx?	In the past 30 days, on how many days was xxx used?	When was the last time you used xxx? *(Age is sufficient, if not used in past 12 months)* Month Year	What is the estimated number of lifetime uses of xxx? *(Use scale card)*	What is the maximum number of days over any consecutive 30-day period that xxx was used? Days out of 30	How old were you when you were using xxx most frequently? Age (range)
Alcohol							
Cannabis (pot, weed, marijuana, hash)							
Cocaine (coke, crack, blow, snow)							
Amphetamine (speed) *NOT prescription; illicit only.*							
Methamphet-amine (crystal meth)							
MDMA (ecstasy, E, X)							
Heroin (smack, junk)							
GHB (Liquid E)							
Ketamine (Special K)							
Magic mush-rooms (shrooms, psilocybin)							
LSD (acid, blotters, tabs)							
Mescaline							
PCP (angel dust)							
Salvia							
Inhalants (nitrous oxide, amyl nitrate, whippets, poppers). *Note specific ones used.*							
Energy Drinks							
Other *Please specify.*							

REMEMBER TO CHECK: Max # of tobacco uses in 30 days: _____ (from first page of interview)

Complete DEPENDENCE & ABUSE questions on Substance Use Questionnaire for all substances used 10 x or more in 30 days. Complete ABUSE questions for substances used 10 x or more ever. (Exception: no abuse questions for tobacco).

SUBSTANCE USE QUESTIONNAIRE

Ask dependence and abuse questions if substance used ≥ 10 times in a consecutive 30-day period; ask abuse questions if substance used ≥ 10 times ever. Do not ask abuse questions for tobacco.

Think about your use of _____ over your lifetime as you answer these next questions.

Substance Dependence		
1	Has there ever been a month or more when you spent a lot of your time getting or using _? If yes, when was this?	Y N
2	Has there ever been a month or more when you spent a lot of time getting over the effects of the _____ you used? If yes, when was this?	Y N
3	Have you ever tried to set limits on how often or how much _____ you would use? If yes, when was this?	Y N
4	*If Yes on [3]* Were you able to keep to the limits you set, or did you often use more than you intended to?	Kept to limits Often used more
5	Has there ever been a period of time in which you needed to use more __ _____ than you used to in order to get the effect you wanted? If yes, when was this?	Y N
6	*If No on [5]* Has there ever been a period of time in which you noticed that using the same amount of _____had less effect on you than it used to? If yes, when was this?	Y N
7	Have you ever wanted to or tried to cut down or stop using _____? If yes, when was this? If no, go to question 12.	Y N
8	*If Yes on [7]* On those occasions, were you able to cut down or stop using _____ every time you wanted to or tried to? If yes, when was this?	Y N
9	*If No on [8]* Did you cut down or stop using at least one time? If yes, when was this?	Y N
10	*If Yes on [8] or [9] – SKIP THIS QUESTION FOR CANNABIS, HALLUCINOGENS, PCP, INHALANTS* *[Show substance-specific withdrawal symptom card]* After you cut back or stopped using _____, did you experience two or more of the symptoms in this list? If yes, when was this?	Y N

11	*If Yes on [10]* *[Show substance-specific withdrawal symptom card]* After you cut back or stopped using _____, did you experience two or more of the symptoms in this list that lasted for longer than a day? If yes, when was this?	Y N
12	Have you ever had any problems with your emotions, nerves, or mental health that were probably caused or made worse by using _____? If yes, when was this?	Y N
13	*If Yes on [12]* Did you continue to use _____ even though you thought using it was causing you to have problems with your emotions, nerves, or mental health?	Y N
14	*If No on [12] or [13]* Have you ever had any physical health problems that were probably caused or made worse by using _____? If yes, when was this?	Y N
15	*If Yes on [14]* Did you continue to use _____ even though you thought using it was causing you to have physical problems?	Y N
16	This question is about important activities such as working, going to school, taking care of children, doing fun things such as hobbies and sports, and spending time with friends and family. Has using _____ ever caused you to give up or spend less time doing these types of important activities? If yes, when was this?	Y N
Substance Abuse		
17	Sometimes people who use _____ have serious problems at home, work or school, such as: • neglecting their children • doing a poor job at work or school • missing work or school • losing a job or dropping out of school Has using _____ ever caused you to have serious problems like this either at home, work, or school? If yes, when was this?	Y N
18	Has there ever been a period in your life in which you regularly used _____ and then did something where using _____ might have put you in physical danger? If yes, when was this?	Y N
19	Has there ever been a period in your life in which using _____ caused you to do things that repeatedly got you in trouble with the law?	Y N
20	Has there ever been a period in your life in which you have had problems with family or friends that were probably caused by your use of _____? If yes, when was this?	Y N
21	*If Yes on [20]* Did you continue to use _____ even though you thought it caused problems with family or friends?	Y N

SUBSTANCE-SPECIFIC WITHDRAWAL SYMPTOMS[18]

Alcohol / Sedatives / Hypnotics / Anxiolytics

- Sweating or feeling that your heart was beating fast
- Having your hands tremble
- Having trouble sleeping
- Vomiting or feeling nauseous
- Seeing, hearing, or feeling things that weren't really there
- Feeling like you couldn't sit still
- Feeling anxious
- Having seizures or fits

Heroin / Opiates / Prescription Painkillers

- Feeling kind of blue or down
- Vomiting or feeling nauseous
- Having cramps or muscle aches
- Having teary eyes or a runny nose
- Feeling sweaty, having enlarged eye pupils, or having body hair standing up on your skin
- Having diarrhea
- Yawning
- Having a fever
- Having trouble sleeping

Amphetamines / Cocaine / Prescription Stimulants

- Feeling tired or exhausted
- Having vivid, unpleasant dreams
- Having trouble sleeping or sleeping more than you usually do
- Increased appetite
- Feeling either very slowed down or like you couldn't sit still

Cigarettes / Tobacco

- Feeling kind of blue or down
- Having trouble sleeping
- Feeling irritable, frustrated or angry
- Feeling anxious
- Having trouble concentrating
- Feeling restless
- Having a decreased heart rate
- Increased appetite or weight gain

[18] These symptoms were presented to participants on cards during the substance abuse and dependence symptom assessment to assist in identification of withdrawal symptoms experienced.

APPENDIX C. Substance Use Risk Profile Scale[19]

ID #: _____

Please circle the number that corresponds best to you

1. I am content.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

2. In stressful situations, I often think what if no one reaches me in time?
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

3. I often don't think things through before I speak
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

4. I would like to skydive.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

5. I am happy.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

6. When I cannot concentrate I worry that I might be going crazy.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

7. I often involve myself in situations that I later regret being involved in.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

8. I enjoy new and exciting experiences even if they are unconventional.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

9. I have faith that my future holds great promise.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

10. It's frightening to feel dizzy or faint.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

11. The most interesting and exciting things are usually illegal or immoral.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

12. I like doing things that frighten me a little.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

[19] This version of the SURPS, as well as a 23-item version, is published in Woicik, P. A., Stewart, S. H., Pihl, R. O., & Conrod, P. J. (2009). The substance use risk profile scale: A scale measuring traits linked to reinforcement-specific substance use profiles. *Addictive Behaviors, 34,* 1042–1055.

13. Sometimes I think I am no good at all.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

14. It frightens me when I feel my heart beat change.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

15. I usually act without stopping to think.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

16. I would like to learn how to drive a motorcycle.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

17. I feel proud of my accomplishments.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

18. I get scared when I'm too nervous.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

19. Generally, I am an impulsive person.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

20. I am interested in experience for its sake even if it is illegal.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

21. I feel that I am a failure.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

22. I get scared when I experience unusual body sensations.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

23. I am stubborn and strong-minded.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

24. I would enjoy hiking long distances in wild and uninhabited territory.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

25. I feel pleasant.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

26. It scares me when I'm unable to focus on a task.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

27. I feel I have to be manipulative to get what I want.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

28. I am very enthusiastic about my future.
(1) Strongly disagree (2) Disagree (3) Agree (4) Strongly Agree

APPENDIX D. Psychiatric Diagnostic Screening Questionnaire:

Representative Items[20]

During the Past 6 Months…

Yes No 92… were you a nervous person on most days?

Yes No 93… did you worry a lot that bad things might happen to you or someone close to you?

Yes No 94… did you worry about things that other people said you shouldn't worry about?

Yes No 95… were you worried or anxious about a number of things in your daily life on most days?

Yes No 96… did you often feel restless or on edge because you were worrying?

[20] Permission to reproduce five representative sample items of the PDSQ was granted by Western Psychological Services (see Appendix H). Five items from the Generalized Anxiety Disorder subscale are presented. Copies of the PDSQ can be obtained from Western Psychological Services (www.wpspublish.com).

APPENDIX E. Assessment of Hyperactivity and Attention[21]

ADHD Questionnaire

1. I often fail to give enough attention to details, or make many careless mistakes in paperwork, work-related tasks, or other activities.

   Never Sometimes Often Always

2. I often fidget with my hands or feet (or play with an object in hand).

   Never Sometimes Often Always

3. I often have difficultly sustaining attention in work-related tasks (unable to keep paying attention for a long time).

   Never Sometimes Often Always

4. I often leave my seat in situations in which remaining seated is expected (have difficultly staying seated for long meetings/lectures and/or meals).

   Never Sometimes Often Always

5. I often do not seem to listen when spoken to directly.

   Never Sometimes Often Always

6. I am very easily bored, I often feel very restless.

   Never Sometimes Often Always

7. I often do not follow through on instructions and fail to finish assignments or chores on time.

   Never Sometimes Often Always

8. I often have difficultly engaging in leisure activities alone (I prefer to surround self with noise and I dislike having it quiet).

   Never Sometimes Often Always

[21] Adapted from Mehringer, A. M., Downey, K. K., Schuh, L. M., Pomerleau, C. S., Snedecor, S. M., & Schbiner, H. (2002). The Assessment of Hyperactivity and Attention (AHA): Development and preliminary validation of a brief self-assessment of adult ADHD. *Journal of Attention Disorders, 5,* 223–231. Reproduced with permission of the author (see Appendix H).

9. I often have difficultly organizing tasks or activities.

Never Sometimes Often Always

10. I am often “on the go” or I act like I am “driven by a motor”.

Never Sometimes Often Always

11. I often avoid, dislike, or am reluctant to engage in tasks that require sustained mental effort.

Never Sometimes Often Always

12. I often talk excessively.

Never Sometimes Often Always

13. I often misplace or lose things necessary for tasks and/or activities.

Never Sometimes Often Always

14. I often blurt out answers before questions have been completed.

Never Sometimes Often Always

15. I am easily distracted by extraneous stimuli (other things going on).

Never Sometimes Often Always

16. I often have difficultly waiting my turn.

Never Sometimes Often Always

17. I am often forgetful of daily activities.

Never Sometimes Often Always

18. I often interrupt or intrude (e.g. butt into conversation).

Never Sometimes Often Always

APPENDIX F. Quetiapine Misuse Letter

An abbreviated version of Study 4 of this dissertation (see Chapter 5) was published in the format of a letter to the editors as McLarnon, M. E., Fulton, H. G., MacIsaac, C., & Barrett, S. P. (2012). Characteristics of quetiapine misuse among clients of a community-based methadone maintenance program. *Journal of Clinical Psychopharmacology*, *32*, 721–723.

Characteristics of Quetiapine Misuse Among Clients of a Community-Based Methadone Maintenance Program

To the Editors:

Quetiapine is an atypical antipsychotic approved for treatment of schizophrenia and bipolar depression. It has become an increasingly popular pharmacotherapy for anxiety and insomnia,[1] with demonstrated efficacy in treating these conditions.[2–4] Similar to other medications with sedative and anxiolytic effects, there have been multiple reports of quetiapine misuse.[1,5–12] Case reports have documented users embellishing or fabricating symptoms to obtain quetiapine[1,7,12,13] as well as its sale and acquisition through illegitimate channels.[1,7,12,14] While its mechanisms of action are unclear, the antihistaminic and anticholinergic effects of quetiapine offer a possible explanation for its misuse potential.[13] In most case reports, quetiapine misuse seems to be motivated by self-medication of insomnia,[7] anxiety,[5,7,11] or depressed mood[5] rather than obtaining euphoric or "mind-altering"[15] effects. However, misuse of quetiapine has yet to be systematically investigated in a larger sample. Past research suggests that individuals with an extensive substance use history are at an elevated risk for misusing sedative or anxiolytic medications,[16] which may increase risk for misusing quetiapine specifically.[13,17] Quetiapine has been reported to increase plasma concentrations of methadone,[18] suggesting another possible motive for its misuse among individuals receiving methadone treatment.

We examined quetiapine misuse among clients from a low-threshold community-based methadone maintenance program in Halifax, Canada. Seventy-four participants (69% men), aged 18 to 64 years (mean [SD], 41.2 [10.6] years), were recruited as part of a larger study. The sample was 77% Caucasian, 10% Aboriginal, 4% African-Canadian, and 10% from other racial or ethnic groups. Seventy-two percent of participants reported an annual income of less than Can $10,000, and 46% had completed less than a high school level of education. Participants were receiving mean (SD) daily methadone doses of 108.3 (45.6) mg to treat prescription opioid dependence and had been clients of the program for a mean (SD) of 43.9 (38.1) months at the time of their participation. All participants provided written informed consent. The local health authority research ethics board approved the study.

Each participant completed a confidential face-to-face interview with a member of the research team, reporting on lifetime use of licit, illicit, and prescription drugs. Forms of quetiapine misuse assessed included alternate routes of administration, deliberate co-administration with other substances, intentionally exceeding the recommended dosage, and use without a valid prescription. Participants also reported on quetiapine diversion, defined as selling or giving away the medication. Participants were presented with a list of motives derived from previous research[17,19] and asked to select those corresponding to their motives for misusing or diverting quetiapine. For the purposes of analysis, prescription drug use, misuse, and diversion were coded dichotomously. Bivariate analyses (independent-sample t tests and χ^2 tests) were conducted to examine relationships between demographic and substance use variables. An α level of $P < 0.05$ was set as a threshold of statistical significance.

All participants (100%) had a history of prescription opioid misuse. The lifetime prevalence rate for misuse of prescription sedative/anxiolytic medications was 85%, whereas that of prescription stimulants was 51%. Participants had used a mean (SD) of 9.0 (4.1) illicit drugs in their lifetimes. Those with the highest prevalence of use were cannabis (96%), crack cocaine (96%), powdered cocaine (92%), LSD (85%), psilocybin (78%), ecstasy (65%), mescaline (54%), heroin (53%), and amphetamine (51%). Eighty percent of participants reported lifetime quetiapine use. Of these, 37% reported exclusively taking quetiapine with a valid prescription, 21% reported exclusively taking it without a prescription, and 42% reported using it both with and without a prescription. Overall, 75% of quetiapine users had engaged in at least one form of misuse. Twenty-eight percent of all quetiapine users reported co-administering quetiapine with another substance; most commonly, the other substance was a prescription sedative or anxiolytic. Two participants (4% of all quetiapine users) reported intentionally co-administering quetiapine with prescribed methadone. Two participants reported using quetiapine by an alternate route of administration; in both cases, it was used intranasally.

Participants' sex, race/ethnicity, income, and level of education were unrelated to quetiapine misuse. Participants who reported any form of quetiapine misuse were significantly younger than those who did not, $t_{55} = 2.41$, $P = 0.02$. Among those who had ever misused quetiapine, onset of misuse occurred concurrently with or after the onset of methadone treatment for 49% and before the onset of methadone treatment for 51%. Individuals with a history of prescription anxiolytic/sedative misuse were more than 8 times more likely to report quetiapine misuse, $\chi^2_1 = 6.42$, $P = 0.03$. In 93% of cases, the onset of anxiolytic/sedative misuse preceded any quetiapine misuse. Likelihood of engaging in quetiapine misuse was unrelated to prescription stimulant use and other illicit drug use.

Among participants who had ever been prescribed quetiapine, the primary reasons for receiving the drug were inducing sleep and/or reducing anxiety (87%), managing withdrawal from other substances (7%), treating psychosis or bipolar disorder (4%), and other reasons (2%). Thirty-eight percent of prescribed users admitted to intentionally taking quetiapine in excess on at least 1 occasion, whereas 51% reported ever diverting the medication. All but one of the prescribed users who had taken quetiapine in excess amounts stated that the primary reason for doing so was to increase its sedative effect, as did 89% of those who had taken quetiapine without a valid prescription. Similarly, more than three quarters (76%) of those who had diverted quetiapine stated that the recipient's intention was to use the medication to induce sleep.

DISCUSSION

This study provides insight into patterns of quetiapine misuse among clients of a methadone maintenance program. Exposure to quetiapine was extremely common within this sample. Overwhelmingly, participants who had been prescribed quetiapine were given the medication off-label for the treatment of insomnia or anxiety. Despite concerns raised in the literature,[9,12,13] we found intranasal and intravenous use to be rare or nonexistent. However, other forms of quetiapine misuse were prevalent, including use in excess amounts, concurrently with other sedative drugs, or without a valid prescription. Given the consequences that can arise from overuse of quetiapine,[20] this finding suggests that

better education is needed regarding the risks of quetiapine misuse, particularly among high-risk, substance-using populations. Consistent with existing case reports,[6,8,12] most participants who reported quetiapine misuse stated that their intent was to increase its therapeutic effect on anxiety or insomnia. Quetiapine misuse was more frequent among participants who had misused prescription sedative/anxiolytic medications. This suggests that clinicians should be aware that individuals with a history of central nervous system-depressant drug misuse might be at an elevated risk to misuse quetiapine.

The present results should be considered in light of the following methodological limitations. The sample was modestly sized and recruited by participant self-selection. All participants were clients of a low-threshold methadone program, and the relative rates of misuse would likely be lower in non–drug-abusing populations. Quetiapine misuse was coded dichotomously, which precluded the ability to conduct analyses based on a quantifiable index of misuse. While the results of this study cannot be broadly generalized, they have important implications for other groups at high risk for problem substance use, including incarcerated or street-involved individuals. Future research is needed to more fully characterize the factors relating to quetiapine misuse and inform strategies to maximize its safe and effective use.

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APPENDIX G. Quetiapine Use Interview

SEROQUEL/QUETIAPINE USE INTERVIEW SCHEDULE

Questions 1–16 refer to use of Seroquel WITH a prescription.	
1. **Do you have, or have you ever had a prescription for a medication called Seroquel, also known as quetiapine?** *If no, skip to question 17.*	*Circle one:* Y / N
2. **How old were you when Seroquel was first prescribed to you?**	Age: _____
3. **Where did you receive this prescription, and from whom?** (e.g. family physician, psychiatrist, correctional services).	
4. **What was/were the reason(s) for receiving a prescription for Seroquel?**	
5. *If unknown,* **Have you ever received a prescription for Seroquel while incarcerated?**	*Circle one:* Y / N
6. **When was your prescription for Seroquel last filled?** *If they cannot recall specific date, ask for an approximation.*	Age: _____ or _____/_____/_____ day / month / year
7. **Is/was your prescription a normal formulation, or sustained/extended release (XR) formulation?**	*Circle one:* Normal / XR
8. **Did your doctor recommend that you take Seroquel according to a particular schedule, or is/was it just taken as needed?** *Get details (dosage, # times taken per day).*	*Circle one:* PRN / Regularly scheduled *Dosage:* *Details:*
9. **In total, for how many months/years have you been prescribed Seroquel throughout your lifetime?**	_____Years _____Months What age(s) were you? _____
10. **Have you been taking Seroquel consecutively throughout this time period, or have you gone on and off of it?**	
11. **About how many days in your entire life have you used Seroquel?** *Show Lifetime Uses Scale Card*	☐ 1-5 ☐ 11-20 ☐ 51-100 ☐ 6-10 ☐ 21-50 ☐ 101-500
12. **Have you ever, even once, shared or given away your prescription for Seroquel? What about trading it with someone? Have you ever sold your prescription?** *If 'yes' to any of the above:* **What was the purpose of sharing/giving away? Trading? Selling?** **How many times (i.e., on how many days) have you shared/given away, traded and/or sold your prescription?** *If unable to remember frequencies, get an estimate (using scale card). Note most frequent means of diversion with a ★*	*Circle:* Yes / No ☐ **Shared/Given Away** Frequency:_____ Purpose:_____ ☐ **Traded** Frequency:_____ Purpose:_____ ☐ **Sold** Frequency:_____ Purpose:_____

13 a. **Have you ever used Seroquel in greater amounts or more often than prescribed?** *If yes:* **In what ways?** **How many times have you used Seroquel in this/these way(s) since it was initially prescribed?**	*Circle:* Yes / No Specify change(s) in amount/frequency:_____ _____ # occasions since first prescription:_____ _____
13 b. *If yes to above question,* **What was the reason(s) for taking Seroquel in greater amounts or more often than prescribed?** *Show Motives for Use card. List off all options; check all that apply; make sure to say the name (i.e.* Seroquel*) at least every third reason; include the prescribed reason if relevant.* **Of all those reasons for taking Seroquel in greater amounts or more often than prescribed** *(list previously indicated reasons)*, **what was your most frequent reason?** *Indicate most frequently adopted motive with a ★*	☐ 1. Out of curiosity ☐ 2. To get high/stoned/drunk/buzzed ☐ 3. To fit in with peers ☐ 4. To increase the effects of another drug, *if yes:* What drug(s)?_____ ☐ 5. To decrease the effects of another drug, *if yes:* What drug(s)?_____ ☐ 6. To study/concentrate ☐ 7. To stay awake ☐ 8. To give you more energy ☐ 9. To reduce appetite/manage weight ☐ 10. To help with sleep ☐ 11. To reduce anxiety ☐ 12. To reduce pain ☐ 13. To avoid withdrawal ☐ 14. Because Seroquel was safer than street drugs ☐ 15. Other(s): _____
14 a. **Have you ever been prescribed Seroquel to help with sleep?** *If yes,* **Have you ever taken this prescription at times of the day other than right before going to sleep?** *If yes:* **When have you taken it?** **How many times in total have you used Seroquel at a time other than before going to sleep?**	*Circle:* Yes / No Specify change(s) in time administered:_____ _____ _____ # occasions since first prescription:_____
14 b. *If yes to above question,* **What was the reason(s) for taking Seroquel at a different time of the day other than before going to sleep?** *Show Motives for Use card. List off all options; check all that apply; make sure to say the name (i.e.* Seroquel*) at least every third reason; include the prescribed reason if relevant.* **Of all those reasons for taking Seroquel at a different time of day,** *(list previously indicated reasons)*, **what was your most frequent reason?** *Indicate most frequently adopted motive with a ★*	☐ 1. Out of curiosity ☐ 2. To get high/stoned/drunk/buzzed ☐ 3. To fit in with peers ☐ 4. To increase the effects of another drug, *if yes:* What drug(s)?_____ ☐ 5. To decrease the effects of another drug, *if yes:* What drug(s)?_____ ☐ 6. To study/concentrate ☐ 7. To stay awake ☐ 8. To give you more energy ☐ 9. To reduce appetite/manage weight ☐ 10. To help with sleep ☐ 11. To reduce anxiety ☐ 12. To reduce pain ☐ 13. To avoid withdrawal ☐ 14. Because Seroquel was safer than street drugs ☐ 15. Other(s): _____
15. **On how many days in the past 30 days did you use Seroquel?**	
16. *If currently prescribed (regularly scheduled):* **On how many of days in the past 30 days have you used Seroquel exactly as prescribed?**	*Number of days:*_____

Questions 17–22 refer to use of Seroquel WITHOUT a prescription.	
17. **Have you ever taken Seroquel when it wasn't your own prescription?**	*Circle:* Yes / No
18. **How old were you the first time you took Seroquel without a prescription?** *Get more specific date of use if in the past year.*	Age: _____ or _____/_____/_____ day / month / year
19. **When was the last time you took Seroquel without a prescription?** *Get age if not in last 12 months*	Age: _____ or _____/_____/_____ day / month / year
20. **About how many days in your entire life have you used Seroquel without having a prescription for it?** *Show Lifetime Uses Scale Card*	☐ 1-5 ☐ 11-20 ☐ 51-100 ☐ 6-10 ☐ 21-50 ☐ 101-500
21. **How have you ever obtained Seroquel without a prescription? Did you ever…** *List off all options, check all that apply,* **Of all those ways that you mentioned you obtained Seroquel without a prescription *(list)*, what was the most frequent way you obtained Seroquel without a prescription?** *Note <u>most frequent</u> source with a ★*	☐ Buy Seroquel from a friend ☐ Buy Seroquel from a dealer or on the street ☐ Buy Seroquel over the internet ☐ Given Seroquel from friend and/or an acquaintance ☐ Given Seroquel from a family member ☐ Steal Seroquel from a friend ☐ Steal Seroquel from a family member ☐ Steal Seroquel from a stranger ☐ Steal money in order to buy Seroquel ☐ Steal material goods (e.g. electronics) in order to get money to buy Seroquel ☐ Deal drugs to get Seroquel ☐ Prostitute yourself in order to get Seroquel ☐ Panhandle in order to get money to buy Seroquel ☐ Use any other ways to obtain Seroquel without a prescription? *If yes list:*_____
22. **Have you ever used Seroquel when you didn't have a prescription for it for any of the following reasons?** *List off all options, check all that apply.* **Of the reasons that you mentioned for using Seroquel without a prescription** *(list)*, **what was the most frequent reason for using it?** *Note <u>most frequent</u> reason with a ★*	☐ 1. Out of curiosity ☐ 2. To get high/stoned/drunk/buzzed ☐ 3. To fit in with peers ☐ 4. To increase the effects of another drug *If yes:* What drug(s)?_____ ☐ 5. To decrease the effects of another drug *If yes:* What drug(s)?_____ ☐ 6. To study/concentrate ☐ 7. To stay awake ☐ 8. To give you more energy ☐ 9. To reduce appetite/manage weight ☐ 10. To help with sleep ☐ 11. To reduce anxiety ☐ 12. To reduce pain ☐ 13. To avoid withdrawal ☐ 14. Because Seroquel was safer than street drugs ☐ 15. Other(s): _____

Questions 23–28 refer to any use of Seroquel, WITH OR WITHOUT a prescription

I've asked you about your use of Seroquel both when you had a prescription for it and when you haven't had a prescription for it. For the next few questions, please think about your use of Seroquel in general; that is, any use of Seroquel regardless of whether it was your own prescription or not.

23. **At what point in your life were you using Seroquel the most heavily?** **How often were you using it at this time?** **What was the typical amount of Seroquel per session you were consuming at this time?**	*Start Date* *End date* _____ (mm/yy) → _____ (mm/yy) Age: _____ Frequency: _____ Amount: _____
24. **When using Seroquel, how have you used it? Have you ever:** **- used Seroquel orally?** *(to clarify: "eating or drinking it")* **- snorted Seroquel?** **- injected Seroquel?** **- smoked Seroquel?** **- used Seroquel any other way?** **Out of all the ways that you used Seroquel in your** life *(list the various methods they have used)*, **what way the most frequent way that you used Seroquel?** *Put a 1 next to this method.* **What was the next most frequent method of using Seroquel?** *Put a 2 next to this method.* *Continue above questioning until all methods have been ranked from most frequent to least frequent.*	☐ Oral Frequency Rank: _____ ☐ Snort Frequency Rank: _____ ☐ Inject Frequency Rank: _____ ☐ Smoke Frequency Rank: _____ ☐ Other(s): *Specify*: _____ Frequency Rank: _____
25. **Have you ever used any other drugs or alcohol while under the influence of Seroquel or used Seroquel while under the influence of other drugs or alcohol?** *(Clarify this if necessary: you want to get at deliberate mixing of two or more substances, not just incidental*) *If yes:* **Please tell me all the substances you've taken together with Seroquel.** *Read list. Make sure to ask them about all the drugs they say they have ever used; do not ask about drugs they say they have never tried.* *Only check off the box if the person is using one drug while still experiencing the effects of the other; e.g. using Seroquel while under the influence of alcohol OR drinking alcohol while under the influence of Seroquel. The person must be experiencing the effects of both drugs at the same time.* **What about any other prescription medications, like prescription stimulants, tranquilizers/sedatives, or painkillers?** *Check all that apply; specify drugs in space provided*. **Are there any other drugs that you have used in combination with Seroquel?**	Circle: Yes / No ☐ Alcohol ☐ Cocaine ☐ Amphetamine ☐ Methamphetamine ☐ Heroin ☐ Opium ☐ LSD ☐ Mescaline ☐ Peyote ☐ GHB ☐ PCP ☐ Inhalants ☐ Pain Relievers *Specify*: _____ ☐ Anxiolytic/sedatives *Specify*: _____ ☐ Prescription stimulants *Specify*: _____ ☐ Others: _____

→ *Script for questions 26-28:*
Think about the [last / first] time you [mis]used Seroquel. *If details can not be recalled, ask about the most recent / earliest recalled time.*
When was this? Do you remember where you were? *City or town; type of event*
Were you the only person using Seroquel?
Who were you with? *Get an estimate of # of people; # males & females; relationship.*
What was the primary purpose for using Seroquel during this session? *(Prompt with Motives for Use card if they do not respond spontaneously)*
Was Seroquel the only substance you were using or were you also using and/or experiencing effects from other substances at the same time?
→ *If Seroquel used in isolation:*
a) How much Seroquel did you consume? *Specify units (e.g. grams, ounces)*
b) How did you use Seroquel? *(e.g. eat/drink, snort, inject, etc.) If used in different ways (e.g. snort & inject) then list how much was used each way.*
→ *If multiple substances used:*
Okay, walk me through this session. What substance did you use first?
a) How much xxxx did you consume? *Specify units (e.g. grams, ounces)*
b) How did you use xxxx?
What substance did you use next?
c) How much xxxx did you consume at this point?
d) How did you use xxxx at this point?
→ *Repeat questions until details of all substances used in this session have been recorded. Use ® to indicate a repeated pattern of use.*
FOR RX MEDICATIONS: **Was that drug prescribed to you?** *Indicate P or NP.*
Were you also smoking tobacco? More, less, or the same as usual?
→ *If first time used represents a recommended prescribed use, ask about details of first time misused, based on what the participant has already reported (e.g. NP use, changed route of admin., inc. dosage, taken at different time, co-admin. w/ other substances.)*

26. LAST TIME USED
When: _____
Where: _____
Only person using Seroquel?_____
With Who: _____
Primary purpose of using Seroquel: _____
Other Substances: Yes / No

Order	Med./Drug	Amount	Admin Route
___	_____	_____	_____
___	_____	_____	_____
___	_____	_____	_____
___	_____	_____	_____

Tobacco: None___ Less___ Same___ More___

27. FIRST TIME USED
When: _____
Where: _____
Only person using Seroquel?_____
With Who: _____
Primary purpose of using Seroquel: _____
Other Substances: Yes / No

Order	Med./Drug	Amount	Admin Route
___	_____	_____	_____
___	_____	_____	_____
___	_____	_____	_____
___	_____	_____	_____

Tobacco: None___ Less___ Same___ More___

28. FIRST TIME MISUSED
When: _____
Where: _____
Only person using Seroquel?_____
With Who: _____
Primary purpose of using Seroquel: _____
Other Substances: Yes / No

Order	Med./Drug	Amount	Admin Route
___	_____	_____	_____
___	_____	_____	_____
___	_____	_____	_____
___	_____	_____	_____

Tobacco: None___ Less___ Same___ More___

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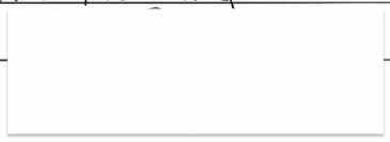
Signature:  Date: 08 Nov 2013