SEX DIFFERENCES IN RISK FACTORS FOR PRESCRIPTION OPIOID NON-MEDICAL USE AMONG YOUTH

By

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To Mum, Dad and Anne-Marie

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ANOVA	Analysis of Variance
CI	Confidence Interval
DEA	Drug Enforcement Administration
DSM-5	Diagnostic and Statistical Manual of Mental Disorders version 5
FDA	Food and Drug Administration
MTF	Monitoring The Future
MU	Medical use
NCHA	National College Health Assessment
N-MAPSS	National Monitoring of Adolescent Prescription Stimulants Study
NMU	Non-Medical Use
NSDUH	National Survey on Drug Use and Health
OMB	Office of Management and Budget
OR	Odds Ratio
SAMHSA	Substance Abuse and Mental Health Services Administration
SD	Standard Deviation
US	United States
VIF	Variance Inflation Factor

Abstract of Dissertation Presented to the Graduate School
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Problematic prescription opioid use has reached epidemic levels in the United States, with Non-Medical Use (NMU) contributing towards an increasing trend in overdose deaths. Research investigating risk factors for prescription opioid NMU among youth is important to identify areas where prevention strategies can be implemented, helping to reduce the fatal consequences of NMU in the US. While there have been studies highlighting sex differences in some risk factors for prescription opioid NMU in adults, there have been none among youth as young as 10 and 11 years nor with a comprehensive range of risk factors. A socio-ecological model framework was used to examine individual, relationship and community level factors which may confer additional risk of prescription opioid NMU or protect against it. The specific objective of the dissertation research was to examine sex differences in risk factors for prescription opioid NMU among US youth.

The National Monitoring of Adolescent Prescription Stimulants Study (N-MAPSS) is a national study that was conducted in 10 US cities from 2008 to 2011. This cross-sectional study design assessed use and NMU of prescription stimulants, opioids and other prescription medications in youth 10 to 18 years of age in urban, rural and suburban US (n=11,048). First, patterns of past 30 day prescription opioid NMU were examined by sex (Chapter 3). Second, the

effect of peer influence and parental guidance on past 30 day prescription opioid NMU were examined by sex (Chapter 4). Third, recalled age of first use of prescription opioids was examined as a risk factor for past 30 day prescription opioid NMU by sex (Chapter 5).

This dissertation enhances our knowledge of the problem of prescription opioid NMU in youth and how it varies between males and females. With this knowledge, we can design targeted prevention strategies for opioid NMU in youth, with the overall aim of reducing the burden of prescription opioid NMU in the US.

CHAPTER 1
INTRODUCTION

Prescription opioids are analgesics used to treat pain and as such are often referred to as prescription pain pills, pain relievers or painkillers. Examples include OxyContin®, Vicodin®, Darvocet®, Lortab®, Percocet®, oxycodone and hydrocodone. In the United States (US), these prescription opioids are currently listed as Schedule II drugs[1] by the Drug Enforcement Administration (DEA) due to their high potential for abuse, with the possibility of severe psychological or physical dependence (Drug Enforcement Administration, 2017). Most prescription opioids are only licensed for use among adults in the US; however, in 2015, extended release oxycodone was approved by the Food and Drug Administration (FDA) for use in children as young as 11 years of age with "pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate" (Yang, Chen, & Bennett, 2016). Prior to this date, off-label use of oxycodone and other prescription opioids among children was relatively common and considered acceptable, though the potential for abuse was still of concern (Yang et al., 2016). Non-medical use (NMU) of prescription opioids has been defined as use of someone else's prescription medication or use of a patient's own prescription in a way other than prescribed, such as to get high or for a reason that it was not intended for (Boyd & McCabe, 2008; Boyd, Teter, West, Morales, & McCabe, 2009; Shield, Jones, Rehm, & Fischer, 2013). NMU can include using someone else's medication to self-treat a medical condition or obtaining medications from a non-healthcare professional (e.g. a friend) or through "doctor shopping" (Boyd & McCabe, 2008). It can also include using a patient's own medication at higher doses than prescribed or in a way other than prescribed, such as by crushing

[1] Drugs are classified into five distinct categories, which is dependent on accepted medical use and abuse potential. Schedule V drugs have the lowest potential for abuse while schedule I drugs have the highest abuse potential and also have no accepted medical use.

pills and snorting or injecting them. The key distinction with using the term "non-medical use", compared to "misuse", is that NMU covers multiple categories of misuse and does not refer to just one specific behavior or pattern (Boyd & McCabe, 2008; National Institute on Drug Abuse, 2016).

Prevalence of Prescription Opioid Use and Consequences

Prescriptions for opioids have increased more than two-fold in the US in the past 25 years, from 107.3 million prescriptions written in 1992 to 246.2 million in 2015 (Pezalla, Rosen, Erensen, Haddox, & Mayne, 2017). The large increase in opioid prescriptions is of concern due to the numerous potentially serious consequences of prescription opioid NMU. There were 22,000 deaths in the US in 2015 from overdose of prescription opioids, an increase of 3000 deaths from 2014 (Centers for Disease Control and Prevention, 2017b). In total, there were 33,000 deaths in 2015 from opioid overdose, which includes heroin overdoses (Centers for Disease Control and Prevention, 2017b). The majority of drug overdoses in the US involve opioids and current estimates indicate that 175 Americans die every day from drug overdose (Christie et al., 2017). Consequences of NMU of prescription opioids are not only seen among adults; between 1997 and 2012, the rate of hospitalizations for prescription opioid poisonings for youth aged 15 to 19 years rose from 3.69 to 10.17 per 100,000 persons (Gaither, Leventhal, Ryan, & Camenga, 2016).

Aside from the potentially fatal consequences of prescription opioid NMU, pressure on healthcare resources is also an issue—for example, for every death due to prescription drug overdose among young adults, there are 22 treatment admissions and 119 emergency room visits (National Institute on Drug Abuse, 2016). Annual societal costs from prescription opioid abuse were estimated to be $55.7 billion in 2011; this accounts not only for healthcare resources ($25 billion), but for lost workplace productivity ($25.6 billion) and criminal justice system processes

($5.1 billion) (Birnbaum et al., 2011). Opioid use disorder is also important to consider with the recurrent use and NMU of prescription opioids; within the Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5), opioid use disorder consists of a "problematic pattern of opioid use leading to clinically significant impairment or distress", as manifested by at least two of the criteria listed in Table 1-1, occurring within a 12-month period (American Psychiatric Association, 2013). According to the National Survey on Drug Use and Heath (NSDUH), two million Americans (0.8%) had opioid use disorder in 2015 (Center for Behavioral Health Statistics and Quality, 2016). In addition, prescription opioid NMU has been identified as a risk factor for heroin use (Cerdá, Santaella, Marshall, Kim, & Martins, 2015; Compton, Jones, & Baldwin, 2016; National Institute on Drug Abuse, 2015; Palamar, Shearston, Dawson, Mateu-Gelabert, & Ompad, 2016), which is also an important public health concern because it is a schedule I drug with no accepted medical use and a high potential for abuse and overdose. Overdose deaths from heroin in the US have risen sharply in recent years, with 10,574 deaths reported in 2014 (National Institute on Drug Abuse, 2015).

NMU of Prescription Opioids among Youth

Prevalence of prescription opioid NMU among youth 10 to 18 years is lower than other age groups in the US, though it is still high enough to be an important public health concern. This age group immediately precedes young adults, who are the age group of greatest concern in the US; young adults 18 to 25 years have been observed to have the highest prevalence of prescription pain reliever NMU in the past 12 months (7.1%), as reported by the NSDUH (Center for Behavioral Health Statistics and Quality, 2017). NMU is related to many negative consequences. For example, among young adults, prescription drug overdose deaths increased four-fold between 1999 and 2014, of which the majority involved opioids (National Institute on Drug Abuse, 2016). Given that young adults may have been non-medical users in their youth and

continued this pattern of use as they grew older, preventing NMU among youth is a high priority. Previous research supports this, since approximately one third of older adolescents (aged 18 years) who use prescription opioids non-medically will continue such use as young adults (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2016; McCabe, Schulenberg, O'Malley, Patrick, & Kloska, 2014; Miech, Johnston, O'Malley, Keyes, & Heard, 2015).

Prevalence rates of prescription opioid use and NMU among youth are also of concern. The 2016 Monitoring The Future (MTF) survey among youth (13-18 years) revealed that older adolescents (12th graders) had the highest annual prevalence of OxyContin® and Vicodin® use (3.4% and 2.9%, respectively), compared to 8th graders (0.8% and 0.9%, respectively) who had the lowest annual prevalence (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2017). The 2016 NSDUH, conducted in the United States among 67,942 people 12 years of age and older, indicated that youth aged 12 to 17 years (n=17,109) had a prevalence of current (past 30 day) pain reliever NMU of 1.0%, while past 12 month prevalence was 3.5% (including those who had past 30 day NMU) (Substance Abuse and Mental Health Services Administration, 2017). Peak annual incidence rates of prescription opioid NMU in youth have previously been observed at age 16 years (Austic, McCabe, Stoddard, Ngo, & Boyd, 2015), but recent data has indicated that NMU initiation may be occurring at younger ages (Austic et al., 2015). Evidence from the literature highlights that addressing the current opioid epidemic is an important priority, though further evidence is needed to design effective prevention strategies to tackle this issue. Prevention strategies for opioid NMU in youth are vital to reduce opioid NMU in the future.

Sex Differences in Prescription Opioid NMU among Youth

While previous studies have not thoroughly investigated sex differences in risk factors for prescription opioid NMU among youth, risk factors regardless of sex have been examined. Marijuana (McCabe et al., 2011; Whiteside et al., 2013), alcohol (McCabe et al., 2011) and

tobacco use (McCabe et al., 2011) as well as poor school grades (Whiteside et al., 2013) have all been previously identified as risk factors for prescription opioid NMU in youth.

Studies of sex differences in adult prescription opioid NMU have been summarized previously (Serdarevic, Striley, & Cottler, 2017); one study using data from the NSDUH examined sex differences in youth (12 years and over) and adults combined, though prescription opioid NMU was assessed in the past 12 months rather than the past 30 days (Back, Payne, Simpson, & Brady, 2010). In addition, data on relationship and community level risk factors was not available for youth in this analysis and non-medical prescription opioid users were compared with medical users and non-users combined (Back et al., 2010). As such, there is a need for further studies that examine sex differences in risk factors for prescription opioid NMU specifically among youth.

Within the dataset proposed for this research, the National Monitoring of Adolescent Prescription Stimulants Study (N-MAPSS), the prevalence of past 30 day prescription opioid NMU is 3.1%, which is similar to that seen for NMU of pain relievers in youth from the past 12 months in the 2016 NSDUH (3.5%) (Center for Behavioral Health Statistics and Quality, 2017). Data is available on a wide variety of risk factors at individual, relationship and community level within N-MAPSS, and the sample has been shown to be mostly representative of US census data (Cottler, Striley, & Lasopa, 2013). As such, this is an appropriate dataset for examining prescription opioid NMU among US youth.

Need to Examine Sex Differences in Risk Factors for Prescription Opioid NMU among Youth 10 to 18 Years

The limitations of previous studies relate to four areas. First, the current literature focuses on youth 12 years and over, leaving out younger children aged 10 and 11 years. Second, previous studies have not examined sex differences in risk factors at individual, relationship and

community level in youth. Third, adults and youth have not been stratified and analyzed separately in previous studies. Fourth, because many of these studies required parental consent to participate and were conducted in the home or school setting, it is possible that social desirability bias was introduced. We can address these weaknesses with the dataset proposed for this research because it contains information on children as young as 10 years of age. The N-MAPSS survey collected numerous risk factors not previously captured in other studies at individual, relationship and community level. For example, N-MAPSS captured data on peer influence and parental guidance, which could not be obtained from prescription claims data or surveys that only examine individual risk factors for prescription opioid NMU. Social desirability bias was minimized in N-MAPSS because parental consent was not required to participate, due to the anonymous study design, and youth completed the surveys outside of home and school settings.

The N-MAPSS study is one of the largest studies of prescription medication use conducted among youth in the US to date. While its primary focus was on the use of prescription stimulants, many questions were also asked of the youth regarding other prescription medications including opioids. We previously conducted a preliminary study of individual level risk factors for prescription opioid NMU, examining sex differences in these risk factors in youth aged 10 to 18 years from N-MAPSS (Osborne, Serdarevic, Crooke, Striley, & Cottler, 2017). In comparison to results from the NSDUH, our preliminary work suggested different patterns in risk factors for opioid NMU in youth compared to those found in a NSDUH study of adults and youth combined. For example, tobacco use was found to be a risk factor for prescription opioid NMU among females in the NSDUH (Back et al., 2010); however, in our study, we found that tobacco use was a risk factor for prescription opioid NMU among both young males and females (Osborne et al., 2017). It is possible that observed differences in results can be explained by sex

differences that arise among youth only. As such, it is important to examine the risk factors for prescription opioid NMU among youth. In addition, this dissertation research goes beyond the known individual level risk factors for prescription opioid NMU and explores sex differences in multiple levels of risk factors within a theoretical framework, which is made possible as a result of the rich data collected.

Theoretical Framework

The theoretical framework which provides the basis for this dissertation is the socio-ecological model. This multi-level model contains four levels that are considered to interact with or influence behavior: individual, relationship, community and societal levels (Figure 1-1) (McLeroy, Bibeau, Steckler, & Glanz, 1988).

The socio-ecological model can be applied to prescription opioid NMU among youth at all levels, though the focus of this dissertation is on the individual, relationship and community levels. The Substance Abuse and Mental Health Services Administration (SAMHSA) uses this model as a basis for prescription drug NMU prevention strategies because it is a multi-level framework that allows different contexts and settings for risk and protective factors to be considered (Substance Abuse and Mental Health Services Administration, 2016). The foundation of the socio-ecological model is that people are influenced by their own specific traits, their relationships with others, the community where they live and the broader society in which those communities are placed (Substance Abuse and Mental Health Services Administration, 2016). The first level (individual) consists of biological and personal factors that increase the likelihood of prescription opioid NMU, while the second level (relationships) consists of close relationships that may impact the risk of prescription opioid NMU, either as risk factors or protective factors. The third level in the socio-ecological model is community, which focuses on the settings in which social relationships occur, such as area or city of residence and neighborhoods. Finally,

the fourth level of the model is the societal level which includes factors such as social norms and educational policies which can lead to inequality. The societal level cannot be explored within this dissertation because there is no variable within the N-MAPSS dataset which can represent this level; however, factors at all other levels are available and can be examined. Within this dissertation, factors at the individual level to be examined include age, sex, depressive symptoms, anxiety symptoms and lifetime use of alcohol, marijuana, tobacco and prescription opioids (Table 1-2). Factors at the relationship level to be examined include home setting (who youth live with), parental warnings against substance use, sources of prescription opioids, number of close friends, number of close friends using other substances and ever obtaining alcohol from friends or parents. At the community level, urban area of residence will be examined.

The socio-ecological model focuses on the multifaceted and interactive effects of different elements, such as personal and environmental factors, that influence a person's behavior. One individual factor should be exclusively highlighted within the context of the model: Sex. Biological sex itself may not be a true risk factor for prescription opioid NMU, but sex differences could arise because behavior is influenced by other factors which differ by sex. For example, at the relationship level, parental monitoring and guidance may differ by sex, with different expectations directed towards males and females (Hyde, 2014; Witt, 1997). Children internalize these sex specific norms at a young age and stereotypes based on sex are subsequently established (Hyde, 2014; Kågesten et al., 2016; Witt, 1997). This could be reinforced at the community level, within areas of residence (urban, sub-urban or rural). Individual level factors such as anxiety symptoms and other substance use may differ by sex because these factors are influenced by determinants at relationship and community levels. For

example, substance use is often influenced by social networks and factors such as peer pressure (Chan, Kelly, Carroll, & Williams, 2017; Karakos, 2014; Kristjansson, Sigfusdottir, & Allegrante, 2013; Mayberry, Espelage, & Koenig, 2009; McDonough, Jose, & Stuart, 2016), which may vary by sex specific norms. Other studies using a socio-ecological framework have shown that relationship level variables, such as parental monitoring and respect, and behavioral outcomes can differ for males and females (Jacobson & Crockett, 2000; Miles et al., 2015). The aims and hypotheses within this dissertation examine whether the influence of individual, relationship and community level factors (Table 1-2) for prescription opioid NMU differ by sex, in the context of the socio-ecological model. Identification of sex differences in risk and protective factors at these levels can help to guide targeted prevention strategies for prescription opioid NMU.

Aims and Hypotheses

The specific objective of the dissertation research is to examine sex differences in risk factors for prescription opioid NMU among US youth. A socio-ecological model framework will be used to examine individual, relationship and community level factors which may confer additional risk of prescription opioid NMU or protect against it.

Aim 1: Examine Sex Differences in Patterns of Prescription Opioid NMU.

This analysis will describe how youth are using their own prescribed opioids and where they are obtained without a prescription. Information is available on source of opioids, route of administration and whether opioids were obtained from a healthcare professional. Three patterns of past 30 day NMU will be examined in detail: use of someone else's opioids only, use by a non-oral route only and both use of someone else's opioids and non-oral use. The influence of relationships with others will be explored by examining sources of opioids (use of opioids that belonged to parents, peers and other sources), while various individual and community level risk

factors for each pattern of NMU will be analyzed by sex. Sex differences will be evaluated in the context of the socio-ecological model framework because males and females are expected to conform to different standards from a young age, with sex specific norms and stereotypes established by parents and other external influences (Hyde, 2014; Witt, 1997). Within this analysis, we will investigate whether males and females obtain opioids from different sources and exhibit different behavior in how they use their prescription opioids non-medically. Based on the socio-ecological model framework and previous research for other substances, our hypothesis is that females will be less likely to engage in more than one pattern of NMU compared to males. This could be due to the protective effect of increased parental guidance, monitoring and support among females (Dunn, Kitts, Lewis, Goodrow, & Scherzer, 2011; Jacobson & Crockett, 2000). An additional hypothesis is that females will be less likely to obtain opioids from more than one source compared to males. This may be due to the protective effect of parental guidance and monitoring among females resulting in a decrease in the number of peers who would share opioids for NMU, thereby decreasing availability and the number of sources. We can test these hypotheses within a socio-ecological model framework, controlling for individual and community level factors. This is important to determine that any identified effect is not merely the result of confounding by another factor, which can be concluded if the effect remains after controlling for individual and community level factors.

Two hypotheses are proposed for the first aim among 10,965 youth (345 with past 30 day NMU of prescription opioids):

Hypothesis 1. Among youth who obtained opioids from other sources, females will be less likely to obtain opioids from two or more sources compared to males, after controlling for factors at individual and community levels.

Hypothesis 2. Among the three patterns of prescription opioid NMU, females will be less likely to use both someone else's opioids and have non-oral use (two patterns of NMU) compared to males, after controlling for factors at individual and community levels.

Aim 2. Examine the Effect of Peer Influence and Parental Guidance on Patterns of Prescription Opioid Use, including NMU, among Males and Females Separately.

This analysis will establish the parental and peer relationship factors that influence past 30 day prescription opioid NMU among youth and whether these factors confer protection or additional risk in the context of the other risk factors found to be associated with prescription opioid NMU. The interaction of parental and peer risk factors will be assessed and the influence of each factor will be examined separately for males and females to investigate sex specific effects. Our previous work has examined the risk factors for prescription opioid NMU at individual level (Osborne et al., 2017), in addition to how youth are obtaining and using their prescription opioids non-medically (Aim 1, Chapter 3). We discovered that females most often reported using opioids that belonged to a parent or classmate, while males most often reported using opioids that belonged to a classmate. These results suggest that parental and peer influences should be examined further with regards to prescription opioid NMU among youth and that sex differences in these relationship level factors are likely to be present. Within the context of the socio-ecological model, parental guidance may have a differential influence for males and females given different expectations and norms. Based on the theoretical framework and our previous findings, we hypothesize that males will be more likely than females to be influenced by peer factors. Females will be more likely than males to be influenced by parental factors, though peer factors will also have some influence. A moderating effect of parental guidance on peer influence may also be present. This can be tested by examining the likelihood

of prescription opioid MU and NMU (with no use of prescription opioids as the reference group) for different relationship level predictors, among males and females separately.

Three hypotheses are proposed for the second aim among 10,965 youth:

Hypothesis 1. For each additional close friend who uses other substances (marijuana or tobacco), the odds of prescription opioid NMU, but not MU, will increase among males, but not females, after controlling for individual, relationship and community level factors, when compared to no use of prescription opioids in the past 30 days.

Hypothesis 2. Females who are given alcohol by their parents (vs females who are not given alcohol by their parents) will have increased odds of prescription opioid NMU, but not MU, compared to no use of prescription opioids in the past 30 days, after controlling for individual, relationship and community level factors.

Hypothesis 3. Parental guidance will moderate the relationship between number of close friends using other substances (tobacco or marijuana) and prescription opioid NMU, but not MU, among females only. Three parental guidance variables will be examined:

- Warnings by a parent against using illicit substances
- Currently living with at least one parent
- Parent has not given alcohol to the child

Aim 3. Examine Sex Differences in the Effect of Recalled Age of First Use of Prescription Opioids on Prescription Opioid NMU among 17 and 18 Year Olds.

This analysis will examine how the recalled age of first use of prescription opioids affects past 30 day NMU and whether this effect is also influenced by sex. All statistically significant individual, relationship and community level factors will be included in the final model, to determine if recalled age of first use is associated with past 30 day NMU after controlling for factors at other levels of the socio-ecological model. Given that peak annual incidence rates of NMU have been previously observed at age 16 years (Austic et al., 2015), recalled age of first

use of prescription opioids and past 30 day NMU should be explored among older adolescents (17 and 18 years) to determine whether past 30 day risk of NMU is influenced by the age opioids were first used (as recalled by the adolescent). Sex differences should be examined due to our previous findings regarding risk factors for prescription opioid NMU among youth (Osborne et al., 2017). In addition, within the context of the socio-ecological model, sex differences in age of first use may occur because of differing parental and peer influences. As such, it is possible that males may be given prescription opioids at a younger age, or obtain them for NMU at a younger age, compared to females. This can be tested by examining the effect of recalled age of first use on likelihood of past 30 day prescription opioid use and NMU for males and females.

Two hypotheses are proposed for the third aim among 278 youth 17 and 18 years of age with past 30 day use of prescription opioids:

Hypothesis 1. Recalled age of first use of prescription opioids will occur earlier for males compared to females regardless of type of use pattern (NMU or MU only).

Hypothesis 2. Recalled age of first use of prescription opioids will occur earlier for past 30 day NMU compared to MU, regardless of sex, after controlling for other individual, relationship and community level factors.

Potential Implications

The expected outcomes of the proposed project will enhance our knowledge of the risk factors for prescription opioid NMU in youth and how these vary between males and females. With this knowledge, we may be able to more efficiently design prevention strategies at individual, relationship and community levels to prevent prescription opioid NMU in youth, with the overall aim of reducing the burden of prescription opioid NMU in the US. At the individual level, prevention strategies could be implemented through education and promotion of attitudes and behaviors that prevent prescription opioid NMU. At the relationship level, the focus could be

on parental prevention and peer programs designed to prevent and reduce prescription opioid NMU. Finally, at the community level, prevention strategies could be targeted to areas where prescription opioid NMU is more prevalent. Tailoring these strategies towards males and females separately based on identified risk factors is likely to reduce costs and increase efficiency. Reducing prescription opioid NMU rates among youth through these strategies may have the following impacts on the opioid epidemic in the US: (1) NMU rates will reduce among young adults, which is the age group of greatest concern in the US, (2) overdose, poisoning, opioid use disorder and hospitalization rates related to prescription opioid NMU will decline, (3) heroin use and overdoses may also decline if associated with prescription opioid NMU and (4) annual societal costs related to prescription opioid NMU will be reduced.

Strengths and Limitations

In N-MAPSS, we were able to obtain a sample distribution for age, gender, race and urban/rural composition nearly comparable to US Census data (Cottler et al., 2013), suggesting a highly representative sample. Participants were recruited from entertainment venues and surveys were conducted outside of the home, unlike the NSDUH. Consequently, participants may have been more comfortable answering questions about the sensitive subject area of drug use, minimizing non-response. The survey was also completely anonymous and no identifying information was collected. Unlike in the NSDUH and MTF studies, parental consent was not required, therefore participants may have been more likely to respond truthfully to questions about drug use, reducing social desirability bias. A main strength of N-MAPSS is that information was collected on risk factors at individual, relationship and community level, allowing us to examine the effect of these on the risk of prescription opioid NMU among youth. A further advantage is that data was collected from youth as young as 10 years of age, which is younger than for other national surveys such as the NSDUH. While NMU may not be common

until later in adolescence, studying youth at younger ages is important to capture data on risk factors which may influence subsequent drug use patterns.

Some limitations are present. Because this study was anonymous, no follow up data are available to allow examination of changing prevalence in opioid NMU over time. In addition, we could not examine whether certain risk factors, such as obtaining alcohol from parents, occurred prior to initiation of NMU. Only recalled age of first use (as self-reported by the participant) was available in this study, which may not be as accurate as using age of first use as reported in medical records or claims data. While we recognize this limitation, identification of NMU within medical records or claims data is difficult and likely to result in under ascertainment of the outcome. Several patterns of NMU, such as using opioids that belong to someone else, are unlikely to be captured at all. Age of first NMU of prescription opioids was not available in N-MAPSS and only recalled age of first use (regardless of NMU or MU) could be analyzed; however, age of initiation of NMU has been examined previously in other studies (Deandrea, Troost, & Anthony, 2013; Meier, Troost, & Anthony, 2012). Our work adds to the literature in that we examined recalled age of first use regardless of pattern of use (NMU or MU only). Another important consideration is that N-MAPSS collected information on past 30 day prescription opioid NMU but no other time periods; it is possible that youth had NMU in the time period prior to the past 30 days but no use in the past 30 days and were thus excluded from our analysis. Under-reporting is possible in this study due to the self-reported design. In addition, information on dose of prescription opioids was not collected, although participants were shown pictures of the opioids at different doses. N-MAPSS also did not obtain information on certain factors, such as parental warnings specifically against prescription opioid NMU, which would have been useful to examine. Finally, NMU of a person's former but not current prescription or

obtainment from another source (e.g. theft) was not specifically asked on this questionnaire. Misclassification of the outcome is possible as a result though this is likely to be non-differential, so estimates of effect would be biased towards the null.

Overall, the N-MAPSS dataset provides a unique opportunity to examine the effect of sex differences on risk factors for prescription opioid NMU among youth within a socio-ecological framework. While some limitations are present, this dataset can adequately address the aims of the dissertation research and has several strengths over other available data sources.

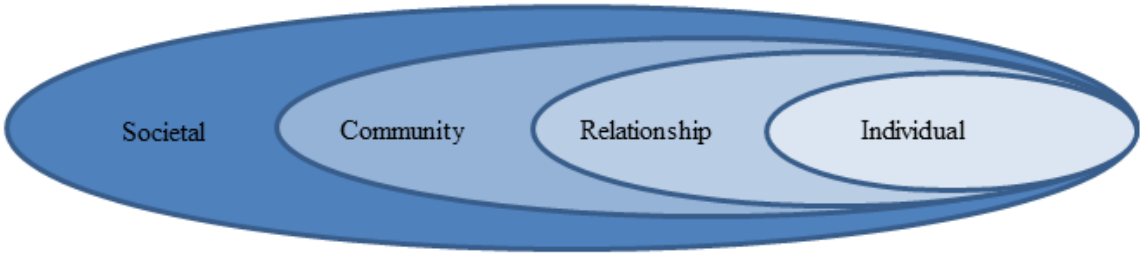


Figure 1-1. The Socio-ecological Model.

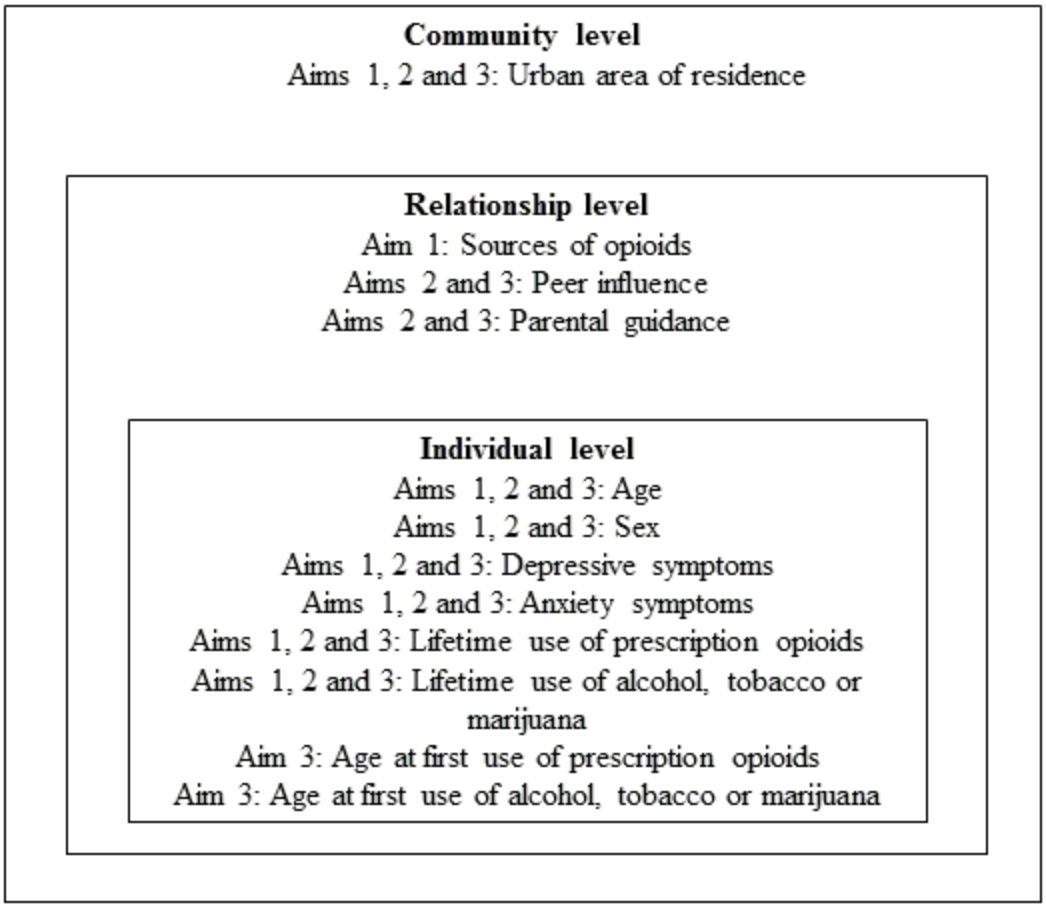


Figure 1-2. N-MAPSS variables to be examined for each aim within the context of the socio-ecological model.

Table 1-1. Opioid use disorder diagnostic criteria (American Psychiatric Association, 2013).

Diagnostic criteria
1. "Opioids are often taken in larger amounts or over a longer period than was intended."
2. "There is a persistent desire or unsuccessful efforts to cut down or control opioid use."
3. "A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects."
4. "Craving, or a strong desire or urge to use opioids."
5. "Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home."
6. "Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids."
7. "Important social, occupational, or recreational activities are given up or reduced because of opioid use."
8. "Recurrent opioid use in situations in which it is physically hazardous."
9. "Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance."
10. Tolerance, as defined by:
a. "A need for markedly increased amounts of opioids to achieve intoxication or desired effect."
b. "A markedly diminished effect with continued use of the same amount of an opioid."
"Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision."
11. Withdrawal, as defined by:
a. "The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal)."
b. "Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms."
"Note: This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision."

Table 1-2. N-MAPSS variables to be examined within levels of the socio-ecological model.

Socio-ecological model level	Variable	Questions	Answers
Individual	Age	How old are you?	10, 11, 12, 13, 14, 15, 16, 17, 18
	Sex	What is your gender?	Male, Female
	Depressive symptoms	In the last 12 months, have you had 2 weeks or more when you felt down or depressed?	No, Yes
	Depressive symptoms	In the last 12 months, have you had 2 weeks or more when you lost interest in things?	No, Yes
	Anxiety symptoms	Have you ever felt worried or stressed for 6 months or more?	No, Yes
	Lifetime use of marijuana	Have you ever used marijuana?	No, Yes
	Age at first use of marijuana	At what age did you first use marijuana?	___ years old
	Lifetime use of alcohol	Have you ever had a beer, a glass of wine, or any other alcoholic drink, not just a sip?	No, Yes
	Age at first use of alcohol	At what age did you first have a full alcoholic drink?	___ years old
	Lifetime use of tobacco	Have you ever smoked a cigarette?	No, Yes
	Age at first use of tobacco	At what age did you smoke your first cigarette?	___ years old
	Lifetime use of prescription opioids	Have you ever taken [Specific drug name [a]]?	No, Yes
	Lifetime use of opioids with a prescription	Was it prescribed for you?	No, Yes
Relationship	Home setting	In the last 7 days, who have you lived with?	Living with mom and dad at the same time, living with mom and dad, but not at the same time, living with mom only, living with dad only, living with other relatives, living with foster parents, other
	Parental warnings against substance use	In the past 12 months, how often has a parent or guardian warned you not to use [substances [b]]?	Never, sometimes, often
	Source of opioids in the past 30 days	In the last 30 days, have you used [Specific drug name [c]] that belonged to…	One of your parents, your brother or sister, a different family member, someone from school, someone from work, someone you don't know, someone not listed above
	Number of close friends	How many close friends do you have?	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, more than 10
	Number of close friends using substances	How many of your close friends have tried [substances [d]], even once?	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, more than 10
	Ever obtained alcohol from friends	Have you ever gotten alcohol from your friend?	No, Yes
	Ever obtained alcohol from parents	Have you ever gotten alcohol from your parent?	No, Yes
Community	Urban area of residence	What is the zip code where you live most of the time?	___ ___ ___ ___ ___

[a] Lifetime prescription opioids assessed were: Percocet®, codeine, Lortab®, Darvocet®; [b] Substances assessed separately: Alcohol, tobacco, marijuana; [c] Past 30 day prescription opioids assessed were: Vicodin®, hydrocodone, OxyContin® and oxycodone; [d] Substances assessed separately: Marijuana, tobacco

CHAPTER 2
DATA SOURCE

The National Monitoring of Adolescent Prescription Stimulants Study (N-MAPSS)

N-MAPSS was a national study conducted in four waves from 2008 to 2011 (Cottler et al., 2013). Wave one was conducted in Fall 2008, wave two in Spring 2009, wave three in Fall 2010 and wave four in Spring 2011. This cross-sectional study design assessed use and NMU of prescription stimulants, opioids and other prescription medications.

Recruitment

Participants 10 to 18 years of age were recruited for the study from entertainment venues, such as malls and other shopping areas, parks and playgrounds, libraries, coffee shops, ball parks, arcades, cinemas, skate parks and recreation centers, in urban, rural and suburban areas of 10 cities across the US (Figure 2-1). A sampling frame of entertainment venues was developed for the study and recruitment days and times were randomized, as per the entertainment venue intercept methodology (Muhib et al., 2001). This approach approximates to random sampling (Muhib et al., 2001). Criteria for venue selection included being in the zip code boundary, being youth friendly, having a large customer base, being age-level appropriate and being amenable to study recruitment. Recruiters approached 21,444 youth during the four waves and invited them to participate in the study. Recruiters were instructed to complete a screener for every potential respondent with whom they made verbal contact. Information documented from observation on the screener was city, date, time, gender, race/ethnicity and number of eligible youth in group. Information documented from verbal contact on the screener was age (could also be observed), grade and zip code. To be eligible for the study, participants had to be 10 to 18 years of age and reside in an urban, suburban or rural zip code of one of ten cities, precoded in manuals for ease of use (see section Geographical Location). Those unaware of their zip code, non-English

readers, those who were cognitively impaired and those in college were excluded from the study. Of 16,143 potentially eligible youth, 3,403 (21.1%) were found to be ineligible (Cottler et al., 2013). Of 12,740 eligible youth, 1,272 did not stop to hear about the study and are noted as refusals (10.0%) (Cottler et al., 2013). In total, 11,048 youth completed the survey. Assent was implied as indicated by survey completion. Parental permission was not solicited as per Washington University and University of Florida Human Protection Research Offices because all survey data were anonymous. The research protocol was approved by the Washington University Human Protection Research Office and the University of Florida Institutional Review Board. Each participant was provided with a $10 gift card from a national electronics store as remuneration.

Geographical Location

Cities included in the survey were selected from among the ten Office of Management and Budget (OMB) regions originating from states with the highest rate of stimulant prescribing patterns (as identified from the IMS Health database), which was the intended primary target of the study. The cities included: Seattle, Los Angeles, Denver, St. Louis, Houston, Cincinnati, Tampa, Philadelphia, New York and Boston. Recruitment goals for urban, rural and suburban areas were established in order to ensure adequate participation of youth from all areas; the goals were 50% urban, 30% suburban and 20% rural. Urban, rural and suburban status was determined by the participant's zip code, accounting for city limits, proximity to the city limits and population density. All zip codes that were contained within a selected city boundary were coded as urban. The urban zip code clusters that contained the city limits comprised the anchor zip code cluster ring for the catchment area. Adjacent zip codes to the anchor zip code cluster ring were coded as suburban and comprised the suburban zip code cluster ring, while zip code clusters that were adjacent to the suburban zip code cluster ring comprised the rural zip code cluster ring.

Suburban and rural areas were not designated based on zip code alone but also by population density; suburban areas consisted of a population density less than urban, but more than rural, because there is no US census definition of a suburb. Zip codes contiguous to suburban areas with fewer than 1000 persons per square mile were considered rural. Recruitment goals also sought an adequate balance of all ages of interest. This venue intercept method proved effective in obtaining a representative sample of youth. Specifically, in N-MAPSS, we were able to obtain a sample distribution for age, sex, race and urban/rural composition comparable to 2010 US Census data (Cottler et al., 2013).

Data Collection

Youth were given hard copies of surveys to answer in a private location in the venues from where they were recruited. Youth aged 10 and 11 were interviewed using the survey where requested to reduce errors due to problems with reading or reading comprehension. Questions about prescription medications contained photographs of the medications to facilitate identification (Figure 2-2). Completion time for the survey was approximately 20 minutes. Those with missing values for recent opioid use are excluded from all analyses (n=83), which leaves a final sample of 10,965 youth; 5234 males and 5731 females.

Survey Development

The survey used within N-MAPSS was developed from two assessments- (1) The Substance Abuse Module, which has been rigorously tested and found to be a reliable screening tool for substance abuse and (2) The Washington University Risk Behavior Assessment for NMU risk factors. The N-MAPSS survey was divided into two sections. The first section asked questions about demographics and assessed mental health and behavioral characteristics. The second section assessed prescription medication use, including stimulants, sedatives and opioids. The survey presented photographs of these medications at different doses and for different

formulations. Specifically for prescription opioids, questions asked about Vicodin® or hydrocodone use in the past 30 days, with pictures of Vicodin® 5mg, 7.5mg and 10mg presented. Questions also asked about OxyContin® or oxycodone use in the past 30 days, with pictures of OxyContin® 10mg, 20mg and 40mg presented (Figure 2-2).

Variables

Prescription Opioids

Past 30 day prescription opioid use was assessed for Vicodin®, hydrocodone, OxyContin® and oxycodone using various questions, as indicated in Table 2-1. Recalled age of first use of prescription opioids was also assessed where respondents reported past 30 day use of prescription opioids. Lifetime prescription opioid use was assessed for Percocet®, codeine, Lortab® and Darvocet®.

Individual Level Variables

Age and sex were assessed in the survey, along with depressive symptoms, anxiety symptoms, lifetime use and age of first use of alcohol, tobacco and marijuana (Table 2-2).

Relationship Level Variables

Factors examined at relationship level were: home setting, number of close friends, number of close friends using substances, parental warnings against substance use and ever obtaining alcohol from friends or parents (Table 2-3). Parental warnings against substance use was analyzed as a binary variable (yes or no) in all analyses.

Community Level Variables

Zip code was collected during the survey which was used to categorize area of residence as urban, suburban or rural (Table 2-4). Urban area of residence was analyzed as a binary variable (yes or no) in all analyses.

Prescription Opioid Use Categories

Prevalence of prescription opioid use within N-MAPSS is summarized in Figure 2-3. NMU was defined as: (1) use other than by mouth (for Vicodin®, hydrocodone, OxyContin® and oxycodone: "In the last 30 days, what are all the ways you used [specific drug name]?") and/or (2) use of someone else's opioids ("In the last 30 days, have you used [specific drug name] that belonged to [List of responses]" (Table 2-2). MU only was defined as those who had a prescription and no evidence of NMU. Respondents who answered "Yes" to the question "In the last 30 days, have you gotten a prescription or refill for [specific drug name] from [List of responses]?" were identified as having a prescription (Table 2-5). Three mutually exclusive groups of past 30 day prescription opioid users were derived: (1) individuals who did not use any prescription opioid (no use in the past 30 days); (2) individuals who only used prescription opioids as prescribed (MU only) in the past 30 days and (3) individuals who reported any NMU, with or without MU, in the past 30 days.

Figure 2-1. N-MAPSS recruitment sites.

102. In the last 30 days, have you taken Vicodin or Hydrocodone? Examples are pictured above.

○ No → **GO TO 107**

○ Yes

103. How old were you the first time you took Vicodin?

___ ___ years old

104. In the last 30 days, what are all the ways you used Vicodin? Choose all that apply.

○ By mouth

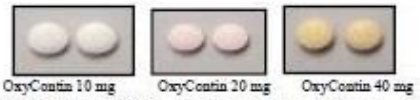
○ Snorted or sniffed

○ Smoked

○ Other: _____

105. In the last 30 days, have you gotten a prescription or refill for Vicodin from…	**NO**	**YES**
a. A psychiatrist?	○	○
b. Your doctor?	○	○
c. Your dentist?	○	○

106. In the last 30 days, have you used Vicodin that belonged to…	**NO**	**YES**
a. One of your parents?	○	○
b. Your brother or sister?	○	○
c. A different family member?	○	○
d. Someone from school?	○	○
e. Someone from work?	○	○
f. Someone you don't know?	○	○
g. Someone not listed above?	○	○



107. In the last 30 days, have you taken OxyContin or Oxycodone? Examples are pictured above.

○ No → **GO TO 112**

○ Yes

108. How old were you the first time you took OxyContin?

___ ___ years old

109. In the last 30 days, what are all the ways you used OxyContin? Choose all that apply.

○ By mouth

○ Snorted or sniffed

○ Smoked

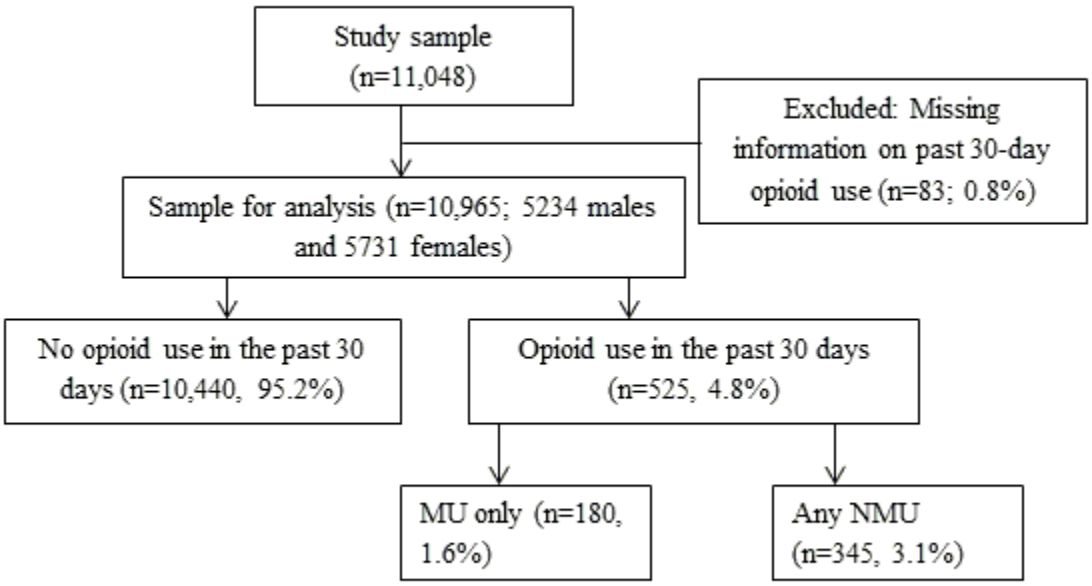
○ Other: _____

110. In the last 30 days, have you gotten a prescription or refill for OxyContin from…	**NO**	**YES**
a. A psychiatrist?	○	○
b. Your doctor?	○	○
c. Your dentist?	○	○

111. In the last 30 days, have you used OxyContin that belonged to…	**NO**	**YES**
a. One of your parents?	○	○
b. Your brother or sister?	○	○
c. A different family member?	○	○
d. Someone from school?	○	○
e. Someone from work?	○	○
f. Someone you don't know?	○	○
g. Someone not listed above?	○	○

20

Figure 2-2. N-MAPSS questionnaire page regarding past 30 day prescription opioid use.



MU=Medical Use; NMU=Non-Medical Use

Figure 2-3. Flow chart of prescription opioid use in N-MAPSS.

Table 2-1. Questions and variables in N-MAPSS for prescription opioids.

Variable	Question no.	Questions	Answers
Prescription opioid use in past 30 days	102, 107	In the last 30 days, have you taken [Specific drug name [a]]? Examples are pictured above.	No, Yes
Age of first use of prescription opioids	103, 108	How old were you the first time you took [Specific drug name [a]]?	___ years old
Types of use of prescription opioids	104, 109	In the last 30 days, what are all the ways you used [Specific drug name [a]]? Choose all that apply.	By mouth, snorted or sniffed, smoked, other
Prescription source in past 30 days	105, 110	In the last 30 days, have you gotten a prescription or refill for [Specific drug name [a]] from…	A psychiatrist, your doctor, your dentist
Source of prescription opioids in past 30 days	106, 111	In the last 30 days, have you used [Specific drug name [a]] that belonged to…	One of your parents, your brother or sister, a different family member, someone from school, someone from work, someone you don't know, someone not listed above
Lifetime prescription opioid use	112e, f, g, h	Have you ever taken [Specific drug name [b]]?	No, Yes
Lifetime use with a prescription	112e, f, g, h	Was it prescribed for you? [b]	No, Yes

[a] Past 30 day prescription opioids assessed were: Vicodin®, hydrocodone, OxyContin® and oxycodone; [b] Lifetime prescription opioids assessed were: Percocet®, codeine, Lortab®, Darvocet®

Table 2-2. Questions and variables in N-MAPSS for individual level variables.

Variable	Question no.	Questions	Answers
Age	2	How old are you?	10, 11, 12, 13, 14, 15, 16, 17, 18
Sex	1	What is your gender?	Male, Female
Depressive symptoms	035b	In the last 12 months, have you had 2 weeks or more when you felt down or depressed?	No, Yes
Depressive symptoms	035a	In the last 12 months, have you had 2 weeks or more when you lost interest in things?	No, Yes
Anxiety symptoms	036a	Have you ever felt worried or stressed for 6 months or more?	No, Yes
Lifetime use of marijuana	114	Have you ever used marijuana?	No, Yes
Age at first use of marijuana	115	At what age did you first use marijuana?	___ years old
Lifetime use of alcohol	124	Have you ever had a beer, a glass of wine, or any other alcoholic drink, not just a sip?	No, Yes
Age at first use of alcohol	125	At what age did you first have a full alcoholic drink?	___ years old
Lifetime use of tobacco	120	Have you ever smoked a cigarette?	No, Yes
Age at first use of tobacco	121	At what age did you smoke your first cigarette?	___ years old

Table 2-3. Questions and variables in N-MAPSS for relationship level variables.

Variable	Question no.	Questions	Answers
Home setting	6	In the last 7 days, who have you lived with?	Living with mom and dad at the same time, living with mom and dad, but not at the same time, living with mom only, living with dad only, living with other relatives, living with foster parents, other
Parental warnings against substance use	118a, 123b, 129h	In the past 12 months, how often has a parent or guardian warned you not to use [substances [a]]?	Never, sometimes, often
Number of close friends	134	How many close friends do you have?	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, more than 10
Number of close friends using substances	135a, 135b	How many of your close friends have tried [substances [b]], even once?	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, more than 10
Ever obtained alcohol from friends	129e	Have you ever gotten alcohol from your friend?	No, Yes
Ever obtained alcohol from parents	129a	Have you ever gotten alcohol from your parent?	No, Yes

[a] Substances assessed separately: Alcohol, tobacco, marijuana; [b] Substances assessed separately: Marijuana, tobacco

Table 2-4. Questions and variables in N-MAPSS for community level variables.

Variable	Question no.	Questions	Answers
Urban area of residence	5	What is the zip code where you live most of the time?	___ ___ ___ ___ ___

Table 2-5. Definition of prescription opioid NMU in N-MAPSS.

Variable	Questions	Responses	Coding
MU only	"In the last 30 days, have you gotten a prescription or refill for [specific drug name [a]] from [list of responses]?	Use with a prescription	MU only = Use with a prescription AND No evidence of NMU
NMU (any)	"In the last 30 days, what are all the ways you used [specific drug name [a]]?")	Use other than by mouth	NMU (any) = Use other than by mouth AND/OR Use of someone else's opioids
NMU (any)	"In the last 30 days, have you used [specific drug name [a]] that belonged to [list of responses]"	Use of someone else's opioids	

[a] Prescription opioids assessed were: Vicodin®, hydrocodone, OxyContin® and oxycodone

CHAPTER 3
SEX DIFFERENCES IN PATTERNS OF NON-MEDICAL PRESCRIPTION OPIOID USE IN YOUTH

Background

Non-medical use (NMU) of prescription opioids is a concern in the United States (US) because prescription opioid use has increased dramatically in the past 25 years and NMU is associated many adverse consequences, including increased risk of overdose (Mojtabai, 2017; National Institute on Drug Abuse, 2014b; Pezalla et al., 2017). In 2015, there were 22,000 deaths in the US from overdose of prescription opioids, an increase of nearly 3000 deaths from 2014 (Centers for Disease Control and Prevention, 2017b). NMU of prescription drugs (including prescription opioids) has been defined as use of someone else's prescription medication or use of a patient's own prescription in a way other than prescribed (Boyd & McCabe, 2008; Boyd et al., 2009; Shield et al., 2013). It can include using someone else's medication to self-treat a medical condition or obtaining medications from a non-healthcare professional (e.g. a friend) or through "doctor shopping" (Boyd & McCabe, 2008). Obtaining opioids from another source or using opioids in a way other than prescribed are two different patterns of NMU, which is the focus of this analysis. Medical Use (MU) is defined as prescription opioid use in accordance with the instructions from a prescriber (McCabe, West, & Boyd, 2013b).

Youth 10 to 18 years are an age group of concern for NMU of opioids for several reasons. First, the prevalence of NMU in this age group is not insignificant. The 2016 National Survey on Drug Use and Health (NSDUH), conducted in the US on 67,942 people 12 years of age and older, indicated that youth aged 12 to 17 years (n=17,109) had a current (past 30 day) prevalence of NMU of pain relievers of 1.0% and a past 12 month prevalence of 3.5% (Substance Abuse and Mental Health Services Administration, 2017). Second, this age group precedes young adults aged 18 to 25 years, who are known to have the highest prevalence of

NMU in the US and may have started prescription opioid NMU in their youth. Analyses of data from the Monitoring the Future (MTF) survey have revealed that approximately one third of older adolescents (aged 18 years) who use prescription opioids non-medically will continue NMU in the future (McCabe et al., 2014; Miech et al., 2015). Third, consequences of NMU in this age group have been observed previously; between 1997 and 2012, the rate of hospitalizations for prescription opioid poisonings for youth aged 15 to 19 years rose from 3.69 to 10.17 per 100,000 persons (Gaither et al., 2016). Given this evidence, earlier interventions to prevent prescription opioid NMU in youth are important.

Strategies to change behavior can be aided by the use of theoretical models which aim to both explain behavior and provide reasoning for how behavior can be changed. The socio-ecological model contains four levels which are considered to interact with or influence behavior: individual, relationship, community and societal levels (McLeroy et al., 1988). Within this analysis, the societal level was not examined. The premise of the model is that people are not only influenced by their own specific traits, but are also affected by their relationships with others, the community where they live and the broader society in which those communities are placed (Substance Abuse and Mental Health Services Administration, 2016). The individual level involves biological and personal factors that influence behavior, while the relationship level consists of close relationships with others. The community level refers to the area where people reside. All of these levels may influence NMU of prescription opioids.

One individual factor should be highlighted within the context of the model: Sex. Sex may not be an actual risk factor for prescription opioid NMU, but sex differences may occur because behavior is influenced by other factors which differ by sex. For example, at the relationship level, parental monitoring and guidance may differ by sex, with different

expectations directed towards males and females (Hyde, 2014; Witt, 1997). Within this analysis, we investigated whether males and females obtained opioids from different sources and exhibited different behavior in how they used their prescription opioids non-medically. Based on the theoretical framework and previous research for other substances, our hypothesis is that females will be less likely to engage in more than one pattern of NMU compared to males. This could be due to the protective effect of increased parental guidance, monitoring and support among females (Dunn et al., 2011; Jacobson & Crockett, 2000). An additional hypothesis is that females will be less likely to obtain opioids from more than one source compared to males. This may be due to the protective effect of parental guidance and monitoring among females resulting in a decrease in the number of peers who would share opioids for NMU, thereby decreasing availability and the number of sources. We can test these hypotheses within a socio-ecological framework, controlling for individual and community level factors. Controlling for other factors is important to determine that any identified effect is not merely the result of confounding. This can be concluded if the effect remains after controlling for individual and community level factors.

Studies of sex differences in adult prescription opioid NMU have been summarized previously (Serdarevic et al., 2017), but there have been limited studies among youth. A recent study of adolescents 13 to 18 years entering substance treatment programs examined past 30 day abuse of prescription opioids and specific routes of administration of hydrocodone products; however, a limitation is that the study did not stratify by sex and did not examine sources of opioids (Cassidy, Oyedele, Mickle, Guenther, & Budman, 2017). A study among high school seniors revealed that 36.9% of those with past 12 month NMU of prescription opioids obtained the medications from their own previous leftover prescriptions, while another common source

was friends or relatives. The distribution of sources was 14.4% leftover previous prescriptions only, 63.2% from another source only and 22.5% both their leftover prescription and another source (McCabe, West, & Boyd, 2013a). This paper revealed significant differences by sex in the sources of opioids, though the age group examined in this study was older adolescents aged 18 years. A major gap in the literature relates to where youth 10 to 18 years obtain their prescription opioids and how they are using them. Considering that sex differences have been previously observed for prevalence of NMU among youth (Osborne et al., 2017) and among patterns of NMU in older adolescents only but not among younger adolescents (for which patterns of NMU have not been studied previously) (McCabe et al., 2013a), it is important to determine if sex differences also exist among patterns of NMU in youth 10 to 18 years of age. As part of the National Monitoring of Adolescent Prescription Stimulants Study (N-MAPSS), we assessed sex differences in the patterns of past 30 day NMU of prescription opioids in a national study of youth 10 to 18 years of age in urban, suburban, and rural US.

Aims and Hypotheses

The aim of this analysis was to examine sex differences in patterns of prescription opioid NMU. This analysis describes how youth are using their own prescribed opioids and where they are obtained without a prescription. Information was available on source of opioids, route of administration and whether opioids were obtained from a healthcare professional. Three patterns of NMU were examined in detail: use of someone else's opioids only, use by a non-oral route only and both use of someone else's opioids and non-oral use. The influence of relationships with others was explored by examining sources of opioids (use of opioids that belonged to parents, peers and other sources), while various individual and community level risk factors for each pattern of NMU were analyzed by sex.

Two hypotheses were proposed among 10,965 youth (345 with past 30 day NMU of prescription opioids):

Hypothesis 1. Among youth who obtained opioids from other sources, females will be less likely to obtain opioids from two or more sources compared to males, after controlling for factors at individual and community levels.

Hypothesis 2. Among the three patterns of prescription opioid NMU, females will be less likely to use both someone else's opioids and have non-oral use (two patterns of NMU) compared to males, after controlling for factors at individual and community levels.

Methods

Study Design

N-MAPSS was a national study conducted in four waves in the US from 2008 to 2011 (Cottler et al., 2013). This cross-sectional survey assessed the MU and NMU of prescription stimulants, opioids and other prescription medications. Participants 10 to 18 years of age were recruited from entertainment venues (such as shopping malls, movie theaters, sports and recreation centers, libraries, arcades, skate parks, and parks) in urban, suburban, and rural areas of 10 cities. This venue intercept approach has been used previously in other studies for recruiting hard to reach populations (Cummings, Auerswald, & Ott, 2014; Muhib et al., 2001; Patrick et al., 2017). It involves creating a sampling frame of all venues where the target population may visit and then randomly selecting date and time for recruitment. As a result, this is not a convenience sample and the approach has been shown to approximate to random sampling (Muhib et al., 2001).

Recruiters approached 21,444 youth during the four waves and invited them to participate; 25% declined to learn about the study and 21% of those expressing initial interest were ineligible. Of those who elected to learn about the study, 10% refused to participate. In

total, 11,048 youth who completed the survey comprise the final sample and represent an overall response rate of 68% (11,048/16,143 potentially eligible youth). Anonymity was maintained throughout and parental permission was not required to participate because no identifying information was collected. Parents were also not allowed to sit with or help their child with the survey answers if they were nearby at the time of survey completion. Survey completion implied assent for all participants, as approved by Washington University and University of Florida Human Protection Research Offices. The research protocol was approved by both Institutional Review Boards.

Since stimulant use was the primary focus of the study, cities were selected from 10 states with the highest rates of stimulant prescribing patterns in 2008 (as identified from the IMS Health database and Office of Management and Budget regions). Selected cities were: Seattle, Los Angeles, Denver, St. Louis, Houston, Cincinnati, Tampa, Philadelphia, New York and Boston. We were able to obtain a sample distribution for age, sex, race and urban/rural composition mostly comparable to the 2010 US Census data, indicating a representative sample (Cottler et al., 2013).

Measurements

Paper copies of the survey were completed by youth in a private location in the venues from which they were recruited. To reduce errors due to problems with reading or reading comprehension, interviewers offered to read the questions to all 10 and 11 year olds in a private space. Questions about prescription medications (including opioids and stimulants) were accompanied by photographs of the medications for ease of identification. Opioids examined in the past 30 days were Vicodin®, hydrocodone, OxyContin® and oxycodone; previous research has shown that these are the most commonly prescribed opioids among children and adolescents (Groenewald, Rabbitts, Gebert, & Palermo, 2016). Past 30 day use of these opioids was assessed

using the following question: “In the last 30 days, have you taken [Specific drug name]? Examples are pictured above”.

Source of opioids was assessed by the question: “In the last 30 days, have you used [Specific drug name] that belonged to…[List of responses]”. Sources were: one of your parents, your brother or sister, a different family member, someone from school, someone from work, someone you don’t know or someone not listed above. Route of administration was assessed by the question: “In the last 30 days, what are all the ways you used [Specific drug name]”. Routes of administration were: by mouth (oral), snorted or sniffed, smoked or other.

The three use patterns for prescription opioids were (1) No use in the past 30 days, (2) MU only in the past 30 days and (3) any NMU in the past 30 days. The third pattern of any NMU in the past 30 days was further stratified by (1) non-oral use only, (2) use of someone else’s opioids only and (3) both non-oral use and use of someone else’s opioids. Non-oral use in the past 30 days was defined as NMU since only oral use is specified in the label for these opioids. Overall, the definition of past 30 day NMU includes youth who used their own prescription in a way other than prescribed in the past 30 days and those who used someone else’s opioids in the past 30 days. Prescription opioid MU in the past 30 days was defined as use of opioids in the past 30 days with a prescription. Past 30 day MU could have occurred in combination with past 30 day NMU or without NMU.

Individual risk factors examined were captured through survey items on sex and age, lifetime use of other prescription opioids (Darvocet®, codeine, Percocet® and/or Lortab®; Never use, MU only and NMU), depressive symptoms, anxiety symptoms, MU of opioids in the past 30 days (including prescriptions from any source) and lifetime use of alcohol, tobacco and marijuana. The relationship level factor examined was past 30 day source of opioids (use of

opioids that belonged to parents, peers or other sources). At the community level, urban area of residence was included.

Analysis

Those with missing values for past 30 day opioid use were excluded from this analysis (n=83/11,048). Descriptive statistics were calculated to summarize patterns of past 30 day opioid use. Prevalence estimates of individual and community level factors among each of the three outcome categories of prescription opioid use were calculated, with chi square and ANOVA tests. Bar charts with frequencies and percentages were used to display sources of opioids by sex, along with routes of administration by sex. Chi square tests and crude odds ratios were used to examine differences in patterns of use between males and females. Fishers exact tests with Monte Carlo estimated p-values (number of samples=10,000) were used to explore associations between potential risk factors and patterns of NMU (non-oral use only, use of someone else's opioids only and both) among males and females separately. ANOVA tests were used to examine trends for continuous variables across the different patterns of NMU for males and females separately. A binomial logistic regression analysis was used to predict both use of someone else's opioids and non-oral use (with use of someone else's opioids only as the reference group), first examining sex as a predictor in the model and then stratifying the model by males and females separately. The model adjusted for the significant covariates from the univariate analysis for patterns of NMU. A final binomial logistic regression analysis was used to predict two or more sources of opioids, examining sex as a predictor and adjusting for other covariates. Model fit was assessed using the Hosmer-Lemeshow test which assesses whether there is a difference between the observed and predicted values of the response variable. Non-significance indicated adequate fit. The variance inflation factor (VIF) was assessed for severity of multicollinearity, though removal of variables was not considered further as a value greater

than 10 was not found. Given an estimated background prevalence of 30% and a sample of 150 males and 150 females, we would have a statistical power of 0.82 to detect a doubling of opioid NMU pattern between males and females at 0.05 alpha. All statistical analyses were calculated using SAS® 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 10,965 youth who provided information about past 30 day prescription opioid use, 10,440 had not used opioids (95.2%) and 525 (4.8%) reported past 30 day opioid use. Overall, past 30 day prevalence of prescription opioid NMU was 3.1% (n=345/10,965) and MU only of opioids was 1.6% (n=180). Of those who had not used prescription opioids within the past 30 days, 48% were male and 52% were female, while for those with MU only within the past 30 days 42% were male and 58% were female (Figure 3-1). For those who reported prescription opioid NMU in the past 30 days, 56% were male and 44% were female.

Sample characteristics are displayed in Table 3-1. All examined risk factors were found to be associated with prescription opioid use status before stratification by sex; age, anxiety symptoms, depressive symptoms and lifetime use of tobacco, alcohol, marijuana and prescription opioids were all found to be significant individual level risk factors. The community level risk factor of urban area of residence was also found to be a significant risk factor. In terms of individual level risk factors, those with prescription opioid MU only or any NMU in the past 30 days were older (16.3 and 16.4 years, respectively) when compared to those with no use in the past 30 days (15.1 years, $p<0.0001$). Lifetime NMU of prescription opioids was more prevalent among those with past 30 day NMU of prescription opioids (49.3%), compared to those with past 30 day MU only (11.1%) and no use in the past 30 days (2.7%; $p<0.0001$). Lifetime use of alcohol, marijuana and tobacco were all found to be more prevalent among youth with past 30 day NMU (91.6, 87.8 and 78.0%) compared to MU only (67.0, 61.5, 44.9%) and no use in the

past 30 days (43.3, 26.8 and 23.7%; all p<0.0001). A higher prevalence of anxiety symptoms (ever felt worried or stressed for 6 months or more) was seen among those with any NMU (45.1%) compared to those with MU only (41.1%) and no use (24.9%, p<0.0001). The same pattern was seen for both depressive symptoms of having two weeks or more in the past 12 months when lost interest in things (58.3, 42.8 and 35.7%, p<0.0001) or felt down or depressed (61.7, 44.4 and 36.3%, p<0.0001). Finally, for the community level risk factor of urban area of residence, living in an urban area was more prevalent among those with no use of prescription opioids in the past 30 days (47.8%) compared to MU only (42.8%) and any NMU (41.5%, p=0.0302).

Three distinct patterns of past 30 day NMU were examined: non-oral use only, use of someone else's opioids only and both non-oral use and use of someone else's opioids (Figure 3-1). Use of someone else's opioids only was the most frequent type of NMU (n=206/345, 59.7% of NMU). Use by a non-oral route only was the least common type of NMU (n=18/345, 5.2% of NMU), while use of someone else's opioids and non-oral use had a prevalence of 35.1% (n=121/345). The proportion of males and females was equally distributed among those using someone else's opioids only (50.5% vs 49.5%); however, a higher proportion of females reported non-oral use only in the past 30 days compared to males (61.1% vs 38.9%), while a higher proportion of males had both non-oral use and use of someone else's opioids compared to females (68.6% vs 31.4%). Upon examination of the crude odds of each pattern of NMU among those who reported NMU (n=345), sex differences emerged (Table 3-2). Females had 1.87 times the odds of using someone else's opioids only compared to males (95% Confidence Interval [CI]: 1.20, 2.92). In contrast, females had 57% lower odds of using both someone else's opioids and non-oral use compared to males (Odds Ratio [OR]=0.43, 95% CI: 0.27, 0.69). No significant

difference was found when comparing the crude odds of non-oral use only between males and females.

Where use of someone else's opioids was reported, the most frequent sources were someone at school (n=164/327, 50.2%) or a parent (n=103/327, 31.5%). When stratified by sex, differences in sources of opioids were observed (Figure 3-2). The most prevalent source among males was using opioids that belonged to someone from school (n=111, 60.0%). Among females, there were two prevalent sources of opioids: a parent (n=59, 41.6%) and someone from school (n=53, 37.3%). Males were more likely to obtain opioids from a classmate compared to females ($p<0.001$) whereas females were more likely to use opioids that belonged to a parent compared to males ($p<0.001$). Females had over twice the crude odds of using opioids that belonged to a parent compared to males (OR=2.11, 95% CI: 1.32, 3.37; Table 3-3). In contrast, females had 61% lower crude odds of using opioids that belonged to a classmate compared to males (OR=0.39, 95% CI: 0.25, 0.60; Table 3-3). Examination of the other sources of opioids did not reveal significant differences in prevalence between males and females. The least prevalent source for males was use of opioids that belonged to a sibling (9.7%), while for females it was use of a co-workers opioids (7.0%). Use of opioids that belonged to a stranger (someone they didn't know) occurred at a prevalence of 20.0% for males and 16.9% for females.

For route of administration, the most frequent non-oral route reported was snorting (n=129, 92.8% of 139 youth reporting non-oral use; Figure 3-3). When stratified by sex, the prevalence of snorting prescription opioids was found to be higher among males compared to females (n=85/267, 31.8% vs n=44/258, 17.1%; $p<0.001$). Females had 49% lower odds of using prescription opioids by snorting compared to males (OR=0.51, 95% CI: 0.32, 0.80; Table 3-4). There was no significant difference in the odds of smoking prescription opioids when comparing

females to males. Smoking was also the least prevalent route of administration at 5.2% for males and 4.3% for females. The most frequent route of administration for both sexes was the licensed oral route, with a prevalence of 88.4% for males and 92.6% for females (Figure 3-3).

The characteristics of males and females for each pattern of NMU (non-oral route only, use of someone else's opioids only and both use of someone else's opioids and non-oral use) were examined further (Table 3-5). Mean age was significantly higher for males with non-oral use only compared to those with use of someone else's opioids only and both use of someone else's opioids and non-oral use ($p<0.001$). For females, mean age was significantly lower for non-oral use only compared to those with use of someone else's opioids only and both use of someone else's opioids and non-oral use ($p<0.001$). For both sexes, mean age was similar for those with use of someone else's opioids only and both use of someone else's opioids and non-oral use. Lifetime NMU of other prescription opioids was more prevalent among males who both used someone else's opioids and had non-oral use in the past 30 days (67.5%), and in the use of someone else's opioids only category (41.2%), compared to the use by non-oral route only category (28.6%; $p=0.003$). This difference in prevalence for lifetime NMU of other prescription opioids was not seen among females. Prevalence of lifetime use of tobacco was highest for those who both used someone else's opioids and had non-oral use compared to those with non-oral use only or use of someone else's opioids only among both males and females ($p=0.007$ and $p<0.001$, respectively). Lifetime use of marijuana was more prevalent among females with non-oral use only (100.0%) and both use of someone else's opioids and non-oral use (97.4%) compared to those with use of someone else's opioids only (75.0%; $p=0.001$). A difference in prevalence among males was not observed for lifetime use of marijuana. Sex differences in characteristics by patterns of NMU were not found for medical use of prescription opioids in the

past 30 days, anxiety symptoms, depressive symptoms, lifetime use of alcohol or urban area of residence by pattern of NMU. None of these were found to be significant risk factors for prescription opioid NMU patterns among males or females.

A binomial logistic regression analysis was conducted, removing those who only used opioids non-orally (n=18). The regression model predicted those who used both someone else's opioids and used opioids non-orally (Table 3-6) with the reference group those who only used someone else's opioids. After adjustment for other covariates, females compared to males were found to have 47% lower odds of both using someone else's opioids and non-oral use (OR=0.53, 95% CI: 0.32, 0.87). After stratification of the binomial logistic regression model by sex (Table 3-7), lifetime use of tobacco was the most significant factor associated with past 30 day use of both someone else's opioids and non-oral use for both males and females; males with lifetime use of tobacco had 2.98 times the odds of both use of someone else's opioids and non-oral use compared to those with no lifetime use of tobacco (95% CI: 1.14, 7.82). Females with lifetime use of tobacco had 7.89 times the odds of both use of someone else's opioids and non-oral use compared to those with no lifetime use of tobacco (95% CI: 1.68, 37.16). Among males, those with lifetime NMU of prescription opioids had 2.62 times the odds of both use of someone else's opioids and non-oral use (95% CI: 1.34, 5.11). No other factors were found to be associated with both use of someone else's opioids and non-oral use for either males or females.

A final binomial logistic regression analysis was conducted, predicting use of opioids from two or more different sources (Table 3-8). The reference group for the regression was use of opioids from one source only. After adjustment for other covariates, females compared to males were not found to have significantly lower odds of using opioids from two or more different sources (OR=0.75, 95% CI: 0.46, 1.22). Youth who reported lifetime use of marijuana

had 2.96 times the odds of obtaining opioids from two or more different sources compared to those who never used marijuana after adjustment for other factors (95% CI: 1.07, 8.18). In addition, those with lifetime MU only and NMU of prescription opioids had over twice the odds of obtaining opioids from two or more different sources compared to those who never used prescription opioids in their lifetime (OR=2.89, 95% CI: 1.09, 7.66 and 2.08, 95% CI: 1.23, 3.50, respectively).

Discussion

Past 30 day prevalence of NMU (3.1%) in this analysis was consistent with that observed for past 12 month NMU of pain relievers among 12 to 17 year olds in the 2016 NSDUH (3.5%) (Substance Abuse and Mental Health Services Administration, 2017)

Use of someone else's opioids only was the most frequently reported pattern of NMU in youth, with females nearly twice as likely to report this pattern of NMU compared to males. In contrast, the likelihood of both use of someone else's opioids and non-oral use was significantly lower among females compared to males, which remained after controlling for other covariates. This supports our hypothesis that females will be less likely to use both someone else's opioids and have non-oral use (two patterns of NMU) compared to males, after controlling for other factors. Within the socio-ecological model framework, this may be due to differing social acceptability for prescription opioid NMU for males and females, which affects prescription opioid NMU behavior. It may also be due to increased parental guidance, monitoring and support among females, which have been previously observed as protective factors against substance use (Dunn et al., 2011; Jacobson & Crockett, 2000). Females were less likely to use both someone else's opioids and have non-oral use after adjusting for age, which suggests that this finding is not merely a result of youth progressing to more than one pattern of NMU as they get older;

however, we recognize that further research is needed to determine which relationships are associated with prescription opioid NMU among males and females.

Interestingly, our results are discordant from the findings of a previous study among older adolescents aged 18 years; among older adolescents, males were more likely to use someone else's opioids only compared to females (McCabe et al., 2013a). In contrast, females were more likely to both use someone else's opioids and misuse their own previous prescription (McCabe et al., 2013a). This suggests that younger adolescents, as studied in this analysis, may have different motivations or risk factors for NMU compared to older adolescents, affecting the way they obtain opioids. This may be driven by sex specific expectations and influences in younger adolescents which are less prevalent in older adolescents. It is an interesting finding that should be explored further, including the motives for such NMU. Unfortunately, little data exists on the motives for NMU of prescription opioids in youth; a recent systematic review concluded that research on the motives for NMU of prescription opioids was limited and should be expanded further (Drazdowski, 2016).

Opioids that belonged to someone else (regardless of non-oral use) revealed two prevalent sources among females (a parent and someone from school) and only one highly prevalent source among males (someone from school). Males were more likely than females to use opioids that belonged to a classmate (someone from school; $p<0.001$), while females were more than twice as likely to use opioids that belonged to a parent compared to males (OR=2.11). This suggests that females may be more heavily influenced by the behavior of their parents than males; however, it also appears that they are influenced by their peers as well. If females are reporting parents or peers as one of the most common sources of opioids, it has to be because they use or have access to opioids. Conversely, examination of other sources revealed that males

had a high prevalence of use of opioids that belonged to a classmate. For males, it appears that family access is not as influential; however, it is possible that the friends they obtain opioids from are getting them from parents. Consequently, obtaining opioids from friends is something that schools need to be aware of and is potentially an important source for targeting prevention strategies. Parents should also be aware that youth may be obtaining opioids from the home without their knowledge, such as from the medicine cabinet, and potentially sharing them with friends. Given the scale of the opioid epidemic in the US, NMU prevention strategies should be a high priority. Currently, 175 Americans die every day from drug overdoses, the majority of which will involve opioids (Christie et al., 2017). Interventions to prevent NMU access are needed now to combat this public health crisis.

Our findings on sources of opioids are supported by results from the NSDUH, which also indicated that most people who use prescription opioids non-medically obtain them from a friend or relative (Jones, Paulozzi, & Mack, 2014). Most people can find others who sell or share prescription opioids in their immediate social networks (Daniulaityte, Falck, & Carlson, 2014); however, our results also indicated that a small percentage of youth are obtaining opioids from other sources, such as a stranger (someone they don't know). Those at greatest risk for overdose are more likely to be obtaining their prescription opioids from these other sources (Jones et al., 2014). Prevalence of obtaining opioids from a stranger was lower than other sources in our study, but this is still a group of concern due to increased risk of harmful outcomes.

Our hypothesis that females will be less likely to obtain opioids from two or more sources compared to males, after controlling for other factors, was not supported. We found no significant difference in the odds of obtaining opioids from two or more sources between males and females. Within the socio-ecological model framework, this suggests that sex differences do

not arise when considering the number of sources that youth obtain opioids from; however, sex differences in individual sources of opioids were observed. As a result, future studies should focus on defining these relationships for males and females in the context of prescription opioid NMU.

Examination of routes of administration of prescription opioids revealed that the majority of youth (regardless of NMU pattern) were using their medication by the oral route; however, of the two distinct NMU routes of use, snorting was more common than smoking prescription opioids in both males and females. This is in concordance with the published literature; a study of adolescents 13-18 years entering substance abuse treatment programs found that snorting was the most prevalent non-oral route of administration (42.5%) for hydrocodone products in this population (Cassidy et al., 2017). In our study, prevalence of snorting prescription opioids among those with NMU was found to be slightly lower at 37.4%; however, our sample was sourced from the general population rather than those entering substance abuse treatment programs. Further analysis of routes of administration revealed that the prevalence of snorting prescription opioids was nearly 50% lower for females compared to males. This is interesting because it appears that females are less likely to alter the intended route of administration when using prescription opioids non-medically, compared to males.

Another important factor to consider when examining NMU of prescription opioids in youth is age. Peak opioid NMU annual incidence has previously been observed at age 16 years and there is evidence that initiation of NMU may be occurring at younger ages (Austic et al., 2015). Results from our study showed that sex differences in mean age by pattern of NMU were present; females had a younger mean age for non-oral use only (15.6 years), while males had an older mean age for non-oral use only (17.1 years). We found that mean age was similar between

those with use of someone else's opioids only and both use of someone else's opioids and non-oral use. Among females, the mean age for these two patterns of NMU was higher than for non-oral use only; however, among males, the mean age for these two patterns of NMU was lower than for non-oral use only. The result should be interpreted with caution because of the small sample size in the non-oral use only group (n=18). Further exploration of this finding in future research is needed, though it may be that age is an important risk factor to consider in prescription opioid NMU among youth.

Another risk factor for pattern of NMU among youth was lifetime tobacco use, which was significant among both males and females. We have previously observed that this is also a risk factor for NMU of prescription opioids among youth regardless of pattern of NMU (Osborne et al., 2017). Lifetime alcohol use was not found to be a risk factor for any specific pattern of NMU for either sex in our analysis; however, lifetime marijuana use was a risk factor among females only. These three substances (tobacco, alcohol and marijuana) have been previously identified as risk factors for NMU of prescription opioids in the existing literature. Consequently, it is important to consider that other risk factors examined in this study which did not differ by sex or pattern of NMU (anxiety symptoms, depressive symptoms, urban area of residence and medical use of prescription opioids in the past 30 days) may still be important risk factors for NMU of prescription opioids in youth.

Finally, examination of lifetime NMU of other prescription opioids revealed an association with pattern of past 30 day NMU among males but not females. After adjustment for other covariates, this effect remained among males only. The decrease in prevalence from use of both someone else's opioids and non-oral use, to use of someone else's opioids only to non-oral use only is suggestive that past NMU of prescription opioids is predictive of current NMU,

especially where more than one pattern of NMU is reported. Given our results, it is possible that this is only true among males. Our finding is in concordance with other studies that have shown that older adolescents (aged 18 years) who use prescription opioids non-medically will continue such use as young adults (Johnston et al., 2016; McCabe et al., 2014; Miech et al., 2015). Sex differences have not previously been examined in this risk factor but should be considered based on the results of our analysis.

Findings from this analysis suggest that future research examining sex differences in prescription opioid NMU among youth should examine parental and peer influences further, in addition to individual level risk factors. Within the socio-ecological model framework, we have observed that both individual and relationship level factors influence patterns of NMU and so this supports further research examining risk factors for NMU of prescription opioids in youth using this model. Further evidence is needed on how parental and peer relationships influence NMU among youth and whether parental influence has a greater effect among females compared to males. It is also important to determine the magnitude of effect of these factors on NMU among youth.

Overall, the results of this analysis suggest that examination of sex differences in sources of opioids and route of administration is important when considering NMU of prescription opioids among youth; however, sex differences in individual and community level factors for the patterns of NMU examined in this study (non-oral use only, use of someone else's opioids only or both) were minimal. As a result, future research into the risk factors for prescription opioid NMU among youth within the context of the socio-ecological model can focus on all NMU, regardless of pattern; however, it is important to consider that there are sex differences in how youth are using these drugs non-medically and where they obtain opioids.

Strengths and Limitations

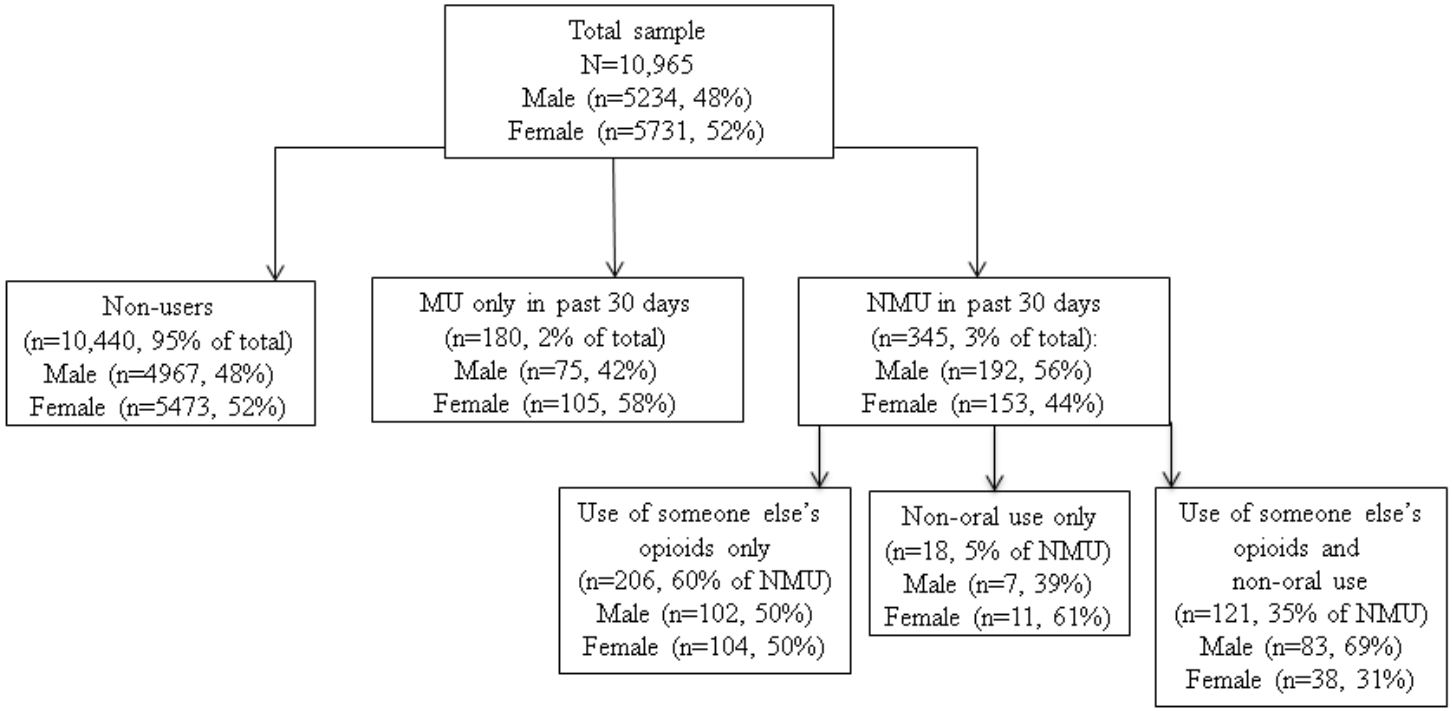
Strengths of this study include recruiting participants from the community, with surveys conducted outside of the home or school. Due to the anonymous nature of the surveys, parental consent was not required, unlike the NSDUH and MTF studies. For this reason, participants might have been more likely to respond truthfully to questions about drug use, which reduces social desirability bias. Moreover, the inclusion of youth from rural, suburban and urban areas and use of the venue intercept method provided a representative sample of youth from across the US.

While we collected information directly from the youth, providing insight into their behavior, we did not collect information from their prescribers. Thus, a limitation of the study is that we could not examine NMU of opioids in relation to doses higher than prescribed. Misclassification of the outcome is possible as a result, though this is likely to be non-differential and therefore estimates of the effect, if biased, would be biased towards the null. However, our findings provide useful results on other patterns of NMU among youth. Further studies are needed to examine high doses as a fourth pattern of use. A further limitation was that the sample size for the non-oral use only group was very small due to the low prevalence of this pattern of NMU, so power to detect sex differences for this group was limited; however, we should have had sufficient power to detect sex differences for the other NMU patterns based on the sample size for these groups.

Conclusion

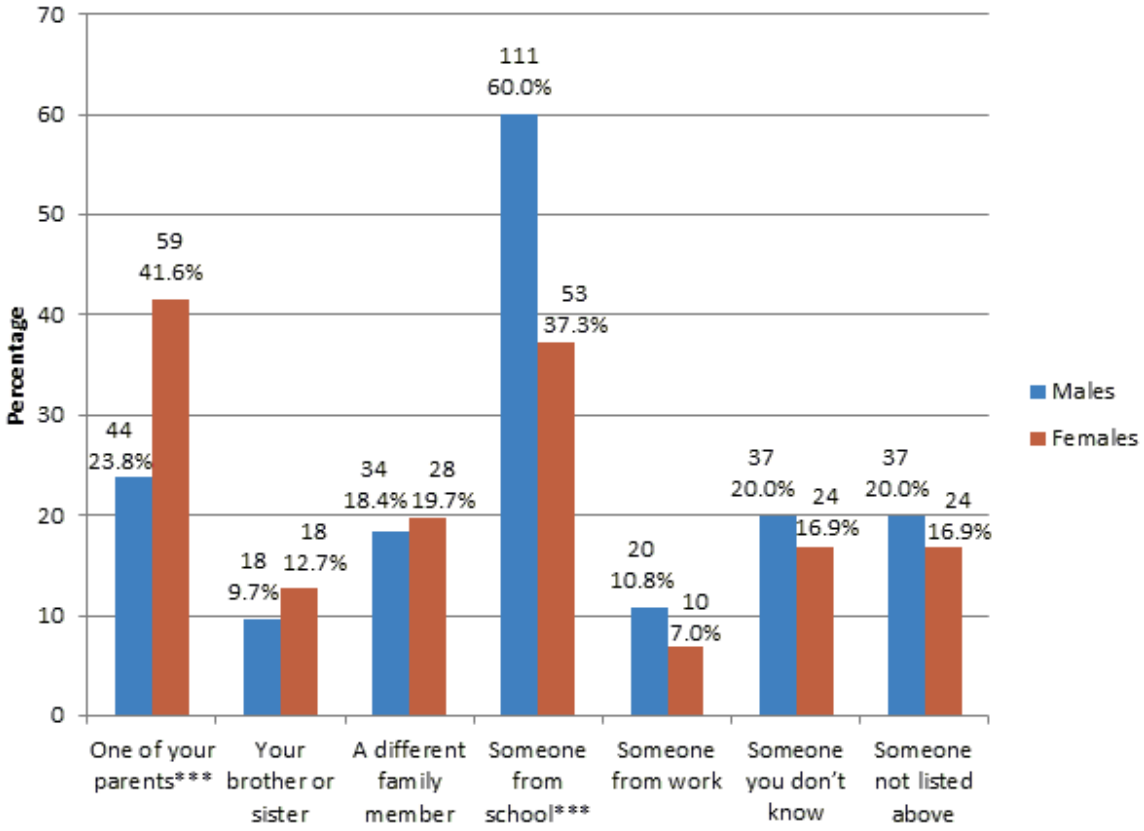
Regardless of sex, the majority of youth endorsing NMU reported using someone else's opioids. Females most often reported using opioids that belonged to a parent or classmate, while males most often reported using opioids that belonged to a classmate. Based on these findings, to

combat the current opioid crisis, we should implement strategies to prevent youth from sharing opioids, especially with friends from school.



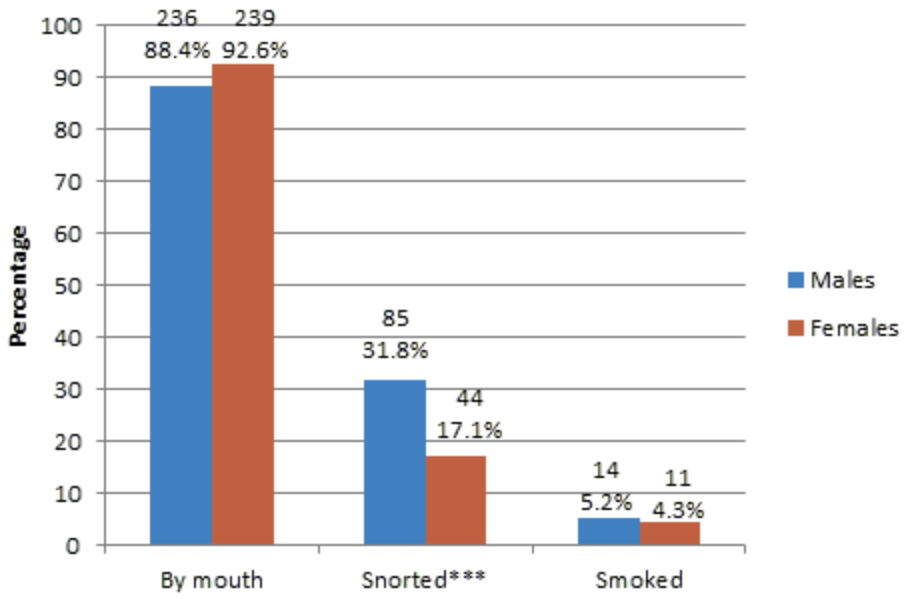
MU= Medical Use; NMU= Non-Medical Use

Figure 3-1. Patterns of prescription opioid use in past 30 days, by sex.



***Chi square p-value <0.001
Data are not mutually exclusive- more than one source of opioids could be specified

Figure 3-2. Sources of opioids when obtained from another individual in past 30 days, by sex (n=327).



***Chi square p-value<0.001

Figure 3-3. Route of administration of prescription opioids in past 30 days, by sex (n=525).

Table 3-1. Individual and community level factors in the whole sample, stratified by past 30 day prescription opioid use.

	No use of opioids in past 30 days (n=10,440) n (%)	Medical use of opioids only in past 30 days (n=180) n (%)	Any non-medical use of opioids in past 30 days (n=345) n (%)	p-value (chi square or ANOVA)
Age				
Mean (SD)	15.1 (2.1)	16.3 (1.6)	16.4 (1.4)	<0.0001
Lifetime use of tobacco				
Never	7949 (76.4)	98 (55.1)	76 (22.0)	<0.0001
Ever	2462 (23.7)	80 (44.9)	269 (78.0)	
Lifetime use of marijuana				
Never	7630 (73.2)	69 (38.6)	42 (12.2)	<0.0001
Ever	2797 (26.8)	110 (61.5)	303 (87.8)	
Lifetime use of alcohol				
Never	5894 (56.7)	59 (33.0)	29 (8.4)	<0.0001
Ever	4499 (43.3)	120 (67.0)	316 (91.6)	
Lifetime use of prescription opioids				
Never	9683 (92.9)	119 (66.1)	153 (44.4)	<0.0001
Medical use only	463 (4.4)	41 (22.8)	22 (6.4)	
Non-medical use	278 (2.7)	20 (11.1)	170 (49.3)	
Two weeks or more in the past 12 months when lost interest in things				
No	6688 (64.3)	103 (57.2)	144 (41.7)	<0.0001
Yes	3715 (35.7)	77 (42.8)	201 (58.3)	
Two weeks or more in the past 12 months when felt down or depressed				
No	6632 (63.7)	100 (55.6)	132 (38.3)	<0.0001
Yes	3777 (36.3)	80 (44.4)	213 (61.7)	
Ever felt worried or stressed for 6 months or more (anxiety symptoms)				
No	7828 (75.1)	106 (58.9)	189 (54.9)	<0.0001
Yes	2597 (24.9)	74 (41.1)	155 (45.1)	
Urban area of residence				
No	5452 (52.2)	103 (57.2)	202 (58.6)	0.0302
Yes	4988 (47.8)	77 (42.8)	143 (41.5)	

SD=Standard Deviation

Table 3-2. Crude odds ratios for pattern of prescription opioid NMU in past 30 days (n=345).

	Use of someone else's opioids only (n=206) OR (95% CI)	Non-oral use only (n=18) OR (95% CI)	Use of someone else's opioids and non-oral use (n=121) OR (95% CI)
Males	ref	ref	ref
Females	1.87 (1.20, 2.92)	2.05 (0.77, 5.41)	0.43 (0.27, 0.69)

OR= Odds Ratio; CI= Confidence Interval; ref= reference group

Table 3-3. Crude odds ratios for sources of opioids when obtained from another individual in past 30 days (n=327).

	Parent (n=103) OR (95% CI)	Brother or sister (n=36) OR (95% CI)	A different family member (n=62) OR (95% CI)	Someone from school (n=164) OR (95% CI)	Someone from work (n=30) OR (95% CI)	Someone you don't know (n=61) OR (95% CI)	Someone not listed (n=61) OR (95% CI)
Males	ref	ref	ref	ref	ref	ref	ref
Females	2.11 (1.32, 3.37)	1.29 (0.65, 2.57)	1.04 (0.60, 1.81)	0.39 (0.25, 0.60)	0.60 (0.27, 1.33)	0.78 (0.44, 1.37)	0.78 (0.44, 1.37)

OR= Odds Ratio; CI= Confidence Interval; ref= reference group

Table 3-4. Crude odds ratios for route of administration of prescription opioids in past 30 days (n=525).

	By mouth (n=475) OR (95% CI)	Snorted (n=129) OR (95% CI)	Smoked (n=25) OR (95% CI)
Males	ref	ref	ref
Females	1.42 (0.75, 2.70)	0.51 (0.32, 0.80)	0.99 (0.43, 2.24)

OR= Odds Ratio; CI= Confidence Interval; ref= reference group

Table 3-5. Patterns of non-medical use among those who used prescription opioids in the past 30 days (n=345).

Characteristic	Patterns of non-medical use among opioid users Males (n=192) Non-oral use only (n=7) n (%)	Use of someone else's opioids only (n=102) n (%)	Non-oral use and use of someone else's opioids (n=83) n (%)	ANOVA p-value or Monte Carlo estimate of Fishers p-value	Females (n=153) Non-oral use only (n=11) n (%)	Use of someone else's opioids only (n=104) n (%)	Non-oral use and use of someone else's opioids (n=38) n (%)	ANOVA p-value or Monte Carlo estimate of Fishers p-value
INDIVIDUAL LEVEL FACTORS								
Age (mean [SD]):	17.1 (0.7)	16.5 (1.4)	16.6 (1.5)	<0.001	15.6 (1.6)	16.2 (1.4)	16.4 (1.5)	<0.001
Lifetime use of prescription opioids:								
Never	5 (71.4)	53 (52.0)	24 (28.9)	0.003	4 (36.4)	54 (51.9)	13 (34.2)	0.084
Medical use only	0 (0.0)	7 (6.9)	3 (3.6)		1 (9.1)	10 (9.6)	1 (2.6)	
Non-medical use	2 (28.6)	42 (41.2)	56 (67.5)		6 (54.6)	40 (38.5)	24 (63.2)	
Medical use of opioids in past 30 days (with a prescription from any source)								
No	7 (100.0)	82 (80.4)	75 (90.4)	0.087	8 (72.7)	83 (79.8)	33 (86.8)	0.480
Yes	0 (0.0)	20 (19.6)	8 (9.6)		3 (27.3)	21 (20.2)	5 (13.2)	
Lifetime use of tobacco								
No	1 (14.3)	28 (27.5)	8 (9.6)	0.007	1 (9.1)	36 (34.6)	2 (5.3)	<0.001
Yes	6 (85.7)	74 (72.6)	75 (90.4)		10 (90.9)	68 (65.4)	36 (94.7)	
Lifetime use of alcohol								
No	0 (0.0)	12 (11.8)	6 (7.2)	0.517	0 (0.0)	10 (9.6)	1 (2.6)	0.356
Yes	7 (100.0)	90 (88.2)	77 (92.8)		11 (100.0)	94 (90.4)	37 (97.4)	
Lifetime use of marijuana								
No	1 (14.3)	11 (10.8)	3 (3.6)	0.095	0 (0.0)	26 (25.0)	1 (2.6)	0.001
Yes	6 (85.7)	91 (89.2)	80 (96.4)		11 (100.0)	78 (75.0)	37 (97.4)	
Anxiety symptoms								
No	4 (66.7)	67 (65.7)	48 (57.8)	0.525	5 (45.5)	50 (48.1)	15 (39.5)	0.660
Yes	2 (33.3)	35 (34.3)	35 (42.2)		6 (54.6)	54 (51.9)	23 (60.5)	
Depressive symptoms								
No	3 (42.9)	47 (46.1)	38 (45.8)	1.000	2 (18.2)	33 (31.7)	9 (23.7)	0.558
Yes	4 (57.1)	55 (53.9)	45 (54.2)		9 (81.8)	71 (68.3)	29 (76.3)	
COMMUNITY LEVEL FACTORS								
Urban area of residence								
No	5 (71.4)	60 (58.8)	47 (56.6)	0.806	6 (54.6)	62 (59.6)	22 (57.9)	0.930
Yes	2 (28.6)	42 (41.2)	36 (43.4)		5 (45.5)	42 (40.4)	16 (42.1)	

SD=Standard Deviation; ANOVA= Analysis of Variance

Table 3-6. Binomial logistic regression results predicting both use of someone else's opioids and non-oral use

	Non-oral use and use of someone else's opioids OR (95% CI) (n=327)
Age	1.00 (0.84, 1.19)
Sex	
Male	ref
Female	0.53 (0.32, 0.87)
Lifetime use of tobacco	
Never	ref
Ever	3.70 (1.72, 7.93)
Lifetime use of marijuana	
Never	ref
Ever	2.15 (0.68, 6.80)
Lifetime use of prescription opioids	
No use	ref
MU only	0.63 (0.19, 2.08)
Any NMU	2.34 (1.39, 3.94)

OR= Odds Ratio; CI= Confidence Interval; ref= reference group; MU= Medical use; NMU= Non-Medical Use; Reference group=Use of someone else's opioids only

Table 3-7. Binomial logistic regression results predicting both use of someone else's opioids and non-oral use, by sex

	Non-oral use and use of someone else's opioids	
	Males (n=185) OR (95% CI)	Females (n=142) OR (95% CI)
Age	0.99 (0.78, 1.24)	0.98 (0.72, 1.32)
Lifetime use of tobacco		
Never	ref	ref
Ever	2.98 (1.14, 7.82)	7.89 (1.68, 37.16)
Lifetime use of marijuana		
Never	ref	ref
Ever	0.85 (0.18, 4.00)	6.18 (0.76, 50.60)
Lifetime use of prescription opioids		
No use	ref	ref
MU only	0.94 (0.22, 4.09)	0.29 (0.03, 2.51)
Any NMU	2.62 (1.34, 5.11)	2.29 (0.96, 5.49)

OR= Odds Ratio; CI= Confidence Interval; ref= reference group; MU= Medical use; NMU= Non-Medical Use; Reference group=Use of someone else's opioids only

Table 3-8. Binomial logistic regression results predicting multiple sources of opioids

	One source of opioids (n=220) n (%)	Two or more sources of opioids (n=107) n (%)	OR* (95% CI)
Age (mean [SD])	16.4 (1.4)	16.4 (1.5)	0.94 (0.79, 1.11)
Sex			
Male	118 (53.6)	67 (62.6)	ref
Female	102 (46.4)	40 (37.4)	0.75 (0.46, 1.22)
Lifetime use of tobacco			
Never	52 (23.6)	22 (20.6)	ref
Ever	168 (76.4)	85 (79.4)	0.76 (0.40, 1.45)
Lifetime use of marijuana			
Never	35 (15.9)	6 (5.6)	ref
Ever	185 (84.1)	101 (94.4)	2.96 (1.07, 8.18)
Lifetime use of prescription opioids			
No use	111 (50.5)	33 (30.8)	ref
MU only	12 (5.5)	9 (8.4)	2.89 (1.09, 7.66)
Any NMU	97 (44.1)	65 (60.8)	2.08 (1.23, 3.50)

SD= Standard Deviation; OR= Odds Ratio; CI= Confidence Interval; ref= reference group; MU= Medical use; NMU= Non-Medical Use; *Reference group= One source of opioids

CHAPTER 4
SEX DIFFERENCES IN RELATIONSHIP LEVEL RISK FACTORS FOR NON-MEDICAL USE OF PRESCRIPTION OPIOIDS IN YOUTH

Background

Prescription opioid use has increased in the US in recent years, leading to concerns about non-medical use (NMU) and the associated consequences; overdoses involving prescription opioids contributed to nearly half of all overdose deaths in 2015 alone, with 22,000 deaths in total (Centers for Disease Control and Prevention, 2017b; Rudd, 2016). In the US, 175 Americans currently die daily from drug overdoses and the majority of these involve opioids (Christie et al., 2017). In addition, there is increasing concern that prescription opioid NMU is a risk factor for heroin use (Compton et al., 2016; Palamar et al., 2016), for which overdose deaths have also risen sharply in recent years (Centers for Disease Control and Prevention, 2017a).

Examining risk factors for prescription opioid NMU in youth is important because prevalence remains high in the US (Substance Abuse and Mental Health Services Administration, 2017). Peak prevalence of initiation of prescription opioid NMU has been previously observed at age 16 years in the US (Meier et al., 2012) and annual incidence rates are also highest at this age among youth (Austic et al., 2015). One study also found that initiation of NMU of OxyContin® reaches its peak at age 16-18 years, though initiation as young as age 13 years was also observed (Deandrea et al., 2013). Additionally, recent studies have indicated that NMU initiation is occurring at younger ages than reported previously (Austic et al., 2015), and that NMU in youth is likely to continue into young adulthood (Johnston et al., 2016; McCabe et al., 2014; Miech et al., 2015). Prevention strategies for opioid NMU in youth are vital to reduce opioid NMU in the US.

Many recent studies have focused on understanding risk factors for prescription opioid NMU in adults, especially young adults 18 to 25 years who are known to have the highest

prevalence of opioid NMU. Studies among youth using national survey data are limited, as analyses of the National Survey on Drug Use and Health (NSDUH) have often combined youth aged 12 to 17 years with adults when examining NMU (Back et al., 2010). Additionally, the Monitoring The Future (MTF) survey fails to ask youth aged 12 to 17 years about prescription opioid NMU as these questions are only included for those aged 18 years and over (Johnston et al., 2016). It is a limitation of the current literature that there are few studies which focus on opioid NMU in youth alone and even fewer that examine sex differences in the risk factors for NMU. Our previous work has examined the risk factors for prescription opioid NMU at the individual level (Osborne et al., 2017), in addition to how youth are obtaining and using their prescription opioids non-medically (Chapter 3). We uncovered that there are sex differences in who youth obtain their prescription opioids from, suggesting that relationship level factors should be examined further with regards to prescription opioid NMU among youth.

A review of the current literature on parental and peer influences in relation to prescription opioid NMU among youth indicated little research that has specifically examined prescription opioids; however, there is a far greater body of research which examines parental and peer influences on other substance use in youth (Chan et al., 2017; Dunn et al., 2011; Goldstick et al., 2018; McDonough et al., 2016). Sex differences in such risk factors have been examined previously; one study examined the effect of limiting time with friends on initiation of NMU of prescription opioids and other drugs between 2002 and 2009 within the NSDUH (Seedall & Anthony, 2013). An estimated 3.7% of 12 to 17 year olds initiated NMU of prescription opioids for the first time each year. Risk of initiation decreased for those whose parents always limit time with friends (3.1%) compared to those whose parents do not always limit time with friends (4.2%). When stratified by sex, the same pattern was observed among

males (2.7% vs 3.8%) and females (3.4% vs 4.7%), though the effect size was larger for females than males (Seedall & Anthony, 2013). These results suggest that parental monitoring in preventing peer influence may have a protective effect on prescription opioid NMU among youth and that the same may be true for parental guidance.

The socio-ecological model is a theoretical model with four levels that are considered to interact with or influence behavior: individual, relationship, community and societal levels (McLeroy et al., 1988). The model theorizes that people are not only influenced by their individual specific traits but also by their relationships with others, the community where they live and the broader society in which those communities are placed (Substance Abuse and Mental Health Services Administration, 2016). In this analysis, we focus on sex differences in relationship level factors, but also explore how these factors influence NMU in the presence of individual and community level factors. The individual level consists of biological and personal factors that affect the likelihood of prescription opioid NMU. Factors to be examined at this level include age, depressive symptoms, anxiety symptoms and lifetime use of prescription opioids, alcohol, tobacco and marijuana. The relationship level consists of close relationships that may impact the risk of prescription opioid NMU, either as risk factors or protective factors. Factors to be examined at this level are home setting (who youth live with), number of close friends, number of close friends using substances, proportion of close friends using substances (relative to number of close friends), parental warnings against substance use and ever obtaining alcohol from friends or parents (parental guidance and peer influence). The community level factor to be examined within this analysis is urban area of residence, representing the community where youth live.

Within the context of the socio-ecological model, sex differences may arise because behavior is influenced by other factors which differ by sex. For example, at the relationship level, parental monitoring and guidance may differ by sex, with different expectations directed towards males and females (Hyde, 2014; Witt, 1997). Although biological sex itself may not be a true risk factor for prescription opioid NMU, examination of sex differences in risk factors may be important due to sex specific norms. Studies of sex differences in adult opioid NMU have been summarized previously (Serdarevic et al., 2017), but few studies focus solely on youth within a theoretical framework.

Our previous work has examined how youth are obtaining and using their prescription opioids non-medically. We discovered that females most often reported using opioids that belonged to a parent or classmate, while males most often reported using opioids that belonged to a classmate. These results suggest that sex differences in parental and peer influences may be present. Within the context of the socio-ecological model, parental guidance may have a differential influence on prescription opioid NMU for males and females given different expectations and norms. Based on the theoretical framework and our previous findings, we hypothesize that males will be more likely than females to be influenced by peer factors. Females will be more likely than males to be influenced by parental factors, though peer factors will also have some influence. A moderating effect of parental guidance on peer influence may also be present. This can be tested by examining the likelihood of prescription opioid MU and NMU (with no use of prescription opioids as the reference group) for different relationship level predictors, among males and females separately. Based on our findings, prevention strategies could focus on sex specific parenting prevention and peer programs designed to prevent and reduce opioid NMU.

Aims and Hypotheses

The aim of this analysis was to examine the effect of peer influence and parental guidance on patterns of prescription opioid use, including NMU, among males and females separately.

This analysis examined the parental and peer relationship factors that influence past 30 day prescription opioid NMU among youth and whether these factors confer protection or additional risk in the context of the other risk factors found to be associated with prescription opioid NMU. The interaction of parental and peer risk factors was assessed and the influence of each factor examined separately for males and females to investigate sex specific effects. Three hypotheses were proposed among 10,965 youth:

Hypothesis 1. For each additional close friend who uses other substances (marijuana or tobacco), the odds of prescription opioid NMU, but not MU, will increase among males, but not females, after controlling for individual, relationship and community level factors, when compared to no use of prescription opioids in the past 30 days.

Hypothesis 2. Females who are given alcohol by their parents (vs females who are not given alcohol by their parents) will have increased odds of prescription opioid NMU, but not MU, compared to no use of prescription opioids in the past 30 days, after controlling for individual, relationship and community level factors.

Hypothesis 3. Parental guidance will moderate the relationship between number of close friends using other substances (tobacco or marijuana) and prescription opioid NMU, but not MU, among females only. Three parental guidance variables will be examined:

- Warnings by a parent against using illicit substances
- Currently living with at least one parent
- Parent has not given alcohol to the child

Methods

Study Design

The National Monitoring of Adolescent Prescription Stimulants Study (N-MAPSS) was a cross-sectional survey conducted in four waves from 2008 to 2011. The primary aim of the study was to examine prescription stimulant use in youth, though information on prescription opioid use was also obtained. Youth were recruited from urban, rural and suburban areas of 10 US cities which had the highest prescribing rates of prescription stimulants according to IMS Health data. The cities were: Seattle, Los Angeles, Denver, St. Louis, Houston, Cincinnati, Tampa, Philadelphia, New York and Boston.

An entertainment venue intercept method was used to recruit the sample, where a sampling frame of all entertainment venues (such as cinemas and shopping malls) which youth may visit was created. Days and times for recruitment at each venue were randomized and so this approach has been shown to approximate to random sampling (Muhib et al., 2001). Participants aged 10 to 18 years were recruited at these venues by trained community health workers, who approached youth and invited them to participate. In total, 21,444 youth were approached and 25% declined to learn more about the study. An additional 21% who expressed interest were subsequently found to be ineligible. Of those who chose to learn more about the study, 10% refused to participate. The total eligible sample recruited consisted of 11,048 youth across all sites. We were able to obtain a sample distribution for age, sex, race and urban/rural composition mostly comparable to the 2010 US Census data, indicating a representative sample (Cottler et al., 2013).

Surveys were completed on paper in private by youth at the venue where they were recruited, and all data was collected anonymously. Parental consent was not required to participate, and implied assent was obtained by survey completion. For those aged 10 to 11

years, a recruiter offered to read questions to the participant in order to avoid complications associated with reading comprehension. Approval for the research protocol was obtained from the Institutional Review Boards of both Washington University and University of Florida.

Measurements

Questions on the survey asked about lifetime and past 30 day use of prescription medications, with pictures of the medications included to aid comprehension. Any NMU of prescription opioids in the past 30 days was defined as: (1) use other than by mouth (for Vicodin®, hydrocodone, OxyContin® and oxycodone: "In the last 30 days, what are all the ways you used [specific drug name]?") and/or (2) use of someone else's opioids ("In the last 30 days, have you used [specific drug name] that belonged to [list of responses]". MU in the past 30 days was defined as those who had a prescription and no evidence of NMU. Respondents who answered "Yes" to the question "In the last 30 days, have you gotten a prescription or refill for [specific drug name] from [list of responses]?" were identified as having a prescription. In this study, there were three mutually exclusive outcome categories of past 30 day prescription opioid users: (1) individuals who did not use any prescription opioid (no use in past 30 days); (2) individuals who only used prescription opioids as prescribed (MU only) in the past 30 days; and (3) individuals who reported any NMU in the past 30 days.

Parental guidance was assessed using the following questionnaire items: home setting (who youth live with; living with both parents at the same time, living with both parents not at the same time, living with one parent only or living with other relatives, foster parents or in another setting), any parental warnings against other substance use (marijuana, tobacco or alcohol; yes or no) and ever obtaining alcohol from parents (yes or no). Peer influence was assessed using the following questionnaire items: number of close friends, number of close friends using other substances (marijuana or tobacco), proportion of close friends using other

substances (relative to number of close friends) and ever obtaining alcohol from friends (yes or no). Other covariates examined in this analysis at individual level were: age, depressive symptoms, anxiety symptoms and lifetime use of prescription opioids (codeine, Darvocet®, Lortab® and Percocet®), alcohol, tobacco or marijuana. At the community level, zip code was used to establish whether the area of residence was urban or non-urban.

Analysis

The final sample size for analysis consisted of 10,965 youth after removal of 83 youth for whom information on past 30 day prescription opioid use was not available. Summary descriptive statistics were calculated, examining the prevalence of no use of prescription opioids in the past 30 days, MU only and any NMU. Prevalence estimates of individual and relationship level factors among each of the three outcome categories of prescription opioid use were calculated, with chi square and analysis of variance (ANOVA) tests. Due to a non-normal distribution, proportion of close friends using other substances was examined using the Kruskal-Wallis test. Results were subsequently stratified by sex and sex specific prevalence estimates of individual and relationship level factors among each of the three outcome categories of prescription opioid use were calculated. Factors examined at the individual level were: depressive symptoms, anxiety symptoms and lifetime use of alcohol, tobacco and marijuana. In addition, the continuous variable of age was summarized by examining the mean and standard deviation for each outcome category. Factors examined at the relationship level were: home setting (who youth live with), parental warnings against substance use, number of close friends, number and proportion of close friends using other substances and ever obtaining alcohol from friends or parents. At the community level, urban area of residence was examined. Chi square tests were used to individually explore associations between individual, relationship and community level factors and prescription opioid use sub-types for categorical variables, while

ANOVA tests were used to examine continuous variables. Normality of distributions was assessed and use of non-parametric tests for non-normal data distributions was only required for proportion of close friends using substances.

Multinomial logistic regression was used to examine the two level outcome: MU only in the past 30 days and any NMU in the past 30 days. No use of prescription opioids in the past 30 days was the reference group for the regression. Separate regression analyses were conducted for males and females, and the moderating effect of parental guidance on the relationship between peer influence and any NMU was assessed prior to building the final model (Figure 4-1). Moderation was considered present where interaction terms were statistically associated ($p < 0.05$) with any NMU. A final regression model was built using backwards elimination, with model fit assessed. Proportion of close friends was not fitted in the model as we fitted the number of close friends and number of close friends using substances individually. Age was included in the final model regardless of significance. The variance inflation factor (VIF) was assessed for severity of multicollinearity. The VIF was found to be greater than 10 for lifetime use of prescription opioids in the final model, so this risk factor was removed. Given an estimated background prevalence of 3.1% and a sample of 5234 males and 5731 females, we would have a statistical power of >0.99 to detect a doubling of opioid NMU between groups at 0.05 alpha. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 10,965 youth analyzed, most of the sample was found not to have used prescription opioids in the past 30 days (n=10,440, 95.2%). Prevalence of MU only of prescription opioids (1.6%) was found to be lower than prevalence of any NMU (3.1%) among youth. Sample characteristics prior to stratification by sex are displayed in Table 4-1. Nearly all

examined risk factors were found to be associated with prescription opioid use status before stratification by sex; age, depressive symptoms, anxiety symptoms and lifetime use of prescription opioids, tobacco, alcohol and marijuana were all found to be significant individual level risk factors, while home setting (who youth lived with), number of friends using substances, proportion of close friends using substances and ever obtaining alcohol from parents or friends were significant risk factors at the relationship level. The community level risk factor of urban area of residence was also found to be a significant risk factor.

In terms of individual level risk factors, those with prescription opioid MU only or any NMU in the past 30 days were older (16.3 and 16.4 years, respectively) when compared to those with no use in the past 30 days (15.1 years, $p<0.0001$). Lifetime use of alcohol, marijuana and tobacco were all found to be more prevalent among youth with past 30 day NMU (alcohol=91.6, marijuana=87.8 and tobacco=78.0%) compared to MU only (alcohol=67.0, marijuana=61.5 and tobacco=44.9%) and no use in the past 30 days (alcohol=43.3, marijuana=26.8 and tobacco=23.7%; all $p<0.0001$). Lifetime NMU of prescription opioids (Darvocet®, Percocet®, Lortab® and codeine) was more prevalent among those with past 30 day NMU of prescription opioids (49.3%), compared to those with past 30 day MU only (11.1%) and no use in the past 30 days (2.7%; $p<0.0001$). A higher prevalence of anxiety symptoms (ever felt worried or stressed for 6 months or more) was seen among those with any NMU (45.1%) compared to those with MU only (41.1%) and no use (24.9%; $p<0.0001$). The same pattern was seen for both types of depressive symptoms- having two weeks or more in the past 12 months where interest in things was lost (NMU=58.3, MU=42.8 and no use=35.7%, $p<0.0001$) or felt down or depressed (NMU=61.7, MU=44.4 and no use=36.3%, $p<0.0001$). In terms of relationship level factors, living with both parents at the same time was more prevalent among those with no use of

prescription opioids in the past 30 days (55.5%) and MU only (57.8%) compared to any NMU (42.3%, p<0.0001). Mean number of close friends using substances (marijuana or tobacco) increased from no use in the past 30 days (2.7 friends) to MU only (4.3 friends) to any NMU (6.0 friends; p<0.0001). The mean proportion of close friends using substances (relative to number of close friends) also increased from no use in the past 30 days (40%), to MU only (70%) to any NMU (90%; p<0.0001). Ever obtaining alcohol from parents was more prevalent among those with any NMU in the past 30 days (47.5%) compared to those with MU only (28.9%) and no use (16.4%; p<0.0001). The same pattern was observed for ever obtaining alcohol from friends (85.8, 55.0 and 32.5%, respectively; p<0.0001). Finally, for the community level risk factor of urban area of residence, living in an urban area was more prevalent among those with no use of prescription opioids in the past 30 days (47.8%) compared to MU only (42.8%) and any NMU (41.5; p=0.0302).

Individual, relationship and community level factors were examined further for each outcome category after stratification by sex (Table 4-2). When stratified by sex, a higher proportion of males had any NMU (3.6%) compared to females (2.7%). In terms of individual level factors, males who had not used prescription opioids in the past 30 days were younger (15.1 years) compared to those who had MU only (16.4 years) and any NMU (16.5 years; p=0.0001). The same pattern was observed for females, with a mean age of 15.0 years for no use in the past 30 days compared to 16.2 years for both MU only and any NMU (p=0.0001). Among males, ever using alcohol, tobacco or marijuana was more prevalent among those with any NMU in the past 30 days (90.6, 80.7 and 92.2%, respectively) compared to those with MU only (70.3, 51.4 and 66.2%, respectively) and those who had not used prescription opioids in the past 30 days (42.5, 24.7 and 30.2%, respectively; all p<0.0001). The same pattern was observed for females.

Both males and females who had any NMU in the past 30 days had a higher prevalence of lifetime NMU of other prescription opioids (52.1 and 45.8%, respectively) compared to those with MU only and no use in the past 30 days (males: 14.7 and 3.3%, respectively; females: 8.6 and 2.1%, respectively; $p<0.0001$ for both). Males who had any NMU were also found to have a higher prevalence of feeling down or depressed for two weeks or more in the past 12 months (54.2%) compared to MU only and non-users in the past 30 days (36.0 and 30.0%, respectively; $p<0.0001$). The same pattern was also observed for females (71.2 vs 50.5 and 42.0%, respectively; $p<0.0001$) and overall prevalence of depressive symptoms among females was greater than for males. Ever experiencing anxiety symptoms for six months or more was more prevalent for both any NMU and MU only among males (37.7 and 34.7%, respectively) when compared to no use of prescription opioids in the past 30 days (20.3%, $p<0.0001$). Among females the same pattern was observed, though overall prevalence of anxiety symptoms in each category was higher (54.3, 45.7 and 29.1%, respectively; $p<0.0001$).

Examination of relationship level factors revealed little difference in terms of prevalence of each home setting (who youth live with) between males and females; however, among both males and females, it was observed that those living with other relatives, foster parents or in another setting had a higher prevalence of any NMU (15.6 and 15.7%, respectively) than MU only (9.3 and 9.5%, respectively) and no use in the past 30 days (9.2 and 8.6%, respectively; $p=0.0389$ and 0.0013). Number of close friends varied for males and females, with males having a higher mean number of close friends across all categories (range: 6.2-7.0 friends; $p=0.0387$) compared to females (range: 5.4-5.8 friends; $p=0.6265$). Mean number of close friends using other substances was also higher among all prescription opioid use categories for males compared to females. Mean number of close friends using other substances increased from no

use in the past 30 days for both males and females (3.1 and 2.4, respectively) to MU only (5.0 and 3.6, respectively) to any NMU in the past 30 days (6.8 and 5.1, respectively; $p<0.0001$ for both). The mean proportion of close friends using substances (relative to number of close friends) also increased among males and females, from no use in the past 30 days (50 and 40%, respectively) to MU only (80 and 60%, respectively) to any NMU (100 and 80%, respectively; $p<0.0001$ for both). Ever obtaining alcohol from friends was more prevalent among youth with any NMU in the past 30 days for both males and females (84.4 and 87.6%, respectively), compared to MU only (56.0 and 54.3%, respectively) and no use of prescription opioids in the past 30 days (31.6 and 33.3%, respectively; $p<0.0001$ for both). Similarly, ever obtaining alcohol from parents was more prevalent among youth with any past 30 day NMU for both males and females (44.8 and 51.0%, respectively), compared to MU only (26.7 and 30.5%, respectively) and no use in the past 30 days (15.5 and 17.1%, respectively; $p<0.0001$ for both). Examination of the community level factor of urban area of residence showed no difference in prevalence of prescription opioid NMU among males or females living in urban or non-urban areas ($p=0.1749$ and $p=0.1246$, respectively).

Multinomial logistic regression revealed that after controlling for other significant covariates, sex differences were present among risk factors for prescription opioid NMU at both individual and relationship level, but not at community level (Table 4-3). Moderation of the effect of each peer influence variable (number of close friends, number of close friends using other substances and ever obtaining alcohol from friends) by parental guidance (home setting [who youth lived with], parental warnings against substance use and ever obtaining alcohol from parents) was assessed and no evidence of moderation was found (all $p>0.05$). As such, all variables were fitted individually in the final model with no interaction term. The reference

group for the multinomial logistic regression was no use of prescription opioids in the past 30 days. Among males, backwards elimination determined that lifetime use of marijuana and tobacco were significant risk factors at the individual level, along with depressive symptoms. In contrast, lifetime use of alcohol, tobacco and marijuana were significant risk factors for females at the individual level, along with anxiety symptoms. At the relationship level, number of close friends, number of close friends using other substances and ever obtaining alcohol from parents were significant risk factors for males. Number of close friends and number of close friends using other substances were significant risk factors for females. Home setting, urban area of residence and ever obtaining alcohol from friends were not found to be significant risk factors for either males or females after controlling for other covariates. Age was also not found to be a significant risk factor for either males or females but was kept in the final model, as adjustment for age when considering NMU of prescription opioids is important.

Results from the final multinomial logistic regression model revealed that males who had ever used tobacco in their lifetime (vs no lifetime use of tobacco) had 3.70 times the odds of any prescription opioid NMU in the past 30 days compared to no use of prescription opioids in the past 30 days (95% Confidence Interval [CI]: 2.00, 6.83) after controlling for other covariates. The same effect was not observed for MU only in the past 30 days (Odds Ratio [OR] =0.91; 95% CI: 0.43, 1.91). Males who had ever used marijuana in their lifetime (vs no lifetime use of marijuana) were over five times as likely to have any prescription opioid NMU in the past 30 days (OR=5.23; 95% CI: 2.18, 12.51) or MU only (OR=5.24; 95% CI: 2.15, 12.78) compared to no use of prescription opioids in the past 30 days. Males who had experienced depressive symptoms for two weeks or more in the past 12 months (vs no depressive symptoms) had 2.53 times the odds of any NMU in the past 30 days, compared to no use of prescription opioids in the

past 30 days (95% CI: 1.57, 4.06). The reverse was seen for MU only among males; those who experienced depressive symptoms for two weeks or more in the past 12 months (vs no depressive symptoms) were 59% less likely to have MU only of prescription opioids in the past 30 days compared to no use of prescription opioids in the past 30 days (OR=0.41; 95% CI: 0.18, 0.95). Among males, for each additional close friend using other substances, there was a 23% increase in the odds of any NMU of prescription opioids compared to no use of prescription opioids in the past 30 days (OR=1.23; 95% CI: 1.11, 1.37). Conversely, for each additional close friend, there was a 13% decrease in the odds of any prescription opioid NMU among males compared to no use of prescription opioids in the past 30 days (OR=0.87; 95% CI: 0.78, 0.97). Finally, males who ever obtained alcohol from their parents (vs never obtained alcohol from their parents) had 2.49 times the odds of prescription opioid NMU compared to no prescription opioid use in the past 30 days (95% CI: 1.54, 4.03).

Among females, lifetime ever users of tobacco (vs never use of tobacco) and marijuana (vs never use of marijuana) had 2.43 and 2.60 times the odds of any prescription opioid NMU in the past 30 days, compared to no use of prescription opioids in the past 30 days (95% CI: 1.38, 4.29 and 1.33, 5.09, respectively) after controlling for other covariates. The most important risk factor for prescription opioid NMU among females was lifetime use of alcohol; those who had ever used alcohol in their lifetime (vs never use of alcohol) were over 13 times as likely to have any NMU of prescription opioids in the past 30 days compared to no prescription opioid use in the past 30 days (OR=13.28; 95% CI: 3.03, 58.22). Females who had ever experienced anxiety symptoms for six months or more (vs no anxiety symptoms) were 75% more likely to have any NMU of prescription opioids compared to no use of prescription opioids in the past 30 days (95% CI: 1.07, 2.85). Number of close friends was found to be a protective factor against

prescription opioid NMU among females; for each additional close friend there was a 14% decrease in the odds of any prescription opioid NMU compared no use of prescription opioids in the past 30 days (OR=0.86, 95% CI: 0.77, 0.96). The number of close friends using other substances had the opposite effect among females; for each additional close friend using other substances there was a 15% increase in the odds of any prescription opioid NMU in the past 30 days compared to no use of prescription opioids in the past 30 days (OR=1.15, 95% CI: 1.04, 1.27).

Discussion

Our analysis aimed to examine the effect of peer influences and parental guidance (relationship level factors) on patterns of past 30 day prescription opioid use, including NMU, among males and females separately. Examination of risk factors prior to adjustment for other covariates revealed that most factors associated with any NMU among the entire study sample remained after stratification by sex. Final adjustment for other covariates showed sex differences in relationship level factors, in addition to sex differences in individual level factors. Sex differences in the community level factor of urban area of residence were not found.

Within the context of the socio-ecological model, we hypothesized that sex differences may arise due to differing sex specific expectations and norms. Examination of peer influence showed minimal difference in the effect of peer influence on prescription opioid NMU by sex. An increased number of close friends conferred a protective effect among both males and females at a similar magnitude. Male and females who have more close friends are less likely to have past 30 day prescription opioid NMU. Conversely, having more close friends who use other substances increased the risk of past 30 day prescription opioid NMU among both males and females, after controlling for other factors including number of close friends. This finding partially confirms our first hypothesis. We hypothesized that for each additional close friend who

uses other substances (marijuana or tobacco), the odds of prescription opioid NMU, but not MU, will increase among males, but not females, after controlling for individual, relationship and community level factors, when compared to no use of prescription opioids in the past 30 days. This effect was observed among females as well as males (which was not hypothesized), suggesting that sex differences in peer influence are minimal after controlling for factors at different levels of the model; however, the magnitude of effect was greater for males than females (OR=1.23 vs 1.15). This finding is concordant with existing literature, as negative peer influence has previously been established as a risk factor for various types of illicit drug use (Chan et al., 2017; McDonough et al., 2016), though this was for other substance use and not prescription opioid NMU.

Causality cannot be assumed for any of the findings in this study as the data are cross-sectional, though causality is important to consider given that prevention approaches may only be effective if there is a causal association between the exposure and the outcome of prescription opioid NMU. Subsequently, it is important to consider whether the association between peer influence and past 30 day prescription opioid NMU is causal. One approach for determining causality is to use the Bradford-Hill criteria for causation; these consist of nine criteria which can be used to provide epidemiologic support for a causal relationship. The criteria are: temporality (the effect occurs after the cause), strength (effect size), consistency (reproducibility), specificity, biological gradient (e.g. dose-response), plausibility, coherence (between epidemiological studies and animal studies), experiment (clinical trials) and analogy. Due to the cross-sectional study design, we cannot confirm temporality because we cannot determine whether the cause (peer influence) preceded the effect (past 30 day prescription opioid NMU); however, we can consider strength of association, analogy and plausibility from the Bradford-Hill criteria for causation. A

strong association was not found for any of the peer influence variables examined because none of the odds ratios were greater than two; however, the association is analogous with findings from studies of other illicit drug use as negative peer influence has previously been associated with other illicit drug use (Chan et al., 2017; McDonough et al., 2016). The association between peer influence and past 30 day prescription opioid NMU is also plausible. Based on this evidence we can conclude that the cross-sectional association between peer influence and past 30 day prescription opioid NMU may be causal, though further evidence from other studies would be needed. Unfortunately, this evidence cannot be provided using the N-MAPSS dataset as all data were collected anonymously and no follow up is possible.

Moderation of the effect of peer influence by parental guidance was not seen in our analysis, disproving our third hypothesis. We hypothesized that parental guidance will moderate the relationship between number of close friends using other substances (tobacco or marijuana) and prescription opioid NMU, but not MU, among females only. Our findings indicated that moderation was not present for either MU only or any NMU in the past 30 days among males or females. This finding is discordant from another study in the published literature which did observe a moderating effect of parental guidance on peer influence for illicit drug use (Chan et al., 2017).

Peer influence may be important to consider when designing prevention efforts in youth. Our results indicate that encouraging and maintaining multiple close friendships could prevent prescription opioid NMU. In addition, discouraging close friendships with those who use illicit substances may decrease the risk of prescription opioid NMU. Approaches such as parents limiting their children's time with friends have been studied previously (Seedall & Anthony, 2013). Based on our analysis, this strategy may have the unintended consequence of reducing the

protective effect of having a large number of close friends. Limiting time with friends who are using other substances (marijuana or tobacco) is likely to have a positive impact by reducing the harmful effect of this factor among both males and females, but this may not be feasible if parents do not have knowledge about their children's friends substance use. Overall, caution should be taken to ensure that close friendships are not discouraged altogether.

Parental guidance was examined within this study to determine if this risk factor varied by the sex of the child. We found that lack of parental guidance in the form of providing alcohol to youth increases the likelihood of prescription opioid NMU among males only, not females. This result indicates that our second hypothesis was not correct. We hypothesized that females who are given alcohol by their parents (vs females who are not given alcohol by their parents) will have increased odds of prescription opioid NMU, but not MU, compared to no use of prescription opioids in the past 30 days, after controlling for individual, relationship and community level factors. This could be because positive and negative parental guidance differ by sex. It is possible that positive parental guidance has a greater influence among females than negative parental guidance, whereas for males, this lack of parental guidance leads to harmful outcomes. Within our analysis, we focused on lack of parental guidance, rather than positive guidance and support. Previous research has shown that females are more heavily influenced by parental support and guidance than males, and that this could be a protective factor against other substance use such as marijuana (Dunn et al., 2011), which would support our theory. Considering the results of our analysis, limiting parental provision of alcohol to youth is a strategy that could be implemented towards both sexes; however, this may have a greater impact in reducing prescription opioid NMU among males rather than females. Moreover, it is important to consider whether our finding regarding parental provision of alcohol to male youth and past

30 day prescription opioid NMU is causal. We cannot consider causality in terms of temporality due to the cross-sectional nature of the data, because it cannot be determined if the cause preceded the effect. The strong association (an odds ratio greater than two) for this factor and the plausible explanation for this finding among males suggests that a causal association may be present. Further evidence from other studies, especially regarding temporality, is needed to confirm whether this finding is causal.

Parental warnings against other substance use had no effect on prescription opioid NMU, which may be because parents did not specifically warn against prescription opioid NMU or because these warnings had little impact on youth behavior. There is no information in the current literature about the effect of direct parental warnings against prescription opioid NMU in youth, but this should be explored further in future studies. Moreover, home setting (who youth lived with) was also found to have no effect on prescription opioid NMU after controlling for factors at different levels of the socio-ecological model. An explanation for this finding could be that who youth live with is not important when considering prescription opioid NMU, but guidance, monitoring and support by their guardian is important.

Individual level risk factors, which we have previously found to be associated with prescription opioid NMU, remained significant for both females and males after adjustment for other covariates, including relationship level factors. Lifetime use of tobacco and marijuana were observed to be risk factors for any NMU of prescription opioids in the past 30 days among both males and females. Causality cannot be confirmed through these statistically significant results alone though. If we consider the Bradford-Hill criteria for causation again, this association may be considered causal given the strong association (odds ratios greater than two) among both males and females, in addition to consistency with previous studies examining these factors.

Given the lack of temporality though, these findings cannot be confirmed as causal associations. Prevention of use of these substances may still have a significant impact on prescription opioid NMU among youth. Both tobacco and marijuana appear to be more significant risk factors among males than females, as evidenced by their larger effect sizes. Strategies could prioritize prevention of tobacco and marijuana use among males to reduce prescription opioid NMU. Marijuana users were also more likely to have prescription opioid MU only, compared to those who did not use prescription opioids in the past 30 days. Consequently, it appears that marijuana use may not be only associated with NMU, but may be reflective of use of prescription opioids for MU. This might be because marijuana can be used to self-treat pain (Hill, Palastro, Johnson, & Ditre, 2017; Romero-Sandoval, Kolano, & Alvarado-Vázquez, 2017); since MU only of prescription opioids suggests they are being used to treat pain, it is possible that the high prevalence of marijuana use among those with prescription opioid MU only is reflective of use for pain treatment. Moreover, in concordance with our previous finding, we found that lifetime alcohol use is a risk factor for any NMU among females, but not males (Osborne et al., 2017). This effect remains after adjustment for other individual and relationship level risk factors. Alcohol appears to be the strongest risk factor for prescription opioid NMU among females and given the very large effect size (odds ratio greater than 13), we should pay attention to this behavior for interventions. The harmful effects of alcohol use in youth have been well documented previously (Herbert, Gilbert, González-Izquierdo, Pitman, & Li, 2015; Jacobus, Squeglia, Sorg, Nguyen-Louie, & Tapert, 2014; Liang & Chikritzhs, 2015; Palamar et al., 2014), so prevention efforts are important both to prevent prescription opioid NMU and to mitigate the risks of alcohol use. Existing literature suggests that supplies of alcohol from non-parental sources are associated with increased risk of drinking among youth (Mattick et al., 2017);

however, within N-MAPSS, there appears to be no additional risk conferred by receiving alcohol from a specific source, such as parents or peers, among females. This indicates that use of alcohol regardless of source is dangerous for females in terms of prescription opioid NMU. Preventing alcohol use among females is a key strategy that should be prioritized and implemented.

Finally, depressive symptoms were found to be associated with an increased risk of prescription opioid NMU among males but not females. Those with depressive symptoms were also significantly less likely to have prescription opioid MU only; the current literature among adults suggests that those with depression may be more likely to have prescription opioid NMU than those without depression (Mason et al., 2016; Zullig & Divin, 2012). There are several explanations for our finding among males. First, if males with MU do not remain as medical users, but progress to NMU, this may explain both the increased odds for prescription opioid NMU and the decreased odds for prescription opioid MU only. Second, it is possible that depressive symptoms are only associated with prescription opioid NMU among males, and not females, because males may be less likely to seek medical help for their depressive symptoms. This has been seen previously in many other studies among adult males (Magaard, Seeralan, Schulz, & Brütt, 2017; Wahto & Swift, 2016). In terms of prevention efforts, our results suggest that young males who exhibit or report depressive symptoms should be offered greater support and information regarding available help and treatment, which may prevent prescription opioid NMU. Conversely, anxiety symptoms were associated with an increased risk of prescription opioid NMU among females but not males. One possible explanation for this result is that prescription opioids may be used non-medically to self-treat various conditions, including anxiety (Young, McCabe, Cranford, Ross-Durow, & Boyd, 2012). In terms of prevention of

prescription opioid NMU, these findings suggest that diagnosis and treatment of conditions such as depressive symptoms and anxiety symptoms among youth may be important for reducing prevalence of NMU.

Overall, the results of this analysis suggest that considering sex differences in relationship level risk factors in addition to individual level risk factors is important when considering past 30 day NMU of prescription opioids among youth.

Strengths and Limitations

Strengths of this study include collection of information on risk factors at individual, relationship and community level, allowing us to examine prescription opioid NMU among youth, within the context of the socio-ecological model. Moreover, this study was conducted outside of the home or school setting, unlike other large national surveys, and did not require parental consent to participate. This is likely to reduce social desirability bias by encouraging youth to answer questions honestly. A further strength of this study is that we had a rich dataset with information on many relationship level factors. This allowed us to test hypotheses about how relationships influence prescription opioid NMU among youth, while controlling for factors at other levels of the model.

A limitation of this study is that data are cross-sectional, so we cannot examine whether certain risk factors, such as obtaining alcohol from parents, occurred prior to initiation of NMU. Differential recall may be present when considering the effect of number of close friends using substances; youth with past 30 day prescription opioid NMU may be more likely to report that all their friends use substances as a justification for their drug use behavior, even if this is not the case. Reverse causality may also be an issue if youth have close friends who use other substances. These close friends may have initiated substance use as a result of the youth's past 30 day NMU of prescription opioids; however, this still suggests that peer influence is a risk

factor for substance use among youth. Finally, it is a limitation that we did not obtain information on factors such as parental warnings against prescription opioid NMU specifically. The results of this study remain useful as we were able to examine different levels of risk factors among a large sample of nationally representative youth. We were also able to make recommendations on prevention efforts which could be tested in the future.

Conclusion

Minimal sex differences in relationship level risk factors for prescription opioid NMU exist; males are more likely to have past 30 day prescription opioid NMU if they have more close friends who have used other substances and parents who have given them alcohol, compared to their counterparts. Conversely, males are less likely to have past 30 day prescription opioid NMU if they have a higher number of close friends. In contrast, females are less likely to have past 30 day prescription opioid NMU if they have a higher number of close friends but are more likely to have NMU if they have more close friends who have used other substances, compared to their counterparts. Individual level risk factors for prescription opioid NMU differed by sex after adjustment for relationship level factors. Prevention efforts should consider both individual and relationship level factors and consider targeting some efforts differently towards males and females.

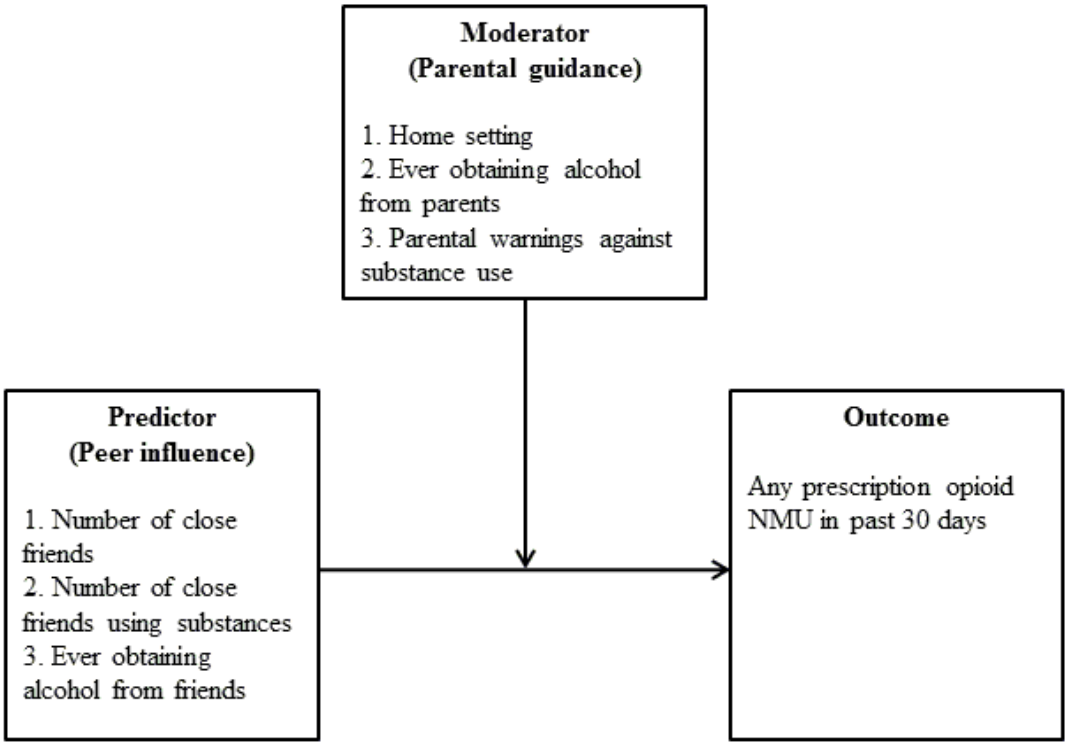


Figure 4-1. Tested moderation models for effect of peer influence on past 30 day prescription opioid NMU among youth

Table 4-1. Individual, relationship and community level factors in the whole sample, stratified by past 30 day prescription opioid use

	No use of opioids in past 30 days (n=10,440) N (%)	Medical use of opioids only in past 30 days (n=180) N (%)	Any non-medical use of opioids in past 30 days (n=345) N (%)	p-value (chi square or ANOVA)
INDIVIDUAL LEVEL FACTORS				
Age				
Mean (SD)	15.1 (2.1)	16.3 (1.6)	16.4 (1.4)	<0.0001
Lifetime use of tobacco				
Never	7949 (76.4)	98 (55.1)	76 (22.0)	<0.0001
Ever	2462 (23.7)	80 (44.9)	269 (78.0)	
Lifetime use of marijuana				
Never	7630 (73.2)	69 (38.6)	42 (12.2)	<0.0001
Ever	2797 (26.8)	110 (61.5)	303 (87.8)	
Lifetime use of alcohol				
Never	5894 (56.7)	59 (33.0)	29 (8.4)	<0.0001
Ever	4499 (43.3)	120 (67.0)	316 (91.6)	
Lifetime use of prescription opioids				
Never	9683 (92.9)	119 (66.1)	153 (44.4)	<0.0001
Medical use only	463 (4.4)	41 (22.8)	22 (6.4)	
Non-medical use	278 (2.7)	20 (11.1)	170 (49.3)	
Two weeks or more in the past 12 months where lost interest in things				
No	6688 (64.3)	103 (57.2)	144 (41.7)	<0.0001
Yes	3715 (35.7)	77 (42.8)	201 (58.3)	
Two weeks or more in the past 12 months where felt down or depressed				
No	6632 (63.7)	100 (55.6)	132 (38.3)	<0.0001
Yes	3777 (36.3)	80 (44.4)	213 (61.7)	
Ever felt worried or stressed for 6 months or more (anxiety symptoms)				
No	7828 (75.1)	106 (58.9)	189 (54.9)	<0.0001
Yes	2597 (24.9)	74 (41.1)	155 (45.1)	
RELATIONSHIP LEVEL FACTORS				
Home setting				
Living with both parents at the same time	5790 (55.5)	104 (57.8)	146 (42.3)	<0.0001
Living with both parents not at the same time	747 (7.2)	9 (5.0)	32 (9.3)	
Living with one parent only	2970 (28.5)	50 (27.8)	113 (32.8)	
Living with other relative, foster parents or in another setting	930 (8.9)	17 (9.4)	54 (15.7)	
Number of close friends				
Mean (SD)	6.0 (3.4)	6.2 (3.3)	6.2 (3.3)	0.5338

Table 4-1. Continued

	No use of opioids in past 30 days (n=10,440) N (%)	Medical use of opioids only in past 30 days (n=180) N (%)	Any non-medical use of opioids in past 30 days (n=345) N (%)	p-value (chi square or ANOVA)
Number of close friends using substances [a]				
Mean (SD)	2.7 (3.3)	4.3 (3.3)	6.0 (3.6)	<0.0001
Proportion of close friends using substances [a]				
Mean (SD)	0.4 (0.4)	0.7 (0.4)	0.9 (0.2)	<0.0001 [b]
Parental warnings against other substance use [a]				
No	1146 (21.7)	17 (22.1)	22 (13.8)	0.0548
Yes	4141 (78.3)	60 (77.9)	138 (86.3)	
Ever obtained alcohol from friends				
No	7050 (67.5)	81 (45.0)	49 (14.2)	<0.0001
Yes	3390 (32.5)	99 (55.0)	296 (85.8)	
Ever obtained alcohol from parents				
No	8730 (83.6)	128 (71.1)	181 (52.5)	<0.0001
Yes	1710 (16.4)	52 (28.9)	164 (47.5)	
COMMUNITY LEVEL FACTORS				
Urban area of residence				
No	5452 (52.2)	103 (57.2)	202 (58.6)	0.0302
Yes	4988 (47.8)	77 (42.8)	143 (41.5)	

SD= Standard Deviation; ANOVA= Analysis of Variance; [a] Data available from waves 3 and 4 only; sample size=5584; [b] Kruskal-Wallis test used due to non-normal data distribution

Table 4-2. Individual, relationship and community level risk factors for past 30 prescription opioid use, stratified by sex

	Males (n=5234)				Females (n=5731)			
	No use of opioids in past 30 days (n=4967) N (%)	Medical use of opioids only in past 30 days (n=75) N (%)	Any non-medical use of opioids in past 30 days (n=192) N (%)	p-value (chi square or ANOVA)	No use of opioids in past 30 days (n=5473) N (%)	Medical use of opioids only in past 30 days (n=105) N (%)	Any non-medical use of opioids in past 30 days (n=153) N (%)	p-value (chi square or ANOVA)
INDIVIDUAL LEVEL FACTORS								
Age	15.1 (2.2)	16.4 (1.6)	16.5 (1.4)	0.0001	15.0 (2.1)	16.2 (1.6)	16.2 (1.4)	0.0001
Mean (SD)								
Lifetime use of tobacco								
Never	3733 (75.4)	36 (48.7)	37 (19.3)	<0.0001	4216 (77.3)	62 (59.6)	39 (25.5)	<0.0001
Ever	1221 (24.7)	38 (51.4)	155 (80.7)		1241 (22.7)	42 (40.4)	114 (74.5)	
Lifetime use of marijuana								
Never	3462 (69.8)	22 (29.7)	15 (7.8)	<0.0001	4168 (76.2)	47 (44.8)	27 (17.7)	<0.0001
Ever	1498 (30.2)	52 (70.3)	177 (92.2)		1299 (23.8)	58 (55.2)	126 (82.4)	
Lifetime use of alcohol								
Never	2843 (57.5)	25 (33.8)	18 (9.4)	<0.0001	3051 (56.0)	34 (32.4)	11 (7.2)	<0.0001
Ever	2100 (42.5)	49 (66.2)	174 (90.6)		2399 (44.0)	71 (67.6)	142 (92.8)	
Lifetime use of prescription opioids								
Never	4606 (92.9)	51 (68.0)	82 (42.7)	<0.0001	5077 (92.9)	68 (64.8)	71 (46.4)	<0.0001
Medical use only	190 (3.8)	13 (17.3)	10 (5.2)		273 (5.0)	28 (26.7)	12 (7.8)	
Non-medical use	162 (3.3)	11 (14.7)	100 (52.1)		116 (2.1)	9 (8.6)	70 (45.8)	
Two weeks or more in the past 12 months where lost interest in things								
No	3276 (66.2)	48 (64.0)	88 (45.8)	<0.0001	3412 (62.6)	55 (52.4)	56 (36.6)	<0.0001
Yes	1676 (33.8)	27 (36.0)	104 (54.2)		2039 (37.4)	50 (47.6)	97 (63.4)	
Two weeks or more in the past 12 months where felt down or depressed								
No	3467 (70.0)	48 (64.0)	88 (45.8)	<0.0001	3165 (58.0)	52 (49.5)	44 (28.8)	<0.0001
Yes	1486 (30.0)	27 (36.0)	104 (54.2)		2291 (42.0)	53 (50.5)	109 (71.2)	
Ever felt worried or stressed for 6 months or more (anxiety symptoms)								
No	3949 (79.7)	49 (65.3)	119 (62.3)	<0.0001	3879 (70.9)	57 (54.3)	70 (45.8)	<0.0001
Yes	1008 (20.3)	26 (34.7)	72 (37.7)		1589 (29.1)	48 (45.7)	83 (54.3)	

Table 4-2. Continued

	Males (n=5234)				Females (n=5731)			
	No use of opioids in past 30 days (n=4967) N (%)	Medical use of opioids only in past 30 days (n=75) N (%)	Any non-medical use of opioids in past 30 days (n=192) N (%)	p-value (chi square or ANOVA)	No use of opioids in past 30 days (n=5473) N (%)	Medical use of opioids only in past 30 days (n=105) N (%)	Any non-medical use of opioids in past 30 days (n=153) N (%)	p-value (chi square or ANOVA)
RELATIONSHIP LEVEL FACTORS								
Home setting								
Living with both parents at the same time	2715 (54.7)	39 (52.0)	85 (44.3)	0.0389	3075 (56.2)	65 (61.9)	61 (40.0)	0.0013
Living with both parents not at the same time	387 (7.8)	5 (6.7)	18 (9.4)		360 (6.6)	4 (3.8)	14 (9.2)	
Living with one parent only	1406 (28.3)	24 (32.0)	59 (30.7)		1564 (28.6)	26 (24.8)	54 (35.3)	
Living with other relative, foster parents or in another setting	457 (9.2)	7 (9.3)	30 (15.6)		473 (8.6)	10 (9.5)	24 (15.7)	
Number of close friends Mean (SD)	6.2 (3.5)	7.0 (3.2)	6.8 (3.4)	0.0387	5.8 (3.3)	5.6 (3.2)	5.4 (3.0)	0.6265
Number of close friends using substances [a] Mean (SD)	3.1 (3.5)	5.0 (3.0)	6.8 (3.4)	<0.0001	2.4 (3.1)	3.6 (3.4)	5.1 (3.6)	<0.0001
Proportion of close friends using substances [a]								
Mean (SD)	0.5 (0.4)	0.8 (0.3)	1.0 (0.1)	<0.0001 [b]	0.4 (0.4)	0.6 (0.4)	0.8 (0.3)	<0.0001 [b]
Parental warnings against other substance use [a]								
No	463 (19.2)	10 (26.3)	11 (12.8)	0.1736	683 (23.8)	7 (18.0)	11 (14.9)	0.1432
Yes	1955 (80.9)	28 (73.7)	75 (87.2)		2186 (76.2)	32 (82.1)	63 (85.1)	
Ever obtained alcohol from friends								
No	3398 (68.4)	33 (44.0)	30 (15.6)	<0.0001	3652 (66.7)	48 (45.7)	19 (12.4)	<0.0001
Yes	1569 (31.6)	42 (56.0)	162 (84.4)		1821 (33.3)	57 (54.3)	134 (87.6)	
Ever obtained alcohol from parents								
No	4195 (84.5)	55 (73.3)	106 (55.2)	<0.0001	4535 (82.9)	73 (69.5)	75 (49.0)	<0.0001
Yes	772 (15.5)	20 (26.7)	86 (44.8)		938 (17.1)	32 (30.5)	78 (51.0)	
COMMUNITY LEVEL FACTORS								
Urban area of residence								
No	2560 (51.5)	40 (53.3)	112 (58.3)	0.1749	2892 (52.8)	63 (60.0)	90 (58.8)	0.1246
Yes	2407 (48.5)	35 (46.7)	80 (41.7)		2581 (47.2)	42 (40.0)	63 (41.2)	

*SD= Standard Deviation; ANOVA= Analysis of Variance; [a] Data available from waves 3 and 4 only; sample size=5584; [b] Kruskal-Wallis test used due to non-normal data distribution

Table 4-3. Results of multinomial logistic regression analysis examining individual and relationship level factors for medical and non-medical past 30 day use of prescription opioids, by sex

	Males (n=2524)		Females (n=2964)	
	Medical use of opioids only in past 30 days OR [a] (95% CI)	Any non-medical use of opioids in past 30 days OR (95% CI)	Medical use of opioids only in past 30 days OR (95% CI)	Any non-medical use of opioids in past 30 days OR (95% CI)
INDIVIDUAL LEVEL FACTORS				
Age	1.20 (0.97, 1.48)	0.95 (0.82, 1.11)	1.15 (0.94, 1.41)	0.96 (0.82, 1.12)
Lifetime use of tobacco				
Never	ref	ref	ref	ref
Ever	0.91 (0.43, 1.91)	3.70 (2.00, 6.83)	0.54 (0.24, 1.22)	2.43 (1.38, 4.29)
Lifetime use of marijuana				
Never	ref	ref	ref	ref
Ever	5.24 (2.15, 12.78)	5.23 (2.18, 12.51)	2.49 (1.06, 5.84)	2.60 (1.33, 5.09)
Lifetime use of alcohol				
Never	-	-	ref	ref
Ever	-	-	1.67 (0.73, 3.83)	13.28 (3.03, 58.22)
Two weeks or more in the past 12 months where felt down or depressed				
No	ref	ref	-	-
Yes	0.41 (0.18, 0.95)	2.53 (1.57, 4.06)	-	-
Ever felt worried or stressed for 6 months or more				
No	-	-	ref	ref
Yes	-	-	1.78 (0.92, 3.45)	1.75 (1.07, 2.85)
RELATIONSHIP LEVEL FACTORS				
Number of close friends	1.03 (0.91, 1.17)	0.87 (0.78, 0.97)	0.99 (0.87, 1.12)	0.86 (0.77, 0.96)
Number of close friends using substances [b]	1.00 (0.88, 1.14)	1.23 (1.11, 1.37)	1.03 (0.89, 1.18)	1.15 (1.04, 1.27)
Ever obtained alcohol from parents				
No	ref	ref	-	-
Yes	1.30 (0.60, 2.81)	2.49 (1.54, 4.03)	-	-

OR= odds ratio; CI= Confidence Interval; ref= reference group; [a] All odds ratios adjusted for other covariates in the model and reference group is no use of prescription opioids in past 30 days; [b] data only used from waves 3 and 4 (sample size=5584)

CHAPTER 5
THE EFFECT OF RECALLED AGE OF FIRST USE OF PRESCRIPTION OPIOIDS ON NON-MEDICAL USE AMONG OLDER ADOLESCENTS: EXAMINATION OF SEX DIFFERENCES

Background

Prescription opioid overdose is a major crisis currently affecting the US; use of prescription opioids has more than doubled since the early 1990's and this trend has contributed to a continuing increase in opioid overdoses (National Institute on Drug Abuse, 2014a; Pezalla et al., 2017). The majority of drug overdoses in the US involve opioids and current estimates indicate that 175 Americans die every day from drug overdose (Christie et al., 2017). In addition, opioid overdoses among females have increased in recent years, although males are still more likely to die from opioid overdoses (Serdarevic et al., 2017). Moreover, females are twice as likely to be prescribed opioids compared to males (Serdarevic et al., 2017), suggesting that sex is an important factor to examine in the context of the opioid epidemic. The consequences among youth are also of great concern; between 1997 and 2012, the rate of hospitalizations for prescription opioid poisonings for youth aged 15 to 19 years rose from 3.69 to 10.17 per 100,000 persons (Gaither et al., 2016).

Non-Medical Use (NMU) of prescription opioids increases the risk of overdose, so efforts to combat NMU are a priority. NMU has been defined previously as: use of someone else's prescription medication, use of a patient's own prescription in a way other than prescribed, use to get high, and use at higher doses than prescribed (Boyd & McCabe, 2008; Boyd et al., 2009; Shield et al., 2013). In contrast, use of a prescription medication as prescribed can be considered Medical Use (MU) (McCabe et al., 2013b).

To further examine prescription opioid NMU among youth, a theoretical model can be used to contextualize NMU behavior. The socio-ecological model is a multi-level model which

theorizes that people are not only influenced by their own specific characteristics but also by their relationships with others, the community where they live and the broader society in which those communities are placed (McLeroy et al., 1988; Substance Abuse and Mental Health Services Administration, 2016). Sex differences may arise in prescription opioid NMU behavior, within the context of the socio-ecological model, because NMU behavior is influenced by other factors which differ by sex. Sex based stereotypes are established in youth due to differing external influences, such as parental guidance, monitoring and support (Hyde, 2014; Kågesten et al., 2016; Witt, 1997). We have previously explored how youth 10 to 18 years in the US are using prescription opioids non-medically and the risk factors for NMU at individual, relationship and community levels of the socio-ecological model (Chapters 3 and 4). In this analysis, we focus on sex differences in the individual level factor of recalled age of first use of prescription opioids, but also explore how this factor influences NMU in the presence of other individual, relationship and community level factors.

Given that peak annual incidence rates of NMU have been previously observed at age 16 years, recalled age of first use of prescription opioids and past 30 day NMU should be explored among older adolescents (17 and 18 years) to determine whether past 30 day risk of NMU is influenced by the age opioids were first used (as recalled by the adolescent). Ideally, it would be optimal to ask about prescription opioid use and NMU in national surveys from a young age and then follow up youth over time; however, evidence is first needed to provide a guideline of what age groups should be targeted. Current surveys only target those 12 years and over, but it is possible that younger age groups should be surveyed. Examination of recalled age of first use among older adolescents only will ensure that youth have passed through the age of initiation for prescription opioid NMU, thus minimizing selection bias. Within the context of the socio-

ecological model, recalled age of first use of prescription opioids may differ by sex because of differential peer and parental influences. Consequently, it is possible that males may be given prescription opioids at a younger age, or obtain them for NMU at a younger age, compared to females. This can be tested by examining the effect of recalled age of first use on likelihood of past 30 day prescription opioid MU and NMU for males and females. We have seen evidence of sex differences in relationship level factors, in addition to individual level factors, among youth aged 10 to 18 years in our previous analyses; therefore, it is important to consider multiple levels of the socio-ecological model when examining sex differences in risk factors for prescription opioid NMU among youth.

The individual level factors included in this analysis are age, depressive symptoms, anxiety symptoms and lifetime use of prescription opioids, alcohol, tobacco and marijuana. The relationship level factors to be examined are home setting (who youth live with), number of close friends, number of close friends using substances, proportion of close friends using substances (relative to number of close friends) and ever obtaining alcohol from parents. The community level factor to be examined within this analysis is urban area of residence, representing the community where youth live. Based on our findings, prevention strategies could focus on the age at which youth first start using prescription opioids, in addition to other individual, relationship and community level risk factors. The societal level will not be examined.

In the context of other literature, age is a risk factor for prescription opioid NMU that has been examined previously. For example, peak annual incidence rates of NMU of prescription opioids among youth have previously been observed at age 16 (Austic et al., 2015). Other studies have also examined the age of initiation of prescription opioid NMU among youth (Deandrea et al., 2013; Meier et al., 2012). The current literature is limited in that no studies explore sex

differences in the age of first use of prescription opioids (regardless of whether for MU or NMU) and the association with NMU in late adolescence. A recent study showed that adolescents with both MU and NMU were more likely to report MU of prescription opioids before they initiated NMU (McCabe et al., 2017), so examining first age of use for both MU and NMU is important.

Aims and Hypotheses

We aimed to examine sex differences in the effect of recalled age of first use of prescription opioids on past 30 day prescription opioid NMU among 17 and 18 year olds.

This analysis examined how recalled age of first use of prescription opioids affected past 30 day NMU and whether this effect was also influenced by sex. All statistically significant individual, relationship and community level factors were included in the final model, to determine if recalled age of first use was associated with past 30 day NMU after controlling for factors at other levels of the socio-ecological model.

Two hypotheses were proposed among 278 youth 17 and 18 years of age with past 30 day use of prescription opioids:

Hypothesis 1. Recalled age of first use of prescription opioids will occur earlier for males compared to females regardless of type of use pattern (NMU or MU only).

Hypothesis 2. Recalled age of first use of prescription opioids will occur earlier for past 30 day NMU compared to MU, regardless of sex, after controlling for other individual, relationship and community level factors.

Methods

Study Design

The National Monitoring of Adolescent Prescription Stimulants Study (N-MAPSS) was a national study of youth 10 to 18 years conducted in four waves from 2008 to 2011. The cross-sectional survey design captured information on demographics, behavioral characteristics,

prescription drug use and other substance use. The primary aim of the study was to examine prescription stimulant use; however, questions were also asked about other prescription medications, including opioids. Overall, the N-MAPSS sample distribution for age, sex, race and rural/urban was mostly comparable to the 2010 US census (Cottler et al., 2013).

Recruitment for the study was conducted using an entertainment venue intercept method, where youth were recruited from a sampling frame of the entertainment venues within their neighborhood (Muhib et al., 2001). Examples of entertainment venues included shopping malls, cinemas and parks. Time and date of recruitment were randomly selected, ensuring this recruitment method approximated random sampling (Muhib et al., 2001). Urban, rural and suburban areas were targeted in 10 metropolitan areas across the US: Tampa, Seattle, St. Louis, Denver, Houston, Cincinnati, Philadelphia, New York, Boston and Los Angeles. Due to the primary aim of the study, cities were selected from the highest prescribing areas for prescription stimulants, according to the Office of Management and Budget regions within the IMS Health database.

Recruiters approached 21,444 youth over the course of study recruitment and invited them to participate; 25% chose not to learn about the study and 21% of those who were initially interested were ineligible. Of those who chose to learn about the study, 10% refused to participate. In total, 11,048 youth completed the survey and comprise the final sample. The survey was completely anonymous and parental consent was not required to participate. The study design was approved by Washington University and University of Florida Human Protection Research Offices and the research protocol was approved by both Institutional Review Boards.

Measurements

The N-MAPSS survey asked questions about past 30 day use of prescription opioids, accompanied by pictures of the medications in case youth were not aware of the drug names. NMU of prescription opioids was defined as: (1) use other than by mouth (for Vicodin®, hydrocodone, OxyContin® and oxycodone: "In the last 30 days, what are all the ways you used [specific drug name]?") and/or (2) use of someone else's opioids ("In the last 30 days, have you used [specific drug name] that belonged to [List of responses]". MU only was defined as those who had a prescription and no evidence of NMU. Respondents who answered "Yes" to the question "In the last 30 days, have you gotten a prescription or refill for [specific drug name] from [List of responses]?" were identified as having a prescription.

Recalled age of first use of prescription opioids was assessed by the question: "How old were you the first time you took [Specific drug name]". This question was a sub-question that was only asked where respondents reported past 30 day use of prescription opioids. Other covariates examined in this analysis at the individual level were: depressive symptoms, anxiety symptoms and lifetime use of prescription opioids (Percocet®, Darvocet®, Lortab® or codeine), alcohol, tobacco or marijuana. At the relationship level: number of close friends, number of close friends using other substances (marijuana or tobacco), proportion of close friends using other substances (relative to number of close friends) and obtaining alcohol from parents. At the community level: urban area of residence.

Analysis

The final sample size for analysis consisted of 278 youth 17 to 18 years of age who had reported past 30 day use of prescription opioids. Non-parametric survival analysis with lifetable estimates was used to examine recalled age at first use. The SAS® Proc Lifetest procedure was used to produce lifetable estimates of the survival function for prescription opioid recalled age of

first use among those who were past 30 day users. The hazard of first using prescription opioids was defined as the instantaneous rate of first using prescription opioids at any given age (time period). The survival function *S(t)* is the probability that a person did not start using prescription opioids from birth until age *t*. Therefore the failure probability (1-*S(t)*) is the cumulative probability of prescription opioid first use (as recalled by the participant) from birth to age *t*. We also tested whether cumulative probability of prescription opioid first use differed by sex and type of prescription opioid use in the past 30 days (MU only or any NMU) using the strata option and log-rank tests.

Descriptive statistics were calculated to summarize past 30 day prescription opioid use (MU and NMU) among males and females. Individual (including recalled age of first use), relationship and community level variables were tabulated with frequencies, percentages, means and standard deviations, stratified by sex and type of past 30 day use (MU only or NMU). Chi square tests were conducted among males and females separately for categorical variables, comparing MU only to NMU. In addition, t-tests were used for continuous variables. Normality of distributions was assessed to ensure appropriateness of the analysis approach. Due to a non-normal distribution, proportion of close friends using other substances was examined using the Wilcoxon rank-sum test.

Finally, binomial logistic regression was conducted predicting any NMU, adjusting for significant covariates as selected using backwards elimination. This allowed examination of the effect of recalled age of first use of prescription opioids after adjustment for other covariates. For the final model, sex and number of close friends were added back in as these are important covariates to adjust for when considering prescription opioid NMU. Model fit was assessed using the Hosmer-Lemeshow test which assesses whether there is a difference between the observed

and predicted values of the response variable. Non-significance indicated adequate fit. The variance inflation factor (VIF) was assessed for severity of multicollinearity, though removal of variables was not considered further as a value greater than 10 was not identified.

Given an estimated background prevalence of 60% and a sample of 135 in each group, we would have a statistical power of 0.75 to detect a doubling of opioid NMU between groups at 0.05 alpha. All statistical analyses were calculated using SAS® 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Examination of males and females aged 17 and 18 years who used prescription opioids in the past 30 days (regardless of MU or NMU) revealed a similar mean age of first use of prescription opioids for both (15.6 and 15.7 years, respectively). Examination of the cumulative probability of prescription opioid first use (as recalled by the participant) by sex revealed no difference between males and females at any age point (p=0.8646; Figure 5-1).

Sample characteristics were examined by prescription opioid use type (MU only or any NMU) and sex (Table 5-1). Mean recalled age at first use of prescription opioids was similar for males and females among those with past 30 day prescription opioid MU only (16.4 vs 16.5 years, respectively) and NMU (15.3 vs 15.0 years, respectively); however, mean recalled age of first use of prescription opioids was significantly younger for those reporting past 30 day prescription opioid NMU compared to MU only for both males (16.4 vs 15.3 years, respectively; p=0.002) and females (16.5 vs 15.0 years, respectively; p<0.001). Examination of other individual level factors revealed that lifetime use of tobacco was more prevalent among those with any past 30 day prescription opioid NMU compared to MU only for both males (82.7 vs 55.6%, respectively; p<0.001) and females (77.8 vs 47.1%, respectively; p<0.001). Mean age of first use of tobacco did not differ between those with past 30 day prescription opioid MU only

and NMU for either males (14.0 vs 13.3 years, respectively; p=0.310) or females (14.2 vs 13.8 years, respectively; p=0.447). Lifetime use of marijuana was more prevalent among males who reported any past 30 day prescription opioid NMU compared to MU only (93.6 vs 80.0%, respectively; p=0.025), though the same pattern was not found for females (77.8 vs 64.7%, respectively; p=0.164. Mean age of first use of marijuana was significantly younger for those with past 30 day prescription opioid NMU compared to MU only for both males (13.1 vs 14.5 years; p=0.004) and females (13.6 vs 14.8 years; p=0.003). Prevalence of lifetime use of alcohol did not differ significantly between those with past 30 day prescription opioid MU only and NMU for either males or females (p=0.051 and 0.174, respectively); however; age at first use of alcohol was significantly younger for those with past 30 day prescription opioid NMU compared to MU only among females (13.7 vs 14.7 years; p=0.009). The same pattern was not found for males (p=0.813). Among males and females, prevalence of lifetime NMU of prescription opioids (Percocet®, Darvocet®, Lortab® or codeine) was higher for those with past 30 day prescription opioid NMU (56.4 and 50.0%, respectively), compared to those with past 30 day MU only (15.6 and 7.8%, respectively; p<0.001). Among females, depressive symptoms were more prevalent for those reporting past 30 day prescription opioid NMU compared to MU only (69.4 vs 47.1%; p=0.021), though the same was not found for males.

In terms of relationship level factors, mean number of close friends using other substances was higher for males with any past 30 day prescription opioid NMU compared to MU only (7.1 vs 5.0 friends, p=0.019). The same pattern was not observed for females. Similarly, the proportion of close friends using other substances was higher for males with any past 30 day prescription opioid NMU compared to MU only (p=0.026). Among females, the proportion of friends using other substances (marijuana or tobacco) did not significantly differ between

prescription opioid MU only and any NMU (p=0.693). Mean number of close friends did not differ between those with prescription opioid MU only and NMU for either males (p=0.854) or females (p=0.854). Among females, ever obtaining alcohol from parents was more prevalent among those reporting any past 30 day prescription opioid NMU compared to MU only (55.6 vs 31.4%; p=0.014). The same pattern was not observed for males (p=0.486). Finally, the community level factor of urban area of residence did not differ between those with past 30 day prescription opioid MU only and NMU for either males or females (p=0.787 and 0.213, respectively).

Failure probability curves comparing cumulative probability of prescription opioid first use (as recalled by the participant) by prescription opioid use type in the past 30 days revealed a significant difference between those with MU only and any NMU (p<0.0001; Figure 5-2). From the age of 11 years, the cumulative probabilities of prescription opioid first use for prescription opioid MU only and any NMU in the past 30 days diverge; earlier recalled ages at first use for prescription opioids are seen among those with any past 30 day prescription opioid NMU compared to MU only. A steady increase in recalled age of first use is seen among those with past 30 day prescription opioid NMU, whereas very little use before the age of 15 years is seen for those with MU only. Table 5-2 also illustrates these trends and shows that a far higher proportion of those with past 30 day prescription opioid MU only started using prescription opioids at 17 and 18 years (54.2%), compared to those with any NMU (33.5%).

A final binomial logistic regression analysis using backwards elimination determined that recalled age at first use of prescription opioids, lifetime use of prescription opioids, tobacco and marijuana, depressive symptoms and number of close friends using substances were significant risk factors for past 30 day prescription opioid NMU after controlling for other covariates (Table

5-3). While sex and number of close friends were not found to be significant risk factors, these were included in the final model as they are important covariates. For recalled age of first use of prescription opioids, each one year increase in age resulted in a 33% decrease in the odds of any past 30 day prescription opioid NMU compared to MU only, after controlling for covariates (Odds Ratio [OR]=0.67, 95% Confidence Interval [CI]: 0.47, 0.96). Those who had ever used prescription opioids (Percocet®, Darvocet®, Lortab® or codeine) non-medically in their lifetime had 6.28 times the odds of past 30 day prescription opioid NMU compared to past 30 day MU only (95% CI: 1.06, 37.15). In contrast, those who only had MU of prescription opioids in their lifetime had 89% lower odds of past 30 day prescription opioid NMU compared to past 30 day MU only (OR=0.11, 95% CI: 0.02, 0.72). In terms of other substance use, lifetime users of tobacco had 7.74 times the odds of any past 30 day prescription opioid NMU compared to MU only (95% CI: 1.50, 39.99). Conversely, lifetime users of marijuana had a 95% decrease in the odds of any past 30 day prescription opioid NMU compared to MU only (95% CI: 0.01, 0.43). Those who reported depressive symptoms for two weeks or more in the past 12 months had 4.22 times the odds of any past 30 day prescription opioid NMU compared to MU only (95% CI: 1.25, 14.17). Finally, for each additional close friend using substances (marijuana or tobacco), the odds of any past 30 day prescription opioid NMU increased by 62% compared to MU only (95% CI: 1.13, 2.32).

Discussion

Our analysis aimed to examine sex differences in the effect of recalled age of first use of prescription opioids on past 30 day prescription opioid NMU among 17 and 18 year olds from a national study of youth. We found that sex differences in recalled age of first use of prescription opioids did not occur, although differences in recalled age of first use by type of past 30 day prescription opioid use (MU only or any NMU) were present. Recalled age of first use remained

a significant risk factor for past 30 day prescription opioid NMU after controlling for other covariates at individual and relationship level. The community level factor of urban area of residence was not found to be a risk factor for prescription opioid NMU.

In terms of sex differences in recalled age of first use of prescription opioids regardless of pattern (MU only or NMU), we found that there was no difference in age of first use by sex. This evidence does not support our first hypothesis. We hypothesized that recalled age of first use of prescription opioids will occur earlier for males compared to females regardless of prescription opioid use pattern (NMU or MU only). As such, it appears that sex may not have an impact on age of first use of prescription opioids (as recalled by participants), although sex differences have been previously observed in other risk factors for NMU (Osborne et al., 2017). Within the context of the socio-ecological model, this suggests that parental and peer influences do not differ by sex with regards to when youth initiate use of prescription opioids. Consequently, while it appears that sex differences arise in prescription opioid NMU and the risk factors for NMU, the risk factor of recalled age of first use of prescription opioids does not differ for males or females. It remains a risk factor for both sexes. This can be concluded based on the finding that recalled age of first use of prescription opioids occurred earlier for past 30 day NMU compared to MU, after controlling for other individual, relationship and community level factors. Our second hypothesis is supported by this finding. This may indicate that those who start using prescription opioids in early adolescence are more likely to become non-medical users, compared to those who don't start using prescription opioids until later in adolescence. The risk of prescription opioid NMU decreases by a third for each one year increase in age. In addition, the majority of those with prescription opioid MU only at age 17 and 18 years did not start using prescription opioids until they were at least 15 years old. While it is possible that those who

started using in later adolescence and reported past 30 day MU only will eventually progress to NMU as young adults, the pattern of our results indicates that those at greatest risk may start using prescription opioids at a younger age. Statistical significance alone is not enough to infer causation though. One approach to assessing causality is to use the Bradford-Hill Criteria for causation. These consist of nine criteria which provide support for a causal association: temporality (the effect occurs after the cause), strength (effect size), consistency (reproducibility), specificity, biological gradient (e.g. dose-response), plausibility, coherence (between epidemiological studies and animal studies), experiment (clinical trials) and analogy. A causal association is possible when considering some of these criteria; temporality should be met since recalled age of first use should occur prior to past 30 day prescription opioid use. The association is not particularly strong but the result is analogous with a key finding from the Epidemiological Catchment Area study; early use of illicit drugs increases the likelihood of substance abuse (Robins & McEvoy, 1990). Our results revealed that children as young as eight years are using prescription opioids, which is a cause for concern; existing national surveys among youth should consider extending the survey to cover younger ages, including eight to 11 year olds. Overall, preventing or delaying use of prescription opioids in younger adolescents (regardless of whether NMU or MU) may prevent subsequent NMU, though further research is needed to confirm this finding. If found to be consistent with other studies, our finding on early use of prescription opioids and past 30 day NMU could be considered in future prevention strategies- prescribing or giving opioids to young adolescents may need to be avoided where possible. This could be considered because of the risk of NMU in the future, and also because there is limited evidence on efficacy or safety within this age group (Cooper et al., 2017; Wiffen et al., 2017). We recognize that prescribing opioids to children with chronic pain or cancer may

be unavoidable in certain cases, but where possible suitable alternatives could be considered. For example, in the scenario of acute pain from bone fractures, ibuprofen has been shown to be at least as effective as acetaminophen in combination with codeine among children (Drendel et al., 2009). In addition, ibuprofen alone or in combination with acetaminophen for dental extraction pain has also been shown to be effective (Gazal & Mackie, 2007). Finding suitable alternatives to prescription opioids, especially in the case of acute pain, is in concordance with the Food and Drug Administration (FDA) prescribing guidelines for youth. For example, extended release oxycodone can be used in children as young as 11 years of age with "pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate" (Yang et al., 2016).

Within this analysis, we also explored other risk factors for past 30 day prescription opioid NMU among youth 17 and 18 years of age, based on the results of our previous analyses among youth 10 to 18 years of age. Interestingly, there were several differences in the risk factors found from our previous work; lifetime use of alcohol was not found to be a risk factor for any past 30 day NMU among females 17 and 18 years of age, though it was the strongest risk factor seen in previous analyses of youth 10 to 18 years (Osborne et al., 2017). In addition, depressive symptoms in the past 12 months were only associated with past 30 day NMU among females aged 17 and 18 years and not males, which is the opposite pattern to what we have observed previously among youth 10 to 18 years. Finally, ever obtaining alcohol from parents was only found to be a risk factor for past 30 day NMU among females aged 17 and 18 years and not males, which is also the opposite result to that observed previously among youth 10 to 18 years. One explanation for these results is that the current analysis only included those 17 and 18 years of age; this age group can be considered older adolescents who are nearing young

adulthood. As such, the risk factors for past 30 day NMU among this age group may be more closely related to those risk factors previously seen among young adults. For example, our finding that depressive symptoms are only a risk factor among females 17 and 18 years is concordant with previous results seen among young adults for depression; results from the National College Health Assessment (NCHA) survey showed that among college students 18 to 25 years, those who felt depressed had 1.18 times the odds of non-medical use of prescription opioids compared to those who did not feel depressed, after adjustment for covariates (95% CI: 1.03, 1.37) (Zullig & Divin, 2012). After stratification by gender, this effect remained only among females (OR=1.26, 95% CI: 1.06, 1.49) and not males. Considering our result for lifetime alcohol use, this may be a result of all youth (regardless of type of prescription opioid use) having initiated alcohol use by the time they reach 17 and 18 years of age; mean age of initiation of alcohol use has been previously observed within the National Longitudinal Study of Adolescent to Adult Health at 15.3 years for males and 15.6 years for females (Richmond-Rakerd, Slutske, & Wood, 2017). As such, lifetime use of alcohol may no longer be a risk factor for either sex in terms of past 30 day prescription opioid NMU among older adolescents aged 17 and 18 years. It could be that this is only an important risk factor among younger adolescents. Finally, ever obtaining alcohol from a parent as a risk factor among females only is discordant from our previous findings; we previously found that this was a risk factor among males but not females (Chapter 4). Considering the socio-ecological model, this could be explained by differing parental and peer influences in older adolescents compared to younger adolescents. It is possible that poor parental guidance has a negative influence among younger males, which does not continue into older adolescence. In contrast, it is possible that negative parental guidance only has an influence among older adolescent females because the positive protective factors

from earlier adolescence no longer negate the effects of this factor. Our finding that number of close friends is no longer a protective factor against prescription opioid NMU among older adolescents 17 and 18 years would support this assertion. Alternatively, it could be that obtaining alcohol from parents is more common among older adolescent females, so the effects of this variable are only apparent among the older age group. This is an area that should be researched further in future studies, because it would appear that sex differences in risk factors for NMU of prescription opioids may vary greatly from younger adolescence to older adolescence.

In the final logistic regression analysis, we found that lifetime use of tobacco and increased number of close friends using substances increases the risk of past 30 day prescription opioid NMU among 17 and 18 year olds compared to MU only. This is in concordance with our findings from analyses of all youth 10 to 18 years within N-MAPSS and suggests that these are risk factors which remain constant throughout adolescence. Conversely, lifetime use of marijuana was a protective factor for past 30 day prescription opioid NMU among youth 17 and 18 years. This finding is discordant from our previous analyses. The result from this analysis may be due to the high number of youth aged 17 and 18 years who had used marijuana within the MU only group. This could be explained by youth using marijuana to self-treat their pain (Hill et al., 2017; Romero-Sandoval et al., 2017), in addition to taking prescription opioids to treat pain (as indicated by MU of prescription opioids). It is possible that the high prevalence of marijuana use among those with prescription opioid MU only is reflective of use for pain treatment. Alternatively, another possible explanation is that those who had used marijuana and potentially other illicit drugs in their lifetime may have had adverse experiences which caused them to change their drug use behavior. As a result, those individuals may be unlikely to engage in past 30 day NMU of prescription opioids, but will have had lifetime use of marijuana. If this

occurred then it would appear that lifetime use of marijuana is associated with past 30 day MU, but not necessarily NMU, of prescription opioids. Subsequently, when non-medical users are compared to medical users, it appears that lifetime use of marijuana confers a protective effect among past 30 day non-medical users and those with past 30 day MU only are at greater risk. In reality, it may be their past drug use behavior which has influenced their current drug use behavior. Another alternative explanation for this finding is that residual confounding is present, where another factor that was not measured and adjusted for is responsible for the apparent protective effect of lifetime use of marijuana. Further research is needed to investigate this finding.

Our findings from this analysis and previous analyses provide evidence that multiple risk factors are involved in prescription opioid NMU among youth, within different levels of the socio-ecological model. Sex differences arise in some, but not all, risk factors for prescription opioid NMU. Moreover, the risk factors among older adolescents differ from younger adolescents. Targeting prevention efforts to multiple risk factors at different levels of the socio-ecological model, by different age groups, is likely to be the most effective strategy to reduce prescription opioid NMU among youth.

Strengths and Limitations

One of the strengths of our analysis is that we captured data on recalled age of first ever use of prescription opioids among those who reported past 30 day use. Our results revealed that youth as young as eight years of age may be using prescription opioids, so research may need to be focusing on younger age groups than previously thought. An advantage of N-MAPSS is that it captured data on age of first use of prescription opioids (as recalled by participants) regardless of pattern of use in later adolescence (MU or NMU).

A limitation of our analysis is that we did not collect data on age of first NMU of prescription opioids and so the age examined in this analysis could be first use either medically or non-medically; however, age of initiation of NMU has been examined previously in other studies (Deandrea et al., 2013; Meier et al., 2012) and so our work adds to the literature in that we examined age of first use regardless of pattern (NMU or MU only). Moreover, another important consideration is that we examined the impact of recalled age of first use on past 30 day prescription opioid NMU; it is possible that youth had NMU in the time period prior to the past 30 days, but no use in the past 30 days, and were excluded from our analysis. In future, capturing NMU within different time periods among youth, such as past year, would be useful to explore the impact of age of first use further.

Finally, only recalled age of first use (as self-reported by the participant) was available in this study, which may not be as accurate as using age of first use as reported in medical records or claims data. This variable may be subject to poor recall or potential recall bias. Recall bias would only be present though if past 30 day medical users were likely to recall their age of first use of prescription opioids differently to past 30 day non-medical users, resulting in differential recall. In this study, any measurement error for age of first use due to poor recall is likely to be non-differential. While we recognize this limitation, identification of NMU within medical records or claims data is difficult and likely to result in under ascertainment of the outcome. Several patterns of NMU, such as using prescription opioids that belong to someone else, are unlikely to be captured at all. Using an anonymous survey design allowed us to capture information on prescription opioid NMU among youth and minimize social desirability bias.

Conclusion

In conclusion, we found that recalled age of first use of prescription opioids was associated with past 30 day NMU among youth 17 and 18 years; risk of past 30 day prescription

opioid NMU decreased by a third for each one year increase in age of first use, after adjustment for other covariates. Sex differences in the effect of this risk factor were not observed. Use of prescription opioids in young adolescents may need to be avoided or delayed where possible, regardless of whether for MU or NMU, to prevent past 30 day NMU. Further research is needed to confirm this finding. This individual level risk factor may be important to consider alongside risk factors at other levels of the socio-ecological model which influence prescription opioid NMU among 17 and 18 year olds.

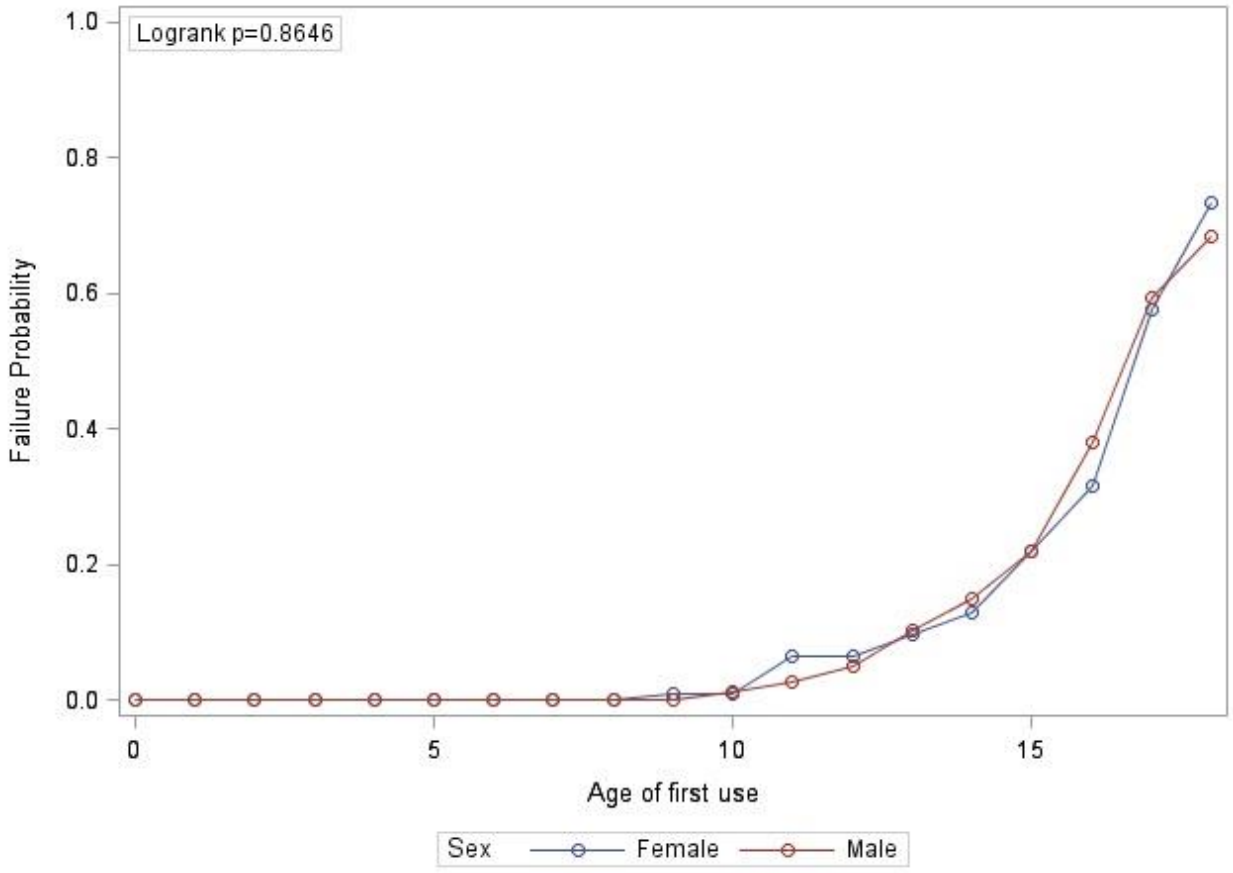


Figure 5-1. Cumulative probability of prescription opioid first use (as recalled by the participant) by sex.

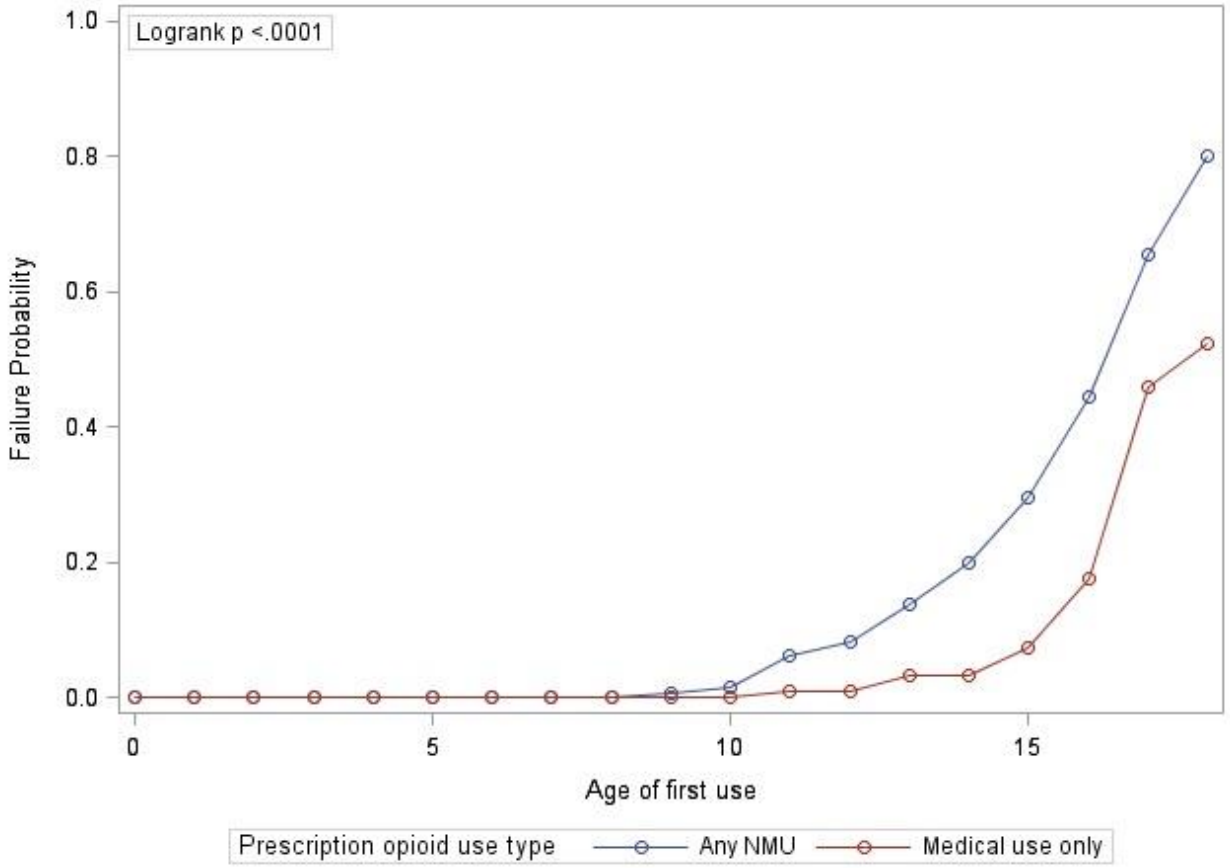


Figure 5-2. Cumulative probability of prescription opioid first use (as recalled by the participant) by past 30 day MU only and any NMU in the past 30 days.

Table 5-1. Sample characteristics among 17 and 18 year olds, stratified by past 30 day prescription opioid use status and sex

	Males			Females		
	Past 30 day MU only N=45 n (%)	Any NMU in past 30 days N=110 n (%)	Chi square or t-test p-value	Past 30 day MU only N=51 n (%)	Any NMU in past 30 days N=72 n (%)	Chi square or t-test p-value
INDIVIDUAL LEVEL FACTORS						
Current age						
17	23 (51.1)	48 (43.6)	0.503	24 (47.1)	36 (50.0)	0.890
18	22 (48.9)	62 (56.4)		27 (52.9)	36 (50.0)	
Recalled age at first use of prescription opioids						
Mean (SD)	16.4 (1.5)	15.3 (2.2)	0.002	16.5 (1.4)	15.0 (2.4)	<0.001
Lifetime use of prescription opioids						
Never	27 (60.0)	43 (39.1)	<0.001	31 (60.8)	30 (41.7)	<0.001
MU only	11 (24.4)	5 (4.6)		16 (31.4)	6 (8.3)	
NMU	7 (15.6)	62 (56.4)		4 (7.8)	36 (50.0)	
Lifetime use of tobacco						
Never	20 (44.4)	19 (17.3)	<0.001	27 (52.9)	16 (22.2)	<0.001
Ever	25 (55.6)	91 (82.7)		24 (47.1)	56 (77.8)	
Age at first use of tobacco						
Mean (SD)	14.0 (2.7)	13.3 (2.9)	0.310	14.2 (2.2)	13.8 (2.2)	0.447
Lifetime use of alcohol						
Never	10 (22.2)	10 (9.1)	0.051	12 (23.5)	9 (12.5)	0.174
Ever	35 (77.8)	100 (90.9)		39 (76.5)	63 (87.5)	
Age at first use of alcohol						
Mean (SD)	13.8 (2.4)	13.7 (2.1)	0.813	14.7 (1.7)	13.7 (2.1)	0.009
Lifetime use of marijuana						
Never	9 (20.0)	7 (6.4)	0.025	18 (35.3)	16 (22.2)	0.164
Ever	36 (80.0)	103 (93.6)		33 (64.7)	56 (77.8)	
Age at first use of marijuana						
Mean (SD)	14.5 (2.2)	13.1 (2.4)	0.004	14.8 (1.7)	13.6 (2.0)	0.003
Two weeks or more in the past 12 months where felt down or depressed						
No	26 (57.8)	51 (46.4)	0.266	27 (52.9)	22 (30.6)	0.021
Yes	19 (42.2)	59 (53.6)		24 (47.1)	50 (69.4)	
Ever felt worried or stressed for 6 months or more						
No	28 (62.2)	70 (64.2)	0.960	23 (45.1)	31 (43.1)	0.968
Yes	17 (37.8)	39 (35.8)		28 (54.9)	41 (56.9)	

Table 5-1. Continued

	Males Past 30 day MU only N=45 n (%)	Any NMU in past 30 days N=110 n (%)	Chi square or t-test p-value	Females Past 30 day MU only N=51 n (%)	Any NMU in past 30 days N=72 n (%)	Chi square or t-test p-value
RELATIONSHIP LEVEL FACTORS						
Number of close friends						
Mean (SD)	6.8 (3.2)	6.7 (3.6)	0.854	5.4 (3.1)	5.5 (3.4)	0.854
Number of close friends using substances [a]						
Mean (SD)	5.0 (2.9)	7.1 (3.7)	0.019	4.6 (3.9)	6.0 (4.3)	0.337
Proportion of close friends using substances [a]						
Mean (SD)	0.78 (0.33)	0.97 (0.08)	0.026 [b]	0.77 (0.34)	0.81 (0.32)	0.693 [b]
Ever obtained alcohol from parents						
No	28 (62.2)	60 (54.6)	0.486	35 (68.6)	32 (44.4)	0.014
Yes	17 (37.8)	50 (45.5)		16 (31.4)	40 (55.6)	
COMMUNITY LEVEL FACTOR						
Urban area of residence						
No	24 (53.3)	63 (57.3)	0.787	26 (51.0)	46 (63.9)	0.213
Yes	21 (46.7)	47 (42.7)		25 (49.0)	26 (36.1)	

SD= Standard Deviation; MU= Medical use; NMU= Non-Medical Use; [a] Data available from waves 3 and 4 only; sample size=1738 youth 17 and 18 years; [b] Wilcoxon rank-sum test used due to non-normal data distribution

Table 5-2. Recalled age at first use of prescription opioids by past 30 day prescription opioid use type (MU only and any NMU) among 17 and 18 year olds

	Past 30 day MU only N=96 n (%)	Any NMU in past 30 days N=182 n (%)
Age at first use of prescription opioids		
<=10 years [a]	1 (1.0)	13 (7.1)
11 years	0 (0.0)	4 (2.2)
12 years	2 (2.1)	10 (5.5)
13 years	0 (0.0)	11 (6.0)
14 years	4 (4.2)	18 (9.9)
15 years	10 (10.4)	27 (14.8)
16 years	27 (28.1)	38 (20.9)
17-18 years	52 (54.2)	61 (33.5)

MU= Medical Use; NMU= Non-Medical Use; [a] Minimum age of first use for MU only was 10 years, minimum age of first use for any NMU was 8 years

Table 5-3. Binomial logistic regression results predicting any NMU in the past 30 days among youth 17 and 18 years

	Any NMU in past 30 days OR (95% CI) N=108
INDIVIDUAL LEVEL FACTORS	
Sex	
Male	ref
Female	1.61 (0.45, 5.69)
Recalled age at first use of prescription opioids	0.67 (0.47, 0.96)
Lifetime use of prescription opioids	
Never	ref
MU only	0.11 (0.02, 0.72)
NMU	6.28 (1.06, 37.15)
Lifetime use of tobacco	
Never	ref
Ever	7.74 (1.50, 39.99)
Lifetime use of marijuana	
Never	ref
Ever	0.05 (0.01, 0.43)
Two weeks or more in the past 12 months where felt down or depressed	
No	ref
Yes	4.22 (1.25, 14.17)
RELATIONSHIP LEVEL FACTORS	
Number of close friends	0.74 (0.53, 1.04)
Number of close friends using substances [a]	1.62 (1.13, 2.32)

MU= Medical Use; NMU= Non-Medical Use; [a] Data available from waves 3 and 4 only; sample size=1738 youth 17 and 18 years; Reference group=Medical Use only

CHAPTER 6
FINAL CONCLUSIONS

Prescription opioid Non-Medical Use (NMU) is associated with many serious consequences, including overdose. Currently, 175 Americans die daily from overdoses and prescription opioids are involved in the majority of overdoses in the US (Christie et al., 2017). Moreover, for every death due to prescription drug overdose among young adults, there are 22 treatment admissions and 119 emergency room visits (National Institute on Drug Abuse, 2016). Prescription opioid NMU has also been identified as a risk factor for heroin use (Cerdá et al., 2015; Compton et al., 2016; National Institute on Drug Abuse, 2015; Palamar et al., 2016), which is another important public health concern. Addressing the current opioid epidemic is a priority to prevent these consequences.

Prevalence of prescription pain reliever NMU among youth 12 to 17 years has previously been observed at 1.0% for current (past 30 day) use and 3.5% for past 12 month use (Substance Abuse and Mental Health Services Administration, 2017). The definition of NMU is important to consider because it can be inconsistent in the literature. Within our analyses, we used a definition of NMU that is consistent with the NSDUH and MTF; use of someone else's opioids and use of a patient's own prescription in a way other than prescribed (Boyd & McCabe, 2008; Boyd et al., 2009; Shield et al., 2013). Previous studies of the risk factors for prescription opioid NMU among youth have been conducted, but limitations are present. These limitations relate to four areas. First, the current literature focuses on youth 12 years of age and over, omitting younger children aged 10 and 11 years. Second, previous studies have not examined sex differences in risk factors at individual, relationship and community level in youth. Third, adults and youth have not been stratified and analyzed separately in previous studies. Fourth, because many of these studies required parental consent to participate and were conducted in the home or school

setting, it is possible that social desirability bias was introduced. We were able to address these weaknesses by analyzing data from the National Monitoring of Adolescent Prescription Stimulants Study (N-MAPSS), within the context of the socio-ecological model.

The socio-ecological model provided a theoretical framework to explain why sex differences may arise in the risk factors for past 30 day prescription opioid NMU. While sex itself may not be a true risk factor for past 30 day prescription opioid NMU, sex differences can arise because behavior is influenced by other factors which differ by sex. N-MAPSS provided a rich data source which allowed examination of factors at individual, relationship and community levels of the model. The aims and hypotheses within this dissertation examined whether the influence of risk factors for past 30 day prescription opioid (Oxycontin®, Vicodin®, oxycodone and hydrocodone) NMU differed by sex. First, we aimed to examine sex differences in patterns of prescription opioid NMU. Second, we aimed to examine the effect of peer influence and parental guidance on patterns of past 30 day prescription opioid use, including NMU, among males and females separately. Finally, we aimed to examine sex differences in the effect of recalled age of first use of prescription opioids on past 30 day prescription opioid NMU among 17 and 18 year olds.

Main Findings

In chapter three, we examined sex differences in patterns of prescription opioid NMU. Past 30 day prevalence of prescription opioid NMU in N-MAPSS was 3.1%, which is similar to that seen for NMU of pain relievers in youth but only from the past 12 months in the 2016 NSDUH (3.5%), not for current (past 30 day) use (1.0%) (Substance Abuse and Mental Health Services Administration, 2017). A higher proportion of males had past 30 day prescription opioid NMU compared to females (3.7 vs 2.7%). Three distinct patterns of past 30 day NMU were examined: non-oral use only, use of someone else's opioids only and both non-oral use and

use of someone else's opioids. Use of someone else's opioids only was the most frequently reported pattern of past 30 day NMU among youth. Females were more likely to report use of someone else's opioids only compared to males. In contrast, using both someone else's opioids and having non-oral use was less likely among females compared to males. Overall, our analyses showed that males were more likely to be using opioids that belonged to a classmate and females were more likely to be using opioids that belonged to a parent or a classmate, regardless of concomitant non-oral use; however, obtaining opioids from two or more sources, compared to one source only, did not differ between males and females. All examined factors at the individual and community level were significantly associated with past 30 day prescription opioid NMU (regardless of pattern), such as age, lifetime use of other prescription opioids (Darvocet®, Lortab®, codeine and Percocet®), tobacco, alcohol and marijuana, depressive symptoms, anxiety symptoms and urban area of residence. Age and lifetime use of tobacco were risk factors for past 30 day prescription opioid NMU pattern that did not differ by sex. Conversely, lifetime use of prescription opioids was a risk factor for past 30 day prescription opioid NMU pattern among males only and lifetime use of marijuana was a risk factor for past 30 day prescription opioid NMU pattern among females only. Depressive symptoms, anxiety symptoms, lifetime use of alcohol and urban area of residence were not associated with past 30 day prescription opioid NMU pattern among males or females.

The findings from chapter three are unique in that we examined the sources of past 30 day opioids among youth aged 10 to 18 years by sex, along with three different patterns of past 30 day prescription opioid NMU. Other studies in the published literature have not focused on examining this information among younger adolescents, and we have observed that risk factors for past 30 day prescription opioid NMU among older adolescents (aged 18 years) differ from

those among all youth aged 10 to 18 years. Specifically, in a study by McCabe et al among older adolescents aged 18 years, males were more likely to use someone else's opioids only compared to females (McCabe et al., 2013a), while females were more likely to both use someone else's opioids and misuse their own previous prescription (McCabe et al., 2013a). While the McCabe study examined misuse of a previous prescription rather than non-oral use, the dissimilar findings from N-MAPSS suggest that younger adolescents have different patterns of past 30 day prescription opioid NMU compared to older adolescents. This may be driven by sex specific expectations and influences in younger adolescents which are less prevalent in older adolescents. Findings from chapter three suggested that parental and peer influences should be examined further, given the observed sex differences in sources of opioids and patterns of NMU. This analysis was undertaken in chapter four.

In chapter four, we examined the parental and peer relationship factors that influence prescription opioid NMU among youth and whether these factors conferred protection or additional risk in the context of the other risk factors found to be associated with past 30 day prescription opioid NMU. Reporting depressive symptoms and obtaining alcohol from parents were associated with increased odds of past 30 day prescription opioid NMU among males but not females. In contrast, lifetime use of alcohol and anxiety symptoms were associated with increased odds of past 30 day prescription opioid NMU among females but not males. For each additional close friend who used other substances (marijuana or tobacco), the odds of past 30 day prescription opioid NMU increased among both males and females, after controlling for other factors (with no use of prescription opioids in the past 30 days as the reference group). Moreover, an increased number of close friends was associated with decreased odds of past 30 day prescription opioid NMU among both males and females. Among males and females,

lifetime use of marijuana and tobacco were associated with increased odds of past 30 day prescription opioid NMU. In addition, we found that parental guidance did not moderate the relationship between number of close friends using other substances (tobacco or marijuana) and past 30 day prescription opioid NMU among either males or females. Age, home setting (who youth live with), parental warnings against substance use, ever obtaining alcohol from friends and urban area of residence were not associated with past 30 day prescription opioid NMU or MU among either sex when compared to no use of prescription opioids in the past 30 days, after adjusting for other factors.

The findings from chapter four add to the existing literature because we examined sex differences in relationship level risk factors for past 30 day prescription opioid NMU among youth 10 to 18 years, within the context of the socio-ecological model. Other studies have not examined the effect of parental and peer influences on prescription opioid NMU among youth 10 to 18 years of age, stratified by sex. We have observed that some of our findings are concordant with the existing literature on other illicit substance use among youth. For example, we found that negative peer influence (close friends using other substances) increased the odds of past 30 day prescription opioid NMU among youth. The same result has been found previously for the effect of negative peer influence on various types of illicit drug use (Chan et al., 2017; McDonough et al., 2016). In contrast, examination of sex differences in parental guidance in N-MAPSS revealed an association with past 30 day prescription opioid NMU for one factor (obtaining alcohol from parents) among males only. Previous research has shown that females are more heavily influenced by parental support and guidance than males as a protective factor for other substance use (Dunn et al., 2011), but in our study we did not find an effect among females. Our findings also indicated that moderation of the effect of peer influence on past 30

day prescription opioid NMU by parental guidance is not present. This finding is discordant from another study in the published literature which did observe a moderating effect of parental guidance on peer influence for other substance use (Chan et al., 2017). The results for N-MAPSS suggest that relationship level risk factors for prescription opioid NMU among youth 10 to 18 years are not necessarily the same as for other substances. In addition, some of these risk factors varied by sex and examining these factors in the context of other factors at different levels of the socio-ecological model was important. Individual level risk factors for prescription opioid NMU differed by sex after adjustment for relationship level factors. Our results suggest that encouraging and maintaining multiple close friendships may prevent prescription opioid NMU. In addition, discouraging close friendships with those who use illicit substances may decrease the risk of prescription opioid NMU. A previous study in the existing literature examined the effect of limiting time with friends on initiation of NMU of prescription opioids and other drugs (Seedall & Anthony, 2013); risk of initiation decreased for those whose parents always limit time with friends (3.1%) compared to those whose parents do not always limit time with friends (4.2%) (Seedall & Anthony, 2013). Based on our findings, this strategy may have the unintended consequence of reducing the protective effect of having a large number of close friends. Caution should be taken to ensure that close friendships are not discouraged altogether. Limiting parental provision of alcohol to youth is a strategy that should be implemented towards both sexes; however, this may have a greater impact in reducing prescription opioid NMU among males rather than females. At the individual level, diagnosis and treatment of conditions such as depressive symptoms and anxiety symptoms among youth may be important for reducing prevalence of NMU. Moreover, preventing alcohol use among females is a strategy that should be prioritized and implemented, while prevention of tobacco and marijuana use is the most

important strategy for males to potentially reduce prescription opioid NMU. Findings from chapter four suggested that sex differences in the risk factors for prescription opioid NMU among youth are present at both individual and relationship levels, but not for all variables.

In chapter five, we examined how recalled age of first use of prescription opioids affected past 30 day NMU among youth 17 and 18 years who had past 30 day prescription opioid use, and whether this effect was also influenced by sex. For each one year delay in age of first use (as recalled by the participant), the odds of past 30 day prescription opioid NMU decreased by a third, after controlling for other factors. Sex differences in the effect of this risk factor were not observed. Recalled age of first use was younger for those who reported past 30 day prescription opioid NMU compared to those who reported MU only. Those who had ever used other prescription opioids (Lortab®, Darvocet®, Percocet® and codeine) non-medically in their lifetime had increased odds of past 30 day prescription opioid NMU, while those who only had MU of other prescription opioids in their lifetime had decreased odds of past 30 day prescription opioid NMU. After adjustment for other factors, lifetime users of tobacco had increased odds of past 30 day prescription opioid NMU, but lifetime users of marijuana had decreased odds of past 30 day prescription opioid NMU. Depressive symptoms and increased number of close friends using substances were also associated with increased odds of past 30 day prescription opioid NMU, after controlling for other factors.

The findings from chapter five are distinctive because they provide information on how age of first use of prescription opioids (as recalled by youth) influences past 30 day prescription opioid NMU among 17 and 18 year olds. Other studies have examined age of initiation of NMU among older adolescents but none has considered age of first use regardless of whether for MU or NMU. Our finding that increased age of first use of prescription opioids decreases the risk of

past 30 day prescription opioid NMU is unique, though concordant with other studies of substance use. For example, a key finding from the Epidemiological Catchment Area study was that early use of illicit drugs increases the likelihood of substance abuse (Robins & McEvoy, 1990). In addition, another study found that early onset of other substance use is associated with various health risk behaviors among adolescents, which is also consistent with our results (DuRant, Smith, Kreiter, & Krowchuk, 1999). Preventing use of prescription opioids in younger adolescents (regardless of whether NMU or MU) may prevent subsequent NMU. This is an important finding which should be evaluated further in other studies but could be considered in future prevention strategies- prescribing or giving opioids to young adolescents may need to be avoided or delayed where possible. This should also be considered given that early NMU of prescription opioids (prior to age 15 years) has been previously associated with an increased risk of mortality (Cottler et al., 2015). Our findings appear to be discordant with some existing literature related to age of first use of other substances; for example, one study showed that age of first use of marijuana and alcohol occurs earlier for males compared to females, among current drug users (Shannon, Havens, Oser, Crosby, & Leukefeld, 2011). Our findings are interesting in the context of other literature, where the progression from first use of prescription opioids to problematic opioid use has been examined. Adult women have been found to progress to problem use of prescription opioids more rapidly than men (Lewis, Hoffman, & Nixon, 2014; Sartor, Kranzler, & Gelernter, 2014). Moreover, another study found that length of time between onset of abuse and dependence for opioids was shorter for women than for men at 15 years and 25 years after initiating opioid use (Ridenour, Maldonado-Molina, Compton, Spitznagel, & Cottler, 2005). Within N-MAPSS, we found that among youth, there is no difference in age of first use (as recalled by the participant) between males and females, suggesting that it is not age

of first use of prescription opioids that is associated with rapid progression among females, but other factors. Our findings on sex differences in individual and relationship level risk factors support this assertion.

Overall, the results from this dissertation may support several strategies to prevent prescription opioid NMU. First, strategies preventing other substance use (alcohol, tobacco and marijuana use) among youth should target males and females separately; these substances are risk factors for past 30 day prescription opioid NMU, so preventing their use may also prevent prescription opioid NMU. Given the individual consequences of alcohol, tobacco and marijuana use among youth, such a strategy would have positive consequences even if the effect on prescription opioid NMU is not considered. Second, strategies at the relationship level in terms of peer influence and parental guidance may need to differ by sex, but this will depend on the target age group. Third, diagnosis and treatment of mental health conditions among youth could be important for reducing prevalence of NMU among both sexes. Moreover, there would be a benefit to youth with this approach in terms of their overall health. Finally, prescribing or giving opioids to youth may need to be delayed where possible, though further studies are needed to confirm this finding.

Future Research

In the future, several further studies are needed to address questions that have arisen from our research. Our analyses suggested that younger adolescents (as studied in N-MAPSS) may have different motivations or risk factors for past 30 day NMU compared to older adolescents (as studied in the existing literature), affecting the way they obtain prescription opioids. This may be driven by sex specific expectations and influences in younger adolescents, which are less prevalent in older adolescents. This finding should be explored further, including the motives for NMU among different age groups. Unfortunately, little data exists on the motives for NMU of

prescription opioids among youth; a recent systematic review concluded that research on the motives for NMU of prescription opioids was limited and should be expanded further (Drazdowski, 2016). Understanding motives in further detail is likely to help inform prevention efforts among youth. Moreover, we did not collect dose of prescription opioids in N-MAPSS and could not examine NMU in relation to doses higher than prescribed. Examination of high doses as a fourth pattern of NMU could be explored further in other studies among youth.

Within N-MAPSS, parental warnings against other substance use (marijuana and tobacco) had no effect on past 30 day prescription opioid NMU, which may be because parents did not specifically warn against prescription opioid NMU or because these warnings had little impact on youth behavior. There is no information in the current literature about the effect of direct parental warnings against prescription opioid NMU in youth, but this should be explored further in future studies. Moreover, we examined a selection of parental and peer influences on prescription opioid NMU among youth. Exploration of other parental and peer influences may provide further insight into sex differences in prescription opioid NMU behavior, which would be expected within the context of the socio-ecological model.

Our findings suggest that risk factors may vary between younger adolescents and older adolescents. There are many studies in the published literature that focus on older adolescents, but few consider those of younger ages. Future research should take this into consideration, especially if using results to design prevention strategies for younger adolescents. In addition, N-MAPSS was a cross-sectional study design, similar to many other surveys on drug use conducted among youth. Longitudinal studies which examine initiation of drug use, including prescription opioid use and NMU, among youth, with follow up throughout adolescence are likely to provide further insight into drug use behavior and inform effective prevention strategies. N-MAPSS also

captured information on past 30 day prescription opioid NMU, rather than NMU within other time periods. A longitudinal study would allow examination of multiple time periods where NMU may occur. It would also be useful for addressing the issue of temporality when considering if the associations we found in this dissertation are causal. In addition, we would be able to examine our finding regarding age of first use of prescription opioids and past 30 day NMU further. Finally, recommendations on prevention strategies should be tested in future studies, as we only examined the risk factors for prescription opioid NMU among youth and did not explore how prevention efforts affect NMU prevalence. Overall, reducing the burden of prescription opioid NMU in the US is an important strategy required to address the current opioid epidemic.

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BIOGRAPHICAL SKETCH

Vicki Leanne Osborne received the Bachelor of Science (Honors) in biomedical science from the University of Portsmouth in 2008 and Master of Science in epidemiology from the London School of Hygiene and Tropical Medicine in 2012. She joined the Drug Safety Research Unit in Southampton, UK to serve as a Research Fellow in 2009, progressing to Senior Research Fellow in 2013. Vicki joined the Department of Epidemiology, College of Public Health and Health Professions and College of Medicine at the University of Florida (UF) in 2015, as a pre-doctoral student under Dr. Linda B. Cottler. Dr. Cottler served as the chair of her dissertation committee and primary research mentor. Vicki received the Ph.D. in epidemiology from the University of Florida in the Spring of 2018.

Vicki's research interests focus on the off-label use and misuse of prescription medications. For this reason, her dissertation examined risk factors for non-medical use of prescription opioids among youth, identifying sex differences in these factors. She has worked in the field of pharmacoepidemiology since 2008 and has extensive experience of working on Post Authorization Safety Studies (PASS) requested by the European Medicines Agency (EMA). Vicki also held a position at the University of Portsmouth as a Partner Associate Lecturer from 2013 to 2015, teaching graduate level students on pharmacovigilance. Vicki joined the Medication Use, Safety and Evidence (MUSE) study in the Department of Epidemiology at the University of Florida as Project Manager in 2016. MUSE is an FDA mandated study of the risks of misuse and abuse with extended release/long acting prescription opioids. She has also worked on various other projects within the department, including analyses of data from the Prescription Drug Misuse, Abuse, and Dependence study in St. Louis and from HealthStreet, a community engagement program at UF. She also assisted with data entry for the Haiti Health Study.

Vicki has been a member of the International Society for Pharmacoepidemiology since 2010 and became an officer for the UF student chapter in 2016. She has also been a member of the American Public Health Association since 2016 and a Member-In-Training of the College on Problems of Drug Dependence (CPDD) since 2017. She has published 18 papers in peer-reviewed journals so far, with a further 48 poster presentations and 10 oral presentations at national and international conferences. In addition, Vicki is the co-author of a book chapter on Event Monitoring in the UK. She has received numerous awards and travel grants including (1) the Grinter Fellowship from UF in 2015 and 2016, (2) the best reviewer award from Pharmacoepidemiology and Drug Safety in 2013 and 2015, (3) travel scholarships from the International Conference on Pharmacoepidemiology in 2016 and 2017, (4) the UF Office of Research travel grant in 2017, (5) the UF Graduate Student Council travel grant in 2017, (6) the UF International Center Certificate of Outstanding Achievement in 2017 and (7) the NIDA Women & Sex/Gender Differences Junior Investigator Travel Award to attend the CPDD 2018 Annual Meeting.