THE RISKS AND CONSEQUENCES OF OPIOID MISUSE

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Submitted to the faculty of the University Graduate School
in partial fulfillment of the requirements
for the degree
Doctor of Philosophy
in the Richard M. Fairbanks School of Public Health,
Indiana University

July 2018

Accepted by the Graduate Faculty of Indiana University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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DEDICATION

In Love and Appreciation,

To my German and American Family

For their Support, Encouragement, and Patience.

ACKNOWLEDGEMENTS

I would like to thank my doctoral advising committee for their time, dedication, and mentorship; without their expertise and kind support, this would have been an unsurmountable task. Specifically, I want to thank Drs. Zollinger and Steele for co-chairing the committee and answering my numerous questions; Dr. Yiannoutsos, my minor advisor, for his biostatistical guidance; Dr. Chambers for his clinical expertise; Dr. Vest for helping me obtain critical data sources; and Dr. Wright for his continuous support.

I acknowledge the Indiana University Richard M. Fairbanks School of Public Health, Department of Epidemiology for accepting me into the PhD program and for the guidance they provided throughout this journey.

I also want to express my gratitude to my dear colleagues at the Center for Health Policy and the Department of Health Policy and Management. Their ongoing support continues to be an invaluable resource.

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Opioid misuse and addiction has been widely identified as a public health problem, contributing substantially to the nation's morbidity and mortality. Over the past two decades, misuse of prescription opioids pain relievers has substantially increased; heroin use has resurged; and, more recently, abuse of high-potency synthetic opioids such as fentanyl have fueled the epidemic. Nearly 12 million Americans (or 4.4%) aged 12 and older misused some type of opioid (prescribed or illegal) in the past year. Furthermore, the percentage of substance use treatment admissions attributable to opioids nearly doubled in the U.S., from 20.8% in 2000 to 40.5% in 2015.

The purpose of this dissertation research was to investigate associations between prescription pain reliever use and subsequent negative health outcomes, including opioid misuse or addiction, and neonatal abstinence syndrome. This research focused on three specific aims:

Specific Aim #1: Examine heroin use among Indiana's substance use treatment population to measure the extent, trends, and patterns of use, as well as to assess the relationship between prescription opioids and subsequent heroin use;

Specific Aim #2: Analyze 2014 INSPECT (Indiana's prescription drug monitoring program) data to identify factors that increase patients' likelihood to engage in opioid-related risk behaviors; and

Specific Aim #3: Review U.S. trends in neonatal abstinence syndrome (NAS) incidence from 2008-2014, measure regional variability, and identify personal and environmental risk factors associated with NAS.

Terrell W. Zollinger, DrPH, Co-chair

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LIST OF ABBREVIATIONS

AHRQ – Agency for Healthcare Research and Quality

AUC – Area Under the Curve

CDC – Center for Disease Control

CI – Confidence Interval

CL – Wald Confidence Limits

DEA – Drug Enforcement Agency

ED – Emergency Department

HCUP – Healthcare Cost and Utilization Project

ICD – International Classification of Diseases

IDU – Injection Drug Use

INSPECT – Indiana Scheduled Prescription Electronic Collection and Tracking

IQR – Interquartile Range

JCAHO – Joint Commission on Accreditation of Healthcare Organizations

MAT – Medication-Assisted Treatment

MMEs - Morphine Milligrams Equivalents

NAS – Neonatal Abstinence Syndrome

NDC – National Drug Code

NIS – National Inpatient Sample

OR – Odds Ratio

PDMP – Prescription Drug Monitoring Program

ROC – Receiver Operating Characteristics

SAMHSA – Substance Abuse and Mental Health Services Administration

SAS® – Statistical Analysis Software

SEP – Syringe Exchange Program

TED-A – Treatment Episode Data Set-Admissions

VA – U.S. Department of Veterans Affairs

CHAPTER 1

1.1. Introduction

Opioid misuse and addiction has been widely identified as a public health problem, contributing substantially to the nation's morbidity and mortality.[1-3] Over the past two decades, misuse of prescription opioids (pain relievers) has substantially increased; heroin use has resurged; and, more recently, abuse of high-potency synthetic opioids such as fentanyl have fueled the epidemic.[4] Nearly 12 million Americans (or 4.4%) aged 12 and older misused some type of opioid (prescribed or illegal) in the past year.[5] Furthermore, the percentage of substance use treatment admissions attributable to opioids nearly doubled in the U.S., from 20.8% in 2000 to 40.5% in 2015.[6]

The consequences of opioid misuse are substantial. Drug overdoses, which are the leading cause of injury-related death in the nation,[7] are occurring at an increasing rate[8] and have tripled in the past 15 years.[3] Overdoses attributable to opioids resulted in more than 750,000 emergency department (ED) visits[9] and over 33,000 deaths in 2015.[4,10] From 2005 to 2014, rates of opioid-related ED visits nearly doubled and rates of opioid-related inpatient stays increased by more than 64 percent.[11] Age-adjusted mortality rates per 100,000 have increased to 5.9 for those involving prescription opioids and 3.4 for those involving heroin in 2014.[12]

Furthermore, neonatal abstinence syndrome (NAS), a condition caused by the abrupt discontinuation of chronic exposure to drugs and other substances used by the mother during pregnancy,[13] has been on the rise. According to recent studies, NAS incidence rates increased nearly five-fold since 2000 to 5.8 per 1,000 hospital births in

2012.[14,15] To illustrate the magnitude of this problem, it has been stated that "approximately one infant [is] born per hour in the United States with signs of drug withdrawal".[14]

1.2. Conceptual Framework

Many factors have contributed to the opioid epidemic (Figure 1.1). Over the past two decades, the United States has seen a substantial increase in the sale of prescription pharmaceuticals,[16] especially opioids.[17] Sales of prescription pain relievers nearly doubled from 105 million in 1998 to 207 million in 2013.[18] Rising sales and wide availability of these drugs have been linked to the increase in opioid misuse, addiction, and overdose deaths.[19-22] The increase in sales has been attributed, at least in part, to two events that started in the 1990s – the push to adopt pain as the fifth vital sign and, subsequently, the aggressive marketing of opioids by the pharmaceutical industry, especially Purdue Pharma which had just released OxyContin®.[4]

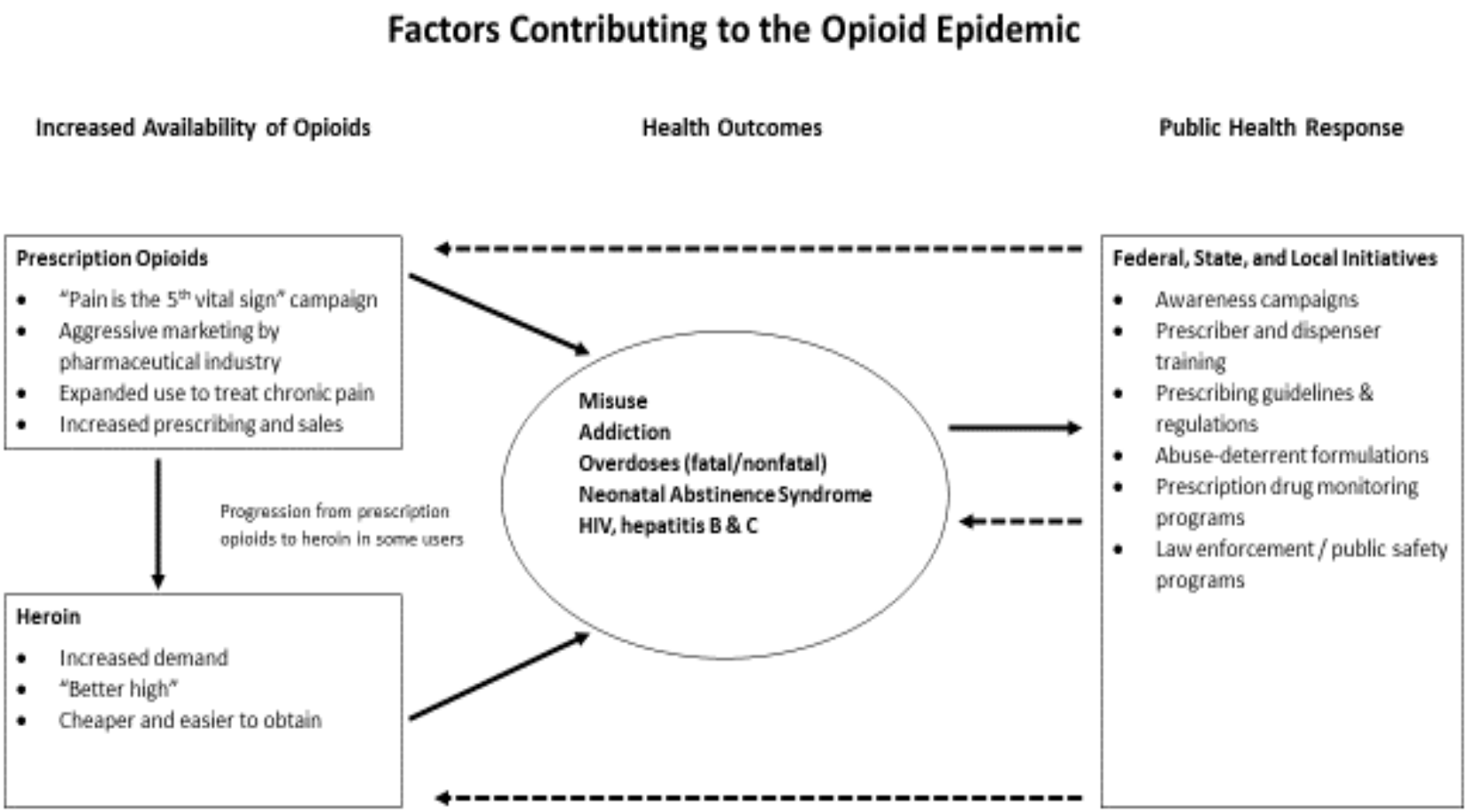
In response to increasing accounts of "undertreatment of pain" and "pseudoaddiction,"[23-25] the American Pain Society began promoting "pain as the 5th vital sign" in the mid-1990s, in an effort to increase awareness among healthcare professionals.[26] The U.S. Department of Veterans Affairs (VA) and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) both endorsed the campaign and changed their pain management standards to focus on patients' rights to assessment and treatment of pain.[26-28] Encouraged by the growing movement, Purdue Pharma promoted a more liberal use of opioids, especially among primary care physicians, and aggressively marketed OxyContin for the non-cancer pain market, leading to a nearly

ten-fold increase in the number of OxyContin prescriptions for non-cancer pain, from 670,000 in 1997 to over 6 million in 2002.[4,29]

More recently, in an effort to control the opioid epidemic, federal and state governments started implementing a variety of policies and programs to curb inappropriate prescribing.[30] These strategies included education on appropriate use as well as the risks and benefits of opioids, promotion of opioid prescribing guidelines for healthcare professionals, development of prescription pain relievers using abuse-deterrent technologies, and implementation of statewide prescription drug monitoring programs (PDMPs).[30-32]

Following these efforts to decrease prescription opioid misuse, the country has also witnessed an increase in heroin use and overdose deaths.[30,33] While the literature on the progression from prescription opioids to heroin is still sparse, some studies suggest a connection since these drugs are pharmacologically similar[34,35] and the rate of heroin use is higher among individuals who first misused prescription opioids.[33,36-38]

Figure 1.1. Conceptual Framework



1.3. Specific Aims

The purpose of this dissertation was to investigate associations between prescription pain reliever use and subsequent negative health outcomes, including opioid misuse or addiction and neonatal abstinence syndrome. This research focused on three specific aims:

Specific Aim #1: Examine heroin use among Indiana's substance use treatment population to measure the extent, trends, and patterns of use, and to assess the relationship between prescription opioids and subsequent heroin use;

Specific Aim #2: Analyze 2014 INSPECT (Indiana Scheduled Prescriptions Electronic Collection and Tracking; i.e., the state's prescription drug monitoring program) data to identify factors that increase patients' likelihood to engage in opioid-related risk behaviors; and

Specific Aim #3: Review U.S. trends in neonatal abstinence syndrome (NAS) incidence from 2008-2014; measure regional variability; and identify personal and environmental risk factors associated with NAS.

CHAPTER 2 The Relationship between Heroin and Prescription Opioid Use in Indiana's Substance Use Treatment Population: A Cross-Sectional Analysis

2.1. Specific Aim #1

Chapter 2 addresses the Specific Aim #1, as outlined in the abstract. The purpose is to examine heroin use among Indiana's substance use treatment population to measure the extent, trends, and patterns of use, as well as to assess the relationship between prescription opioids and subsequent heroin use.

2.2. Introduction

Heroin is a highly addictive opioid[39] and, although it represents less than five percent of all illicit drug use, its impact is said to exceed that of more widely used substances.[40] The majority of individuals with a heroin use disorder develop dependence (84%).[41] Many negative consequences are associated with the use of this drug, some of which are attributable to its primary route of administration, injection. These outcomes include: addiction;[42,43] infections of HIV, hepatitis B and C, and tuberculosis;[44-47] pregnancy complications and neonatal abstinence syndrome;[48-50] and drug overdoses.[7,51] Drug overdoses are the leading cause of injury-related death in the nation[7] and the U.S. mortality rate for overdoses involving heroin nearly tripled from 1.0 per 100,000 in 2010 to 2.7 per 100,000 in 2013. Furthermore, the economic burden of heroin addiction in the United States was an estimated $21.9 billion in 1996[40] and the costs specifically associated with heroin-related overdoses were estimated at $4.6 billion in 2009.[52]

Although heroin use within the general population is fairly low, there has been a

significant increase from 2005 through 2011 in past-year initiation, use, and dependence.[53] The reasons for the rise are still uncertain, but a connection to the prescription opioid epidemic has been proposed. There is biological plausibility for this argument, since both drugs belong to the opioid category and, therefore, share similar chemical structures and comparable pharmacological effects.[53,54] Concerns have been voiced among treatment providers, researchers, and policymakers that nonmedical use of prescription opioids may progress to heroin use, so understanding the relationship between the two is crucial for developing clinical guidelines and public health interventions.[43,51,53,55] Greater availability of prescription opioids has been linked to higher substance misuse rates;[21] consumption, treatment admissions, and overdose deaths attributable to prescription pain relievers have increased substantially over the past 15 years, paralleling the increase in opioid sales.[43,56] While the literature on progression from prescription opioids to heroin is still sparse, Muhuri, et al.[53] found a strong association between prior nonmedical pain reliever use and subsequent heroin initiation in U.S. residents ages 12 to 49. They estimated that the rate of heroin initiation among individuals who engaged in prior nonmedical use of prescription opioids was approximately 19 times greater than those who did not.[53]

It has been suggested that heroin users are not a homogeneous group and that those who progressed from prescription opioids to heroin are socio-demographically different from other heroin users.[55] Patterns and trends of use vary within the United States and the Midwest has been particularly impacted by heroin.[7] While there are no state-level prevalence estimates for heroin use available for Indiana, existing data

indicate that this drug has become a significant public health problem in the state. In Indiana, the percentage of substance use treatment admissions for heroin quadrupled from 2.6 percent in 2001 to 11.1 percent in 2012[57] and the number of overdose deaths listing heroin as a contributing cause[i] increased from 3 in 2000 to 152 in 2013.[58,59] There has also been a marked increase in heroin trafficking as evidenced by the number of heroin seizures across Indiana, which increased an estimated 300 percent between 2011 and 2013. Most of the heroin seizures occurred around Interstate 65, which connects Chicago, a major hub for heroin, to Indianapolis.[60]

The purpose of this study was to examine heroin use among Indiana's substance use treatment population to gain a better understanding of the extent, trend, and pattern of use within the state, as well as to assess the relationship between prescription opioid misuse and subsequent heroin use. While Muhuri et al.[53] already established this link within the general U.S. population ages 12 to 49, the question remains if the same pattern holds true for Indiana and with a population presumably more severely impacted, since my study sample included low-income individuals who received substance use treatment services.

2.3. Methods

2.3.1. Study Design, Population, and Data Source

This study used a retrospective, cross-sectional examination of administrative records from the Treatment Episode Data Set - Admissions (TEDS-A), covering a five-

[i] Underlying cause of death ICD-10 codes: X40-X44, X60-X64, X85 or Y10-Y14 with contributing cause of T40.1.

year study period from January 1, 2008, through December 31, 2012. TEDS-A is a national census data system of annual admissions to substance use treatment facilities. State law requires publicly funded drug treatment programs to routinely collect information on the number and characteristics of persons admitted to their programs and report these data to a state agency.[57] In Indiana, these data are reported to the Indiana Family and Social Services Administration's Division of Mental Health and Addiction. Treatment settings include inpatient/outpatient, residential, short- and long-term programs, and a small percentage of programs that provide medication-assisted opioid therapy. The collected information is then submitted in standard format to the Substance Abuse and Mental Health Services Administration's (SAMHSA) Center for Behavioral Health Statistics and Quality. TEDS-A records represent admissions rather than individuals, thus individuals may be admitted to treatment more than once in a given year.[57] All Indiana treatment admissions from 2008 through 2012 were included in the analyses, resulting in 117,230 observations. This study was determined to be exempt from IRB review by the Indiana University Institutional Review Board.

2.3.2. Analyses

Four types of analyses were conducted for this study with treatment admission as the unit of analysis: (1) Descriptive statistics were employed to summarize the characteristics of those represented among Indiana's treatment admissions; (2) Simple logistic regression analyses were used to review the five-year trend of heroin and prescription opioid misuse. For this analysis, heroin misuse (binary variable) and prescription opioid misuse (binary variable) were the dependent variables, separately,

and year of treatment admission was the independent variable. The observed percentages of misuse by year were plotted for each drug; (3) To test the relationship between heroin and prescription opioid misuse, a multiple logistic regression analysis was conducted, adjusting for client characteristics and time. Heroin misuse was the outcome of interest or dependent variable and prescription opioid misuse was the independent variable; the covariates included gender, age group, race, ethnicity, and year of treatment admission; (4) Age of first use was compared among those who reported using both heroin and prescription opioids to determine which of these substances tended to be initiated first.

Whenever appropriate, odds ratios and 95% Wald confidence intervals (95% CI) were computed. All analyses were conducted using Statistical Analysis Software SAS® version 9.4. Results with *p*-levels less than 0.05 were deemed statistically significant.

2.4. Results

2.4.1. Description of Study Population

The number of substance use treatment admissions in Indiana rose from 19,111 in 2008 to 25,026 in 2012 as shown in Table 2.1. While the majority of admissions were for males, the percentage of women among the treatment admissions increased consistently from 32.5% in 2008 to 37.2% in 2012. Throughout the five-year period, most of Indiana's treatment admissions were for whites, non-Hispanics, and individuals aged 21 through 49 years.

Alcohol and marijuana were the most widely used substances among those admitted for treatment; however, treatment admissions for alcohol and marijuana

misuse decreased proportional during these five years from 71.0% to 59.4% and from 55.1% to 47.2%, respectively. Admissions for cocaine use dropped from 21.4% in 2008 to 15.9% in 2012. At the same time, admissions for prescription opioids rose from 13.7% to 22.0%, replacing cocaine as the third most frequently reported drug of misuse. Admissions for heroin use nearly tripled from 4.1% to 11.1%. Furthermore, polysubstance use was common within Indiana's treatment admissions with nearly two-thirds of clients reporting the use of two or more substances.

Client characteristics were somewhat differently distributed among heroin and prescription opioid users compared to the overall treatment population as shown in Table 2.2. Combined data from 2008 through 2012 show that among admissions for heroin and prescription opioid use, the percentage of women (41.5% and 48.5% respectively) was considerably higher than among the overall treatment population (35.6%); also, heroin or prescription opioid users were slightly younger. The majority of all clients admitted for treatment were white (79.8%); however, the percentage of whites was notably higher among heroin (87.4%) and prescription opioid users (93.4%). Among heroin users, marijuana (28.3%), cocaine (25.2%), and prescription opioids (22.9%) were, in addition to heroin, the most widely used substances. Those admitted for prescription opioid use reported also using marijuana (40.8%), alcohol (34.9%), and benzodiazepines (18.0%), in addition to prescription opioids. Polysubstance use was more prevalent among both heroin (79.3%) and prescription opioid misusers (82.6%) compared to the overall treatment population (60.7%). Injection drug use (IDU), which is often the preferred route of heroin administration, was reported in 69.0% of admissions

for heroin use, compared to 17.7% of admissions for prescription opioid use and 8.6% of the overall treatment population.

2.4.2. Heroin and Prescription Opioid Trends from 2008 through 2012

Findings from the simple logistic regression analyses shown in Figure 2.1 indicated there was a significant increasing trend in heroin use in Indiana's treatment population throughout the five-year period, from 4.1% (n=777) in 2008 to 11.1% (n=2,767) in 2012. Similarly, prescription opioid use among Indiana's treatment population rose significantly from 13.7% (n=2,615) in 2008 to 22.0% (n=5,498) in 2012 (all $p<0.0001$).

2.4.3. Association of Heroin and Prescription Opioid Use

In addition, a multiple logistic regression analysis was conducted to assess if the risk (odds) of heroin use was greater among admissions of clients who also reported using prescription opioids. The analysis adjusted for client characteristics that are known to affect drug use patterns in general; i.e., gender, race, ethnicity, and age, as well as year of treatment admission. The adjusted odds ratios are shown in Table 2.3.

The overall model was significant in predicting heroin use ($p<0.0001$), showing an 18 percent increase in the odds of using heroin among admissions where clients also reported use of prescription opioids (OR=1.18; 95% CL: 1.11-1.25), adjusting for client characteristics and time. Furthermore, heroin use was linked to being female (OR=1.20; 95% CL: 1.15-1.26), white (OR=1.53; 95% CL: 1.34-1.75), Hispanic (OR=1.18; 95% CL: 1.06-1.31), and of younger age, especially aged 21 to 34 (OR=1.93; 95% CL: 1.76-2.12). Year of treatment admission was also associated with heroin use. Between 2008 and

2012, each subsequent year increased the odds of reported heroin use by 31 percent (OR=1.31; 95% CL: 1.28-1.33).

2.4.4. Opioid Initiation among Dual Users

Overall, 1.8% of the treatment population were dual users; i.e., they reported using both heroin and prescription opioids. One-tenth (10.1%) of prescription opioid users and more than one-fifth (22.9%) of heroin users reported using both drugs. Among admissions with dual use, 51.2% (n=721) initiated prescription opioids before heroin, while only 8.2% (n=115) used heroin prior to prescription opioids; in 40.7% (n=573), no differences could be ascertained since initiation of both drugs occurred within the same age category.

Distribution of initiation patterns differed by drug use category as shown in Table 2.4. Among admissions with dual use, nearly one-third (32.8%) initiated prescription opioids prior to the age of 18, while only 16.7% began using heroin at this age. Most opioid initiation in that group occurred between the ages of 18 and 34, with 77.0% of dual users initiating heroin and 58.6% initiating prescription opioids at that time. The percentage of clients who used heroin prior to the age of 18 for the first time was higher among those who did not engage in dual use (25.6%) compared to those who engaged in dual use (16.7%).

2.5. Discussion

Overall opioid use, i.e., prescription and heroin, has increased steadily for at least the past five years in Indiana's substance use treatment population and findings from this study indicated a clear relationship between the use of heroin and prescription

opioids. Thus far, only a limited number of studies have formally tested the transition from prescription opioids to heroin[51,53] and some small-scale studies have shown that for a large proportion of heroin users, prescription pain relievers served as a gateway to heroin,[38,55] particularly among heavy users.[61] Primary reasons frequently cited for switching included lower costs, easier access and increased availability, as well as greater effectiveness of heroin in producing a "high," combined with the reformulation of OxyContin® in 2010, which made it more difficult to abuse.[43,51,62,63]

While the existing data set used for this study did not allow to formally test the question of transitioning, the results suggested this occurs frequently, since the majority of clients in treatment who used both drugs reported using prescription opioids prior to heroin initiation. Nearly one-third of dual users started using prescription opioids during adolescence, while a considerably lower percentage reported initiating heroin use during that period.

The literature, as well as the present study, support the belief that the increase in heroin use has been a corollary of the prescription drug epidemic.[43,51,53,55] Some concerns have been voiced that the rise in heroin consumption was an unintended consequence of national and state efforts to prevent misuse and diversion of prescription opioids. While the increase in heroin use occurred largely after the implementation of statewide strategies and policies to reduce prescription opioid misuse, it is yet to be determined if this relationship was causal. Prevention efforts were successful in reducing use and availability of prescription opioids, which may have encouraged some patients to switch to heroin. However, these public health

approaches aimed at mitigating prescription-drug misuse were a direct response to the rising numbers of pain reliever misuse and deaths, which preceded the increase in heroin use. It has been suggested that "inappropriate prescribing of opioid medications,"[64] sometimes out of fear to undertreat pain,[24] has unintentionally contributed to the escalation in opioid dependence and its consequences.

Findings of this study have significant public health implications related to IDU. Heroin users are at an increased risk for HIV and hepatitis B and C transmissions due to the large percentage of users who inject the drug intravenously.[51] IDU has been linked to the spread of these diseases primarily by the mechanism of sharing contaminated needles and syringes. A large percentage of injection drug users, especially those with a history of arrests and lower socio-economic status, share their injection paraphernalia, even though they have knowledge of the associated risks of infection.[65,66] This study found that in 69% of the admissions for heroin use, clients reported injection as their primary route of administration, a percentage nearly four times higher than for prescription opioid use admissions and eight times higher than for the overall treatment population. The high percentage of drug injection practices among Indiana's substance use treatment population puts them at significant risk for infection with HIV as well as hepatitis B and C, which also spreads the risk to family and friends with whom they share injection equipment or have sexual relationships. Providing broad access to evidence-based programs, particularly medication-assisted therapies, has been shown to be cost-effective in treating opioid addiction and reducing negative consequences, including the transmission of HIV.[67-69] However, the extension of such services would

require an expansion of the state's addiction workforce to narrow the gap between demand and supply.[70,71]

2.5.1. Strengths and Weaknesses of the Study

A strength of the study was its large sample size (n=117,230) and reliability of the data. TEDS-A data have been routinely collected by state agencies under federal guidance of SAMHSA since 1989.

Several limitations of the data have been identified. Records represent admissions rather than individuals; thus, individuals may be admitted to treatment more than once in a given year. Only publicly funded substance use treatment providers are required to collect and submit client information. Thus, the number and characteristics of clients receiving these services depends, to some extent, on external factors, including funding levels and selective targeting of high-risk groups. Additionally, Indiana only collects data on clients who are at or below the 200% federal poverty level. Hence, findings presented in this report may not be representative of the state's entire treatment population. Though the dataset does not represent the total demand for treatment in the state, it does comprise a significant proportion of all admissions to substance use treatment.

Another limitation of the dataset was the absence of information on clients' mental health or smoking status since both have been identified as risk factors for addiction.[72,73]

2.5.2. Suggestions for Future Research

Demographic characteristics of heroin users in treatment have shifted over the

past 50 years, away from inner-city minority groups. Now the majority of users are white and nearly evenly distributed between males and females.[74] It has been suggested that individuals who progressed from prescription opioids to heroin are socio-demographically different from heroin users who did not follow this trajectory.[55] Even findings from this study suggest that heroin users who do not engage in prescription opioid misuse may start using heroin at an earlier age than those who engage in dual use. Follow-up studies on client characteristics comparing these two groups could assist clinicians and the treatment community in developing evidence-based intervention programs for specific high-risk populations.

2.5.3. Conclusion

The misuse of prescribed and illicit opioids has increased dramatically over the past few years in Indiana. While this study found a significant association between prescription drug misuse and heroin use, it is likely that other factors play a major role as well. Public health strategies to curb the opioid epidemic need to include policies and laws to educate healthcare providers and regulate prescribing practices; improve access and reduce barriers to medication-assisted treatments; and integrate screening for substance use and mental health disorders into primary care. This will help address issues related to prescription opioid as well as heroin misuse.

Table 2.1 Characteristics of Indiana's substance use treatment population, by year

		2008	2009	2010	2011	2012
Gender	Male	12,897	12,372	17,287	17,244	15,717
		(67.5%)	(66.2%)	(63.7%)	(63.2%)	(62.8%)
	Female	6,214	6,316	9,837	10,037	9,309
		(32.5%)	(33.8%)	(36.3%)	(36.8%)	(37.2%)
Age	12-20 years	2,716	2,550	3,592	3,212	2,926
		(14.2%)	(13.7%)	(13.2%)	(11.8%)	(11.7%)
	21-34 years	9,272	9,025	13,048	13,562	12,457
		(48.6%)	(48.3%)	(48.1%)	(49.7%)	(49.8%)
	35-49 years	5,555	5,450	7,823	7,723	6,925
		(29.1%)	(29.2%)	(28.8%)	(28.3%)	(27.7%)
	50+ years	1,542	1,663	2,661	2,784	2,718
		(8.1%)	(8.9%)	(9.8%)	(10.2%)	(10.9%)
Race	White	14,937	14,412	20,505	21,829	20,277
		(78.2%)	(79.1%)	(79.3%)	(80.6%)	(81.0%)
	Black	3,118	2,929	4,051	4,070	3,774
		(16.3%)	(16.1%)	(15.7%)	(15.0%)	(15.1%)
	Other	1,056	891	1,298	1,189	973
		(5.5%)	(4.9%)	(5.0%)	(4.4%)	(3.9%)
Ethnicity	Hispanic	905	771	1,193	1,212	1,139
		(4.7%)	(4.3%)	(4.7%)	(4.8%)	(4.7%)
	Not Hispanic	18,206	17,335	24,040	24,006	23,070
		(95.3%)	(95.7%)	(95.3%)	(95.2%)	(95.3%)
Reported Substance Use	Alcohol	13,562	12387	16,093	16,210	14,853
		(71.0%)	(66.3%)	(59.3%)	(59.4%)	(59.4%)
	Marijuana	10,520	9,518	12,773	13,088	11,817

		2008	2009	2010	2011	2012
		(55.1%)	(50.9%)	(49.1%)	(48.0%)	(47.2%)
	Cocaine	4,091	3,389	4,151	4,513	3,966
		(21.4%)	(18.1%)	(15.3%)	(16.5%)	(15.9%)
	Prescription Opioids	2,615	2,571	4,291	5,337	5,498
		(13.7%)	(13.8%)	(15.8%)	(19.6%)	(22.0%)
	Heroin	777	1,015	1,770	2,658	2,767
		(4.1%)	(5.4%)	(6.5%)	(9.7%)	(11.1%)
	Methamphetamine	1,757	1,774	2,633	3,159	3,018
		(9.2%)	(9.5%)	(9.7%)	(11.6%)	(12.1%)
	Benzodiazepines	1,153	1,160	1,791	2,046	2,002
		(6.0%)	(6.2%)	(6.6%)	(7.5%)	(8.0%)
	Other Drugs	801	1,632	4,326	5,463	4,994
		(4.2%)	(8.7%)	(16.0%)	(20.0%)	(20.0%)
Polysubstance Use	No drugs reported	31	830	2,643	691	276
		(0.2%)	(4.4%)	(9.7%)	(2.5%)	(1.1%)
	One drug reported	7,546	7,048	8,763	9,388	8,864
		(39.5%)	(37.7%)	(32.3%)	(34.4%)	(35.4%)
	Two drugs reported	6,760	5,919	7,753	8,071	7,186
		(35.4%)	(31.7%)	(28.6%)	(29.6%)	(28.7%)
	Three drugs reported	4,774	4,891	7,965	9,131	8,700
		(25.0%)	(26.2%)	(29.4%)	(33.5%)	(34.8%)
Treatment Admissions		19,111	18,688	27,124	27,281	25,026

Note: Since polysubstance use can and does occur, the individual drug categories are not mutually exclusive.

Table 2.2 Characteristics of Indiana's substance use treatment population – overall, heroin users, and prescription opioid users

Treatment Admissions		Overall (includes all treatment episodes)	Heroin Users	Rx Opioid Users
Gender	Male	75,517 (64.4%)	5,262 (58.6%)	10,459 (51.5%)
	Female	41,713 (35.6%)	3,725 (41.5%)	9,853 (48.5%)
Age	12-20 years	14,996 (12.8%)	1,074 (12.0%)	1,955 (9.6%)
	21-34 years	57,364 (49.4%)	5,771 (64.2%)	12,896 (63.5%)
	35-49 years	33,476 (28.6%)	1,581 (17.6%)	4,352 (21.4%)
	50+ years	11,368 (9.7%)	560 (6.2%)	1,105 (5.4%)
Race	White	91,960 (79.8%)	7,631 (87.4%)	18,643 (93.4%)
	Black	17,942 (15.6%)	773 (8.9%)	609 (3.1%)
	Other	5,407 (4.7%)	325 (3.7%)	714 (3.6%)
Ethnicity	Hispanic	5,220 (4.7%)	421 (5.2%)	457 (2.4%)
	Not Hispanic	106,657 (95.3%)	7,631 (94.8%)	18,513 (97.6%)
Reported Substance Use	Alcohol	73,105 (62.4%)	1,873 (20.8%)	7,087 (34.9%)

Treatment Admissions		Overall (includes all treatment episodes)	Heroin Users	Rx Opioid Users
	Marijuana	57,716 (49.2%)	2,545 (28.3%)	8,285 (40.8%)
	Cocaine	20,110 (17.2%)	2,265 (25.2%)	2,052 (10.1%)
	Prescription Opioids	20,312 (17.3%)	2,060 (22.9%)	20,312 (100.0%)
	Heroin	8,987 (7.7%)	8,987 (100.0%)	2,060 (10.1%)
	Methamphetamine	12,341 (10.5%)	541 (6.0%)	2,090 (10.3%)
	Benzodiazepines	8,152 (7.0%)	799 (8.9%)	3,651 (18.0%)
	Other Drugs	17,216 (14.7%)	1,591 (17.7%)	2,729 (13.4%)
Polysubstance Use	No drugs reported	4,471 (3.8%)	0 (0.0%)	0 (0.0%)
	One drug reported	41,609 (35.5%)	1,855 (20.6%)	3,540 (17.4%)
	Two drugs reported	35,689 (30.4%)	2,420 (26.9%)	4,959 (24.4%)
	Three drugs reported	35,461 (30.3%)	4,712 (52.4%)	11,813 (58.2%)
IDU		10,062 (8.6%)	6,204 (69.0%)	3598 (17.7%)
Treatment Admissions		117,230	8,987	20,312

Table 2.3 Client characteristics associated with heroin use in Indiana's substance use treatment population

Effect	N	% Heroin	Adjusted OR (95% Wald CL)	*p*-Value
Prescription opioids				
Used	20,312	10.1%	1.18 (1.11-1.25)	<.0001
Not used*	96,918	7.2%		
Gender				
Female	41,713	8.9%	1.20 (1.15-1.26)	<.0001
Male*	75,517	7.0%		
Race				
White	91,960	8.3%	1.53 (1.34-1.75)	<.0001
Black	17,942	4.3%	0.86 (0.74-1.01	.0610
Other*	5,407	6.0%		
Hispanic				
Yes	5,220	8.1%	1.18 (1.06-1.31)	.0035
No*	106,657	7.2%		
Age				
12-20	14,996	7.2%	1.43 (1.28-1.60)	<.0001
21-34	57,364	10.1%	1.93 (1.76-2.12)	<.0001
35-49	33,476	4.7%	0.89 (0.80-0.99)	.0307
50 and up*	11,368	4.9%		
Year of admission [Δ]			1.31 (1.28-1.33)	<.0001
2008	19,111	4.1%		
2009	18,688	5.4%		
2010	27,124	6.5%		
2011	27,281	9.7%		
2012	25,026	11.1%		

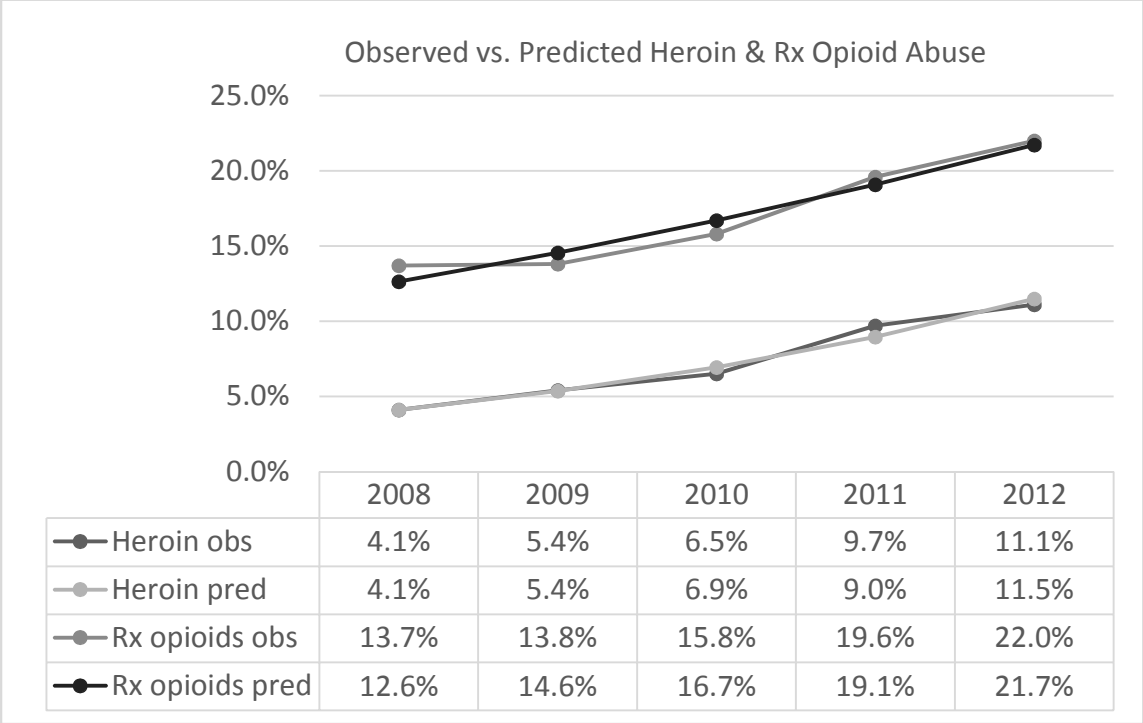
* Reference groups (OR=1.00)

[Δ] Year of treatment admission was entered as a continuous variable in the logistic regression analysis.

Table 2.4 Age of first heroin and prescription opioid use among clients receiving substance use treatment in Indiana

	Age of first heroin use (dual use with Rx opioids)	Age of first Rx opioid use (dual use with heroin)	Age of first heroin use (no Rx opioid use)	Age of first Rx opioid use (no heroin use)
11 and under	14 (1.0%)	250 (1.8%)	75 (1.5%)	236 (1.9%)
12-14	43 (3.0%)	1,127 (8.3%)	296 (6.1%)	1,003 (8.0%)
15-17	182 (12.7%)	3,089 (22.7%)	879 (18.0%)	2,758 (21.9%)
18-20	372 (25.9%)	3,099 (22.7%)	1,278 (26.2%)	2,830 (22.5%)
21-24	348 (24.3%)	2,285 (16.8%)	968 (19.8%)	2,132 (16.9%)
25-29	267 (18.6%)	1,691 (12.4%)	768 (15.7%)	1,608 (12.8%)
30-34	117 (8.2%)	908 (6.7%)	334 (6.9%)	789 (7.0%)
35-39	57 (4.0%)	539 (4.0%)	158 (3.2%)	523 (4.2%)
40-44	19 (1.3%)	338 (2.5%)	66 (1.4%)	331 (2.6%)
45-49	10 (0.7%)	183 (1.3%)	35 (0.7%)	184 (1.5%)
50-54	4 (0.3%)	91 (0.7%)	15 (0.3%)	97. (0.8%)
55 and above	1 (0.1%)	31 (0.2%)	7 (0.1%)	26 (0.2%)

Figure 2.1 Trend in Indiana substance use treatment admissions with observed and predicted heroin and prescription opioid use



	2008	2009	2010	2011	2012
Heroin obs	4.1%	5.4%	6.5%	9.7%	11.1%
Heroin pred	4.1%	5.4%	6.9%	9.0%	11.5%
Rx opioids obs	13.7%	13.8%	15.8%	19.6%	22.0%
Rx opioids pred	12.6%	14.6%	16.7%	19.1%	21.7%

CHAPTER 3 Assessment of Risk Behaviors in Patients with Opioid Prescriptions: A Study of Indiana's INSPECT Data

3.1. Specific Aim #2

Chapter 3 addresses the Specific Aim #2, as outlined in the abstract. The purpose is to Analyze 2014 INSPECT (Indiana's prescription drug monitoring program) data to identify factors that increase patients' likelihood to engage in opioid-related risk behaviors.

3.2. Introduction

Prescription opioid misuse is a widely recognized public health problem.[12,22,63,75] Factors that possibly contributed to the epidemic include increased availability of prescription opioids, social acceptability of using medications for nonmedical purposes, and aggressive marketing by the pharmaceutical industry.[18,21,29,38,76,77] There are considerable geographic differences in opioid prescribing rates among states,[78] which cannot be solely explained by variations in pain prevalence, but may reflect a lack of consensus on the appropriate use of opioids in the treatment of chronic non-cancer pain, patients' increasing demands for opioids, and regional differences in rates of opioid diversion.[79] A direct relationship between the rise in opioid prescribing, often out of a concern to avoid undertreatment of pain,[24] and the increase in opioid-related adverse events has been demonstrated.[12,80]

One chief strategy to curb prescription drug misuse is prescription drug monitoring programs (PDMPs). These statewide electronic surveillance programs gather information from pharmacies each time a controlled substance is dispensed. Thus,

PDMPs can serve as monitoring tools, tracking potential misuse and diversion of controlled substances, as well as clinical tools, assisting healthcare providers in decision-making processes. Sajid et al.[81] have shown that in a clinical setting, PDMPs can be utilized as a tool to measure treatment outcomes in opioid addiction.

Evidence suggests that PDMPs are effective in addressing the prescription drug epidemic by identifying "questionable activity" (e.g., doctor- and pharmacy-shopping, prescription fraud, problematic prescribing), aiding clinical decision-making prior to prescribing or dispensing controlled substances, and tracking trends in providers' prescribing patterns.[82] Even though PDMPs are considered highly effective, they remain a largely underutilized resource to improving public health outcomes.[82]

One of the challenges in using PDMPs to screen for questionable or high-risk activity has been the lack of standardized criteria on how to define these concepts. Various measures and thresholds have been suggested; however, little commonality exists in the criteria used by individual state PDMPs to identify risk patterns concerning patients (e.g., doctor-shopping) or healthcare professionals (e.g., inappropriate prescribing).[83,84] In addition, setting the proper thresholds of these measures is also a difficult task. Just as with any diagnostic procedure, low thresholds will result in a more sensitive screening process identifying higher numbers of potential misusers, but also lead to more false-positive determinations. Such misclassification is likely to stigmatize patients, overwhelm healthcare providers trying to make clinically sound decisions, and burden the criminal justice system in their efforts to control diversion. On the other hand, setting high thresholds will reduce the number of patients being flagged for

questionable activity, but also fail to identify individuals who may be at risk for opioid-related adverse events (false negatives) and who would benefit from clinical interventions.

Chronic opioid therapy for non-cancer pain is controversial and high doses of prescribed opioids may place patients at risk for overdoses and other adverse events.[85] Several current clinical practice guidelines on treating adults with chronic pain advise against using doses higher than 90-200 morphine milligram equivalents (MMEs) or combining opioids and benzodiazepines.[86] Researchers found that daily doses of 100 MMEs or more significantly increased the risk of overdose,[87] linking it to an eleven-fold increase in overdose-related mortality.[88] Visiting multiple healthcare providers and/or pharmacies has also been associated with overdose deaths. A study found that seeing four or more prescribers or obtaining opioids from four or more pharmacies increased the risk of opioid-related mortality about six-fold.[88] Benzodiazepines are generally safe unless taken in combination with opioids, as their combined effects produce significant respiratory depression.[89] According to one study, most overdose deaths attributable to benzodiazepines also involved other drugs, primarily opioids (71%).[90] Due to the concern of these opioid-related adverse events, the Centers for Disease Control and Prevention (CDC) recently published comprehensive guidelines for prescribing opioids for chronic pain: identifying high MMEs, multiple providers, and concurrent use of opioids and benzodiazepines as major concerns.[31]

The purpose of this study was to utilize Indiana's PDMP database to identify patient and prescription characteristics that are highly associated with opioid-related

risk behaviors. Findings from this study may aid in the clinical decision-making process and help more appropriately identify those who are at risk and would benefit from possible treatment or intervention.

3.3. Methods

3.3.1. Data Sources

This study utilized de-identified data from the Indiana Scheduled Prescription Electronic Collection and Tracking (INSPECT) program, which is Indiana's PDMP.[91] Each time a controlled substance (schedules II through V) is dispensed in Indiana, pharmacies are mandated to submit key information, including patient, prescriber, pharmacy, and drug characteristics, electronically to the INSPECT database. Since this project utilized previously collected data devoid of identifying information, institutional review board approval was not needed.

INSPECT data from 2014 were analyzed for this study. The complete dataset contained 13,066,666 observations with each observation representing the dispensation of a controlled substance. Drug categories and daily dosages of MMEs for opioids were determined based on the 11-digit National Drug Code (NDC). From these data, a total of 1,419,160 dispensations (10.9%) with missing or invalid NDC were excluded from the analyses, resulting in a dataset with 11,647,506 observations. All individuals receiving an opioid prescription in 2014 were included in the primary analyses. The number of unique individuals who filled at least one prescription for an opioid medication was 1,538,120.

3.3.2. Variables

INSPECT variables of interest included patient characteristics (gender, age), drug information (NDC, quantity, and number of days supplied), date when the drug was dispensed, as well as prescriber and pharmacy information. Identification (ID) numbers were assigned to each patient, prescriber, and pharmacy. These ID numbers were scrambled for de-identification and cannot be traced back to individuals or facilities.

Using a conversion syntax from the CDC, controlled substances were coded as opioids, benzodiazepines, or other pharmaceuticals, and daily dosages of MMEs for opioids were computed.[92]

3.3.3. Definition of High-Risk Activity

The outcomes of interest for this study were high-risk behaviors among patients using opioids. Rather than focusing on only one behavior associated with opioid-related adverse events, several were examined. Based on a review of existing literature and in line with CDC guidelines, the following activities have been associated with opioid-adverse events, particularly overdoses, and were examined in this study:[31,86-88] (1) consuming large daily doses of opioids >90 MME per opioid prescription; (2) obtaining prescriptions for opioids from four or more prescribers within the 12-month period; (3) receiving opioids from four or more pharmacies within the 12-month period; and (4) using opioids and benzodiazepines concurrently (both prescriptions having been filled within the same calendar month) at least once during the year.

3.3.4. Analyses

Descriptive statistics were employed to summarize the study population and examine the distribution of individual risk behaviors that, according to the literature,

have been linked to opioid-related adverse events.

Three logistic regression analyses were conducted to identify factors that increased patients' likelihood to engage in high-risk behaviors: (1) binary logistic regression analysis to assess the probability of patients engaging in at least one of the four risk behaviors (i.e., receiving any one opioid prescription >90 MME; having 4 or more opioid prescribers; having 4 or more opioid dispensers; concurrently using opioids and benzodiazepines) versus not engaging in any of these four high-risk activities; (2) ordinal (cumulative) logistic regression analysis to predict the odds of being in a higher risk behavior category (i.e., engaging in more risk behaviors) in a multi-level – ordinal – outcome (0 through 4 risk behaviors); in this model, the cumulative logit represents a summary of the odds ratios obtained from separate binary logistic regressions of the ordered multi-level outcome;[93] and (3) binary logistic regression analysis to predict the likelihood of patients engaging in all four risk behaviors versus engaging in less than all the behaviors or none at all.

Independent variables in all three analyses included gender and age category of each patient, as well as annual dispensation of opioids, benzodiazepines, and other controlled substances (i.e., all controlled prescription drugs Schedules II-V, except opioids and benzodiazepines; may include stimulants such as Ritalin, barbiturates such as Phenobarbital, anticonvulsants such as Lyrica, etc.). The latter variables were converted into categories for the analyses, because the continuous distributions were highly positively skewed (there was a small but non-negligible number of individuals in the database with extremely high levels of annual dispensation of opioids, which

prevented analyses based on models which assume a symmetric bell-shaped-like distribution of the measurements).

Opioids, the focus of this study, were categorized to represent average monthly prescriptions; e.g., 1 to 12 annual opioid dispensations represented "up to one monthly prescription," 13 to 24 dispensations, "up to two monthly prescriptions," etc., since a one-month supply is usually provided with each prescription. Prescriptions of benzodiazepines and other controlled substances were converted into binary categories (0 or 1 benzodiazepine prescription per year vs. 2 or more; 1 to 12 other controlled substances per year vs. more than 12). While concurrent use of opioids and benzodiazepines was one of the study's outcomes, having a benzodiazepine prescription did not necessarily imply co-use of both pharmaceuticals; this was only the case if both prescriptions were filled within the same calendar month. Also, having additional opioid prescriptions did not automatically add to a patient's MME, since MME was calculated per prescription and not as a cumulative measure.

Receiver operating characteristic (ROC) curves were plotted and the areas under the ROC curves (AUCs) were calculated for the two binary logistic regression analyses (analyses 1 and 3) to measure the accuracy of the independent variables in detecting high-risk activity.[94] Lastly, chi-square tests were used to examine if the AUC from the full model was superior to the individual AUCs.

Whenever appropriate, odds ratios and 95% Wald confidence intervals were computed. All analyses were conducted using Statistical Analysis Software SAS® version 9.4 (SAS Institute, Cary, NC). Results with *p*-values less than 0.05 were deemed

significant.

3.4. Results

3.4.1. Description of Study Population

The INSPECT database documented that more than 6.2 million (53.9%) of the 11.6 million pharmaceuticals dispensed in 2014 were opioids and nearly 3 million (25.1%) were benzodiazepines. While the vast majority of patients were Indiana residents, a small percentage (2.3%) were out-of-state residents. About one-tenth (11.3%) of prescriptions were paid for privately and the rest were covered by health insurance. The most frequently dispensed opioids were hydrocodone (59.7%) and oxycodone (16.0%). The distribution of MME was positively skewed (median=33.8; interquartile range [IQR]=39.2).

A little more than half of the 1,538,120 patients were female (57.0%) and the majority (70.4%) was over the age of 35 (Table 3.1). The number of opioid dispensations (median=2.0; IQR=3.0) and maximum MMEs (median=37.5; IQR=31.3) per patient was highly skewed, as was the number of unique opioid prescribers (median=1.0; IQR=1.0) and dispensers (median=1.0; IQR=0.0).

3.4.2. Distribution of Risk Behaviors

Three quarters of the patients (74.4%) did not fall in any of the risk categories; i.e., they did not receive high daily doses of opioids, did not visit multiple providers or dispensers, or engage in polypharmacy of opioids and benzodiazepines. However, 8.4% of patients obtained at least one prescription with a daily dose exceeding 90 MME (for some patients, daily doses >90 MME occurred multiple times throughout the year);

6.5% visited 4 or more different opioid prescribers; 3.1% obtained their opioids from 4 or more pharmacies; and 17.2% concurrently used opioids and benzodiazepines. Furthermore, a small number of patients were at the extreme end of the spectrum, obtaining exceptionally high doses of opioids, visiting a large number of prescribers and pharmacies, and concurrently using opioids and benzodiazepines for most of the year (Table 3.1).

The study assessed the distribution of risk behaviors, from 0 (no risk behaviors present) to 4 (all four risk behaviors present). While most of Indiana's patients with opioid prescriptions (74.4%) did not exhibit any of the risk behaviors, 18.4% presented with one, 5.3% with two, 1.6% with three, and 0.4% with all four risk behaviors (Table 3.1).

3.4.3. Predictors of High-Risk Activity

Results of the logistic regression analyses (Models 1 through 3) showed the following:

Model 1: Findings from the multiple logistic regression analysis indicated that having at least one risk behavior present was significantly associated with the annual number of prescriptions (opioids, benzodiazepines, or other pharmaceuticals). Averaging up to two opioids per month (i.e., 13 to 24 prescriptions for the year), as opposed to only up to one monthly opioid (i.e., 1 to 12 annual prescriptions; reference group) increased the patients' odds to engage in at least one risk behavior 11-fold (odds ratio [OR]=11.36; 95% confidence interval [CI]: 11.16-11.55). In fact, averaging more than four pain relievers per month (i.e., 49 or more during the year) resulted in an 80-

fold increase in the odds of engaging in at least one risk behavior (OR=80.26; 95% CI: 64.65-99.64). Furthermore, receiving two or more benzodiazepines during the year was associated with a nearly 36-fold increase in the odds of engaging in at least one risk behavior (OR=35.91; 95% CI: 35.43-36.39) compared to having zero or only one annual benzodiazepine prescription. Averaging more than one monthly prescription of other controlled substances increased the odds by 31 percent (OR=1.31; 95% CI: 1.25-1.38). Adults, especially those ages 36 to 55, were more likely to engage in one or more risk behavior than younger patients (Table 3.2).

To investigate the accuracy of the predictor variables in detecting high-risk activity, an ROC analysis was conducted. The ROC results showed that the AUCs of all predictor variables individually were significantly greater than 0.5 (*p*-values < .0001) and that the full model was superior in discriminating between patients who engaged in at least one high-risk activity and those who did not (AUC= .9281; *p*<.0001) (Figure 3.1).

Model 2: The cumulative (ordinal) logistic regression analysis indicated a significant relationship between the rising number of dispensations and increasing number of risk behaviors in patients. Compared to patients averaging only up to one monthly opioid prescription, those receiving up to two opioid prescriptions per month increased their odds of engaging in more risk behaviors almost 10-fold (OR=9.67; 95% CI: 9.55-9.80); each additional monthly prescription added to the odds, leading to a nearly 53-fold increase in patients averaging more than four opioids per month (OR=52.78; 95% CI: 48.12-57.89). Additionally, receiving more than one annual benzodiazepine prescription raised the odds that patients would fall into a higher risk-

behavior category more than 20-fold (OR=20.67; 95% CI: 20.45-20.89). Averaging more than one monthly prescription of other controlled substances added an additional 9 percent to the odds (OR=1.09; 95% CI: 1.05-1.13). Adults aged 36 to 55 years had the highest odds of engaging in more risk behaviors than any of the other age groups (Table 3.2).

Model 3: For the third analysis, a multiple logistic regression was utilized to model the probability of having all four risk behaviors present. More opioid and benzodiazepine prescriptions were linked to higher odds of engaging in all four risk behaviors, while greater dispensation of other controlled substances did not have a significant impact on this outcome. Averaging up to four monthly opioid prescriptions was associated with the highest increase (OR=68.55; 95% CI: 59.25-79.30) in this model and having two or more annual benzodiazepine prescriptions also raised the odds of engaging in all four risk behaviors 13-fold (OR=12.98; 95% CI: 12.00-14.04). Both being 18 to 35 years old and being male increased the odds of engaging in all four risk behaviors (Table 3.2).

Based on findings from the ROC analysis, the predictor variables were highly accurate in detecting patients who engaged in all four risk behaviors (AUC=.9528; $p<.0001$) (Figure 3.2).

3.5. Discussion

More than 6.2 million opioids were dispensed in Indiana in 2014, enough to provide nearly one prescription for every resident in the state (population in 2014 was 6,596,855). The majority of patients did not fall into any of the identified risk categories;

yet a substantial number of individuals did exhibit a range of behaviors that potentially could lead to opioid-related adverse events. Only a small percentage (0.4%) of all patients were on the extremely high-end of the risk spectrum; however, these individuals would most likely benefit from clinical interventions to prevent negative opioid-related consequences.

This study tested three outcomes linked to opioid-related risk behaviors. These outcomes were modeled from least (one or more risk behaviors were present) to most severe (all four risk behaviors were present). Findings from the analyses all pointed toward the same general conclusions: (1) increasing the number of opioid prescriptions and (2) adding an even fairly small number of benzodiazepine prescriptions substantially increased a patient's likelihood to engage in opioid-related risk behaviors. For healthcare professionals, this means that prescribing, on average, a second monthly opioid can increase the patient's risk by a factor of 10 or more (depending on the model) and each additional monthly opioid prescription would add significantly to the risk. Similarly, prescribing two or more benzodiazepines annually represents at least a 13-fold risk increase among patients who have had one or more opioid prescriptions in the same year. Risk behaviors were least likely to occur in young patients under the age of 18 and primarily associated with adults aged 36 to 55. Gender did not seem to play much of a role, except for Model 3, which showed that male patients were more likely to engage in all four risk behaviors compared to their female counterparts. Though only one-fourth of patients engaged in one or more risk behaviors, this group obtained over half of all opioid prescriptions and opioid consumption proportionally rose with

increasing number of risk behaviors.

Other studies observed similar associations between the number of prescriptions and risk behaviors, such as having 12 or more opioid prescriptions per year more than doubled the risk for prescription opioid misuse;[95] an increasing number of prescriptions was associated with doctor- and pharmacy-shopping;[96] and higher numbers of prescriptions, especially for opioids or benzodiazepines, increased the risk of drug-related mortality.[88,96]

However, to my knowledge this is the only study that incorporated multiple models to measure the association between prescription drug dispensations and opioid-related risk behaviors using PDMP data. Furthermore, it is important to note that the AUCs for both models were above 0.9, reflecting the models' excellent accuracy in discriminating between patients who engaged in opioid-related risk activities and those who did not.

3.5.1. Strengths and Limitations of the Study

A strength of the current study was its large sample size (n=1,538,120 unique opioid patients) and completeness of the dataset, since submission to INSPECT in 2014 was mandatory within a seven-day time frame. Several limitations were noted. Concurrent use of opioids and benzodiazepines was one of the study's outcomes. Though a prescription of benzodiazepines did not automatically imply concurrent use, 78% of the nearly 340,000 patients with a benzodiazepine script had both opioid and benzodiazepine prescriptions filled within the same month and suggested concurrent use.

Computation of the daily dose MME was not a cumulative measure, but instead was based on any one opioid prescription throughout the year. While it is a limitation that the overall or accumulated MME was not computed for any given period, this was necessary to circumvent circularity, since the number of opioid prescriptions (independent variable) would have automatically increased MME.

PDMPs identify prescribers by their individual Drug Enforcement Agency (DEA) number. Patients who see multiple providers at the same clinic may be inappropriately marked as "doctor-shoppers," because the database is unable to recognize when providers are working together.[84] Another limitation is that Indiana's PDMP is currently not connected to any other database; i.e., prescription drug history cannot be directly linked to health or other outcomes and the risk identified by these analyses cannot be correlated with any clinical outcomes. Furthermore, no information was available on patients' mental health or smoking status, both of which have been identified as strong risk factors for substance misuse behaviors.[72] It is also important to note that the study's findings are specific to Indiana and may not be generalizable to other states.

3.5.2. Conclusion

Prescribing at least two monthly opioids, on average, significantly increased patients' odds to engage in opioid-related risk behaviors, as did the prescription of two or more benzodiazepines per year. Only a small percentage of opioid patients fell into the highest category of risk behaviors. However, these patients comprised nearly 5,000 Indiana residents potentially at risk for opioid-related problems, such as opioid use disorders, respiratory depression, overdoses, or diversion.

Findings from this study are relevant to the clinical decision-making process and could be used to improve provider-patient communication by encouraging healthcare professionals to routinely utilize INSPECT prior to prescribing controlled substances, to educate patients on the risks and benefits of using and abusing opioids by themselves as well as with other controlled substances, and to better screen patients for symptoms of opioid use disorders, particularly those at high-risk. PDMPs have the potential to be a crucial element in the nation's response to the prescription drug epidemic. Continued national and state-level funding is essential to maintain and expand the states' capacity to develop and use PDMP data, allow for data-sharing across state lines, and integrate PDMP data with other databases, such as electronic health records.

Table 3.1 Patient characteristics and distribution of risk behaviors among unique patients with at least one opioid prescription

Number of unique opioid patients		1,538,120
Female		876,870 (57.0%)
Age Group	0-17 years	71,078 (4.6%)
	18-35 years	384,719 (25.0%)
	36-55 years	510,767 (33.2%)
	56 and older	571,556 (37.2%)
Maximum MME	*Max MME $\leq$ 90	1,408,991 (91.6%)
	Max MME between 90-200	10,148 (6.6%)
	Max MME between 200-500	24,191 (1.6%)
	Max MME > 500	3,322 (0.2%)
High daily doses of opioids	*0	1,408,991 (91.6%)
(number of times patient has received	1-12	111,312 (7.2%)
MME > 90)	13+	17,689 (1.2%)
Multiple opioid prescribers	*1-3	1,438,345 (93.5%)
(number of opioid prescribers per patient)	4-10	97,957 (6.4%)
	11+	1,818 (0.1%)
Multiple opioid dispensers	*1-3	1,490,302 (96.9%)
(number of pharmacies from which patient	4-10	47,383 (3.1%)
has obtained opioids)	11+	435 (0.0%)
Co-use of opioids and benzodiazepines	*0	1,272,616 (82.7%)
(number of months in which co-use	1-6	208,130 (13.5%)
occurred)	7-12	57,374 (3.7%)
Number of risk behaviors present	*0	1,143,604 (74.4%)
	1	282,811 (18.4%)
	2	81,224 (5.3%)
	3	25,085 (1.6%)
	4	5,396 (0.4%)

Note: Unit of analysis is the individual patient.
**No risk behavior.*

Table 3.2. Predictors of opioid-related risk behaviors, Models 1 – 3

		Model 1: Probability of engaging in at least one risk behavior (binary outcome)	Model 2: Probability of falling into a higher risk-behavior category (ordinal outcome)	Model 3: Probability of engaging in all 4 risk behaviors (binary outcome)
Effect		Adjusted OR (95% Wald CI)	Adjusted OR (95% Wald CI)	Adjusted OR (95% Wald CI)
Opioid prescriptions	1-12	REF	REF	REF
	13-24	11.36 (11.16-11.55)	9.67 (9.55-9.80)	14.66 (13.60-15.79)
	25-36	33.54 (31.82-35.36)	29.76 (28.92-30.63)	40.11 (36.76-43.76)
	37-48	52.79 (44.97-61.97)	49.01 (45.54-52.74)	68.55 (59.25-79.30)
	49+	80.26 (64.65-99.64)	52.78 (48.12-57.89)	57.86 (47.45-70.56)
Benzodiazepine prescriptions	0-1	REF	REF	REF
	2+	35.91 (35.43-36.39)	20.67 (20.45-20.89)	12.98 (12.00-14.04)
Other prescriptions	0-12	REF	REF	REF
	13+	1.31 (1.25-1.38)	1.09 (1.05-1.13)	0.95 (0.83-1.09)
Gender	Female	REF	REF	REF
	Male	1.01 (1.00-1.02)	1.04 (1.03-1.04)	1.29 (1.22-1.36)
Age group	0-17 years	REF	REF	REF
	18-35 years	2.69 (2.59-2.79)	2.93 (2.83-3.04)	2.47 (1.56-3.90)
	36-55 years	3.41 (3.28-3.53)	3.42 (3.30-3.54)	1.58 (1.00-2.49)
	56 years & older	3.21 (3.09-3.33)	3.17 (3.06-3.28)	1.10 (0.70-1.74)
		P<.0001	*P*<.0001	*P*<.0001

Figure 3.1. ROC and AUC for Model 1 (at least one risk behavior present)

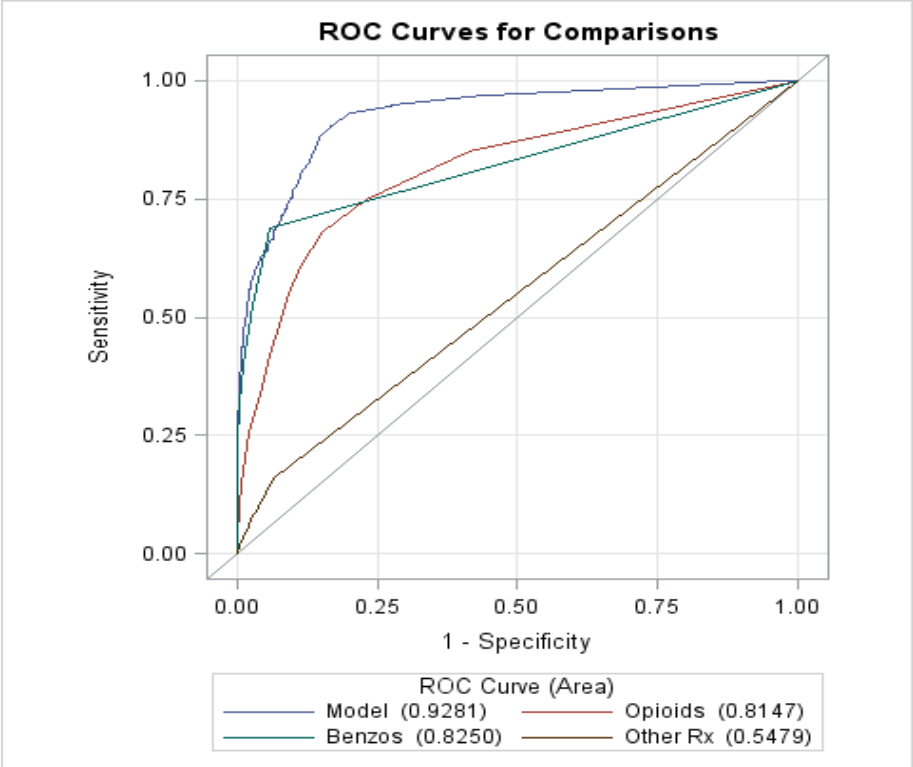
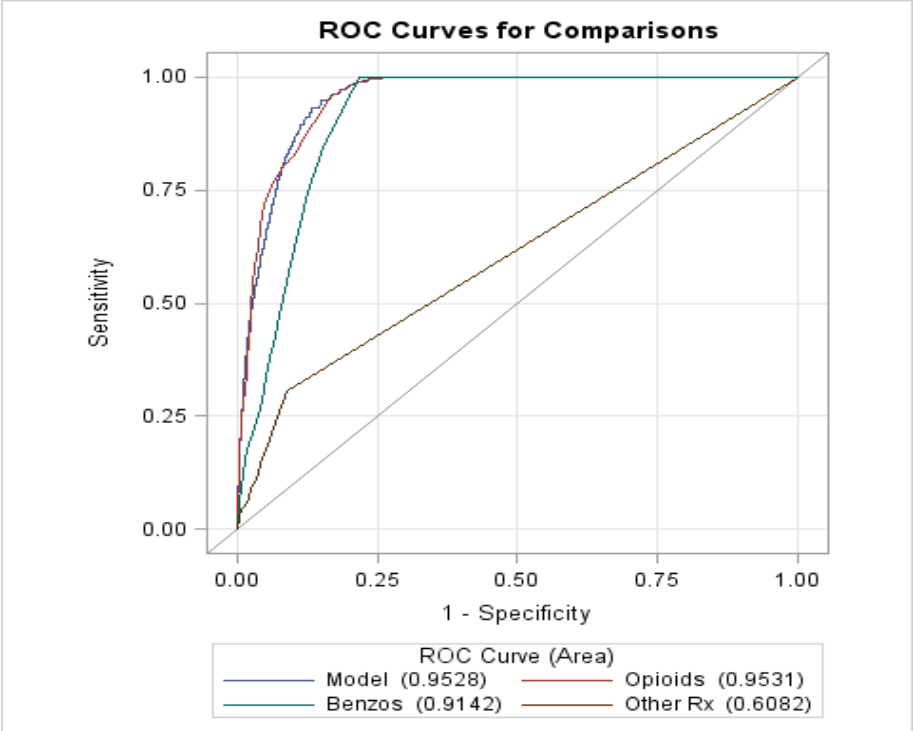


Figure 3.2. ROC and AUC for Model 3 (all four risk behaviors present)



CHAPTER 4 The Ongoing Rise in Neonatal Abstinence Syndrome (NAS) Across the U.S.

4.1. Specific Aim #3

Chapter 4 addresses the Specific Aim #3, as outlined in the abstract. The purpose is to review U.S. trends in neonatal abstinence syndrome (NAS) incidence from 2008-2014, measure regional variability, and identify personal and environmental risk factors associated with NAS.

4.2. Introduction

The opioid epidemic significantly contributes to the nation's disease burden,[97] accounting for more than 33,000 overdose deaths in 2015.[98] U.S. prevalence rates of opioid misuse have increased substantially in recent years,[2,99] including among pregnant women.[14] The rise in misuse and overdose deaths has often been linked to increasing sales and availability of opioids.[20,21] According to data from the 2013 National Survey on Drug Use and Health (NSDUH), 5.4% of pregnant women ages 15 to 44 years used an illicit substance in the past month, of which an estimated 15,000 pregnant women reported misusing prescription opioids (pain relievers) and 4,000 indicated heroin use.[100] Furthermore, antepartum maternal opioid use increased from 1.2 mothers per 1,000 live births in 2000 to 5.6 mothers per 1,000 live births in 2009.[14] With the increase in opioid misuse, the country has also seen a rise in the incidence of neonatal abstinence syndrome (NAS).[15]

NAS, also called neonatal withdrawal, is a direct response in the newborn infant to the abrupt discontinuation of chronic intrauterine exposure to drugs and other substances used by the mother during pregnancy. Clinical features of NAS include

tremors, irritability, excessive high-pitched crying, difficulty sleeping, poor feeding, poor weight gain, dehydration, vomiting, diarrhea, and in severe cases, seizures.[13,101-103] The onset, duration, and severity of NAS is determined by drug characteristics, including type, dosage, and pharmacological properties; by maternal drug history and metabolism; by infant metabolism and excretion; as well as other factors.[13,101] While various drugs can lead to NAS, opioids are the most common cause of neonatal withdrawal.[101] Before the 1970s, morphine or heroin were the predominant reasons for the development of the condition, but in recent years, this has changed to include all opioids, prescribed and illegal.[13] Even methadone or buprenorphine used as part of a medication-assisted treatment (MAT) program can result in NAS; however, comprehensive MATs together with prenatal care are accepted as the standard-of-care for pregnant women with opioid addiction[104,105] and can improve health outcomes for both mother and child.[106-108]

According to studies by Patrick et al., the rate of newborns diagnosed with NAS rose from 1.2 per 1,000 hospital births in 2000 to 5.8 in 2012, reflecting a nearly 400-percent rate increase.[14,15] Although the duration of NAS is relatively short[109,110] and long-term effects on brain development are largely unknown,[13,111] the health care costs associated with the condition are substantial. Hospitalization in neonatal intensive care units are expensive and can disrupt infant-family attachment.[112] Hospital charges in the United States due to NAS more than doubled from $720 million in 2009 to $1.5 billion in 2012, often disproportionally affecting those with lower socio-economic status since infants born with NAS were more likely to be covered by Medicaid and to mothers who

reside in poorer neighborhoods.[14,15]

Since the prevalence of NAS has increased consistently in recent years and the costs of caring for infants with the condition has also risen substantially, more specific information is needed to better understand the epidemiology of NAS cases. The purpose of this study was to build on previous research by: (1) examining trends in the national NAS incidence from 2008 through 2014; (2) measuring regional variability in NAS incidence; and (3) identifying personal and environmental risk factors associated with the occurrence of the syndrome.

4.3. Methods

4.3.1. Study Design and Data Source

Infants with NAS were identified through a retrospective cross-sectional analysis of data from the National Inpatient Sample (NIS) for 2008 through 2014.[113] NIS is part of the Agency for Healthcare Research and Quality's (AHRQ) Healthcare Cost and Utilization Project (HCUP). It is the largest publicly available all-payer inpatient health care database in the United States and yields national estimates of hospital inpatient stays. NIS records include patient demographics, diagnosis and procedure codes, hospital characteristics, length of stay, total charges, and expected payment source. The NIS dataset initially contained a sample of U.S. hospitals with all discharges from these hospitals. Since 2012, however, NIS has been comprised of a sample of discharges from all HCUP-participating hospitals in the U.S. The new design enables more precise and stable national estimates. Due to the redesign, a one-time decrease in the historical trends for discharge counts was expected in the 2012 statistics. Since this study spans

from 2008 through 2014, the analyses utilized AHRQ's trend discharge weights to minimize the effects of the redesign on estimated trends that cross the 2012 data year.[114]

The NIS datasets used for this study contained over 53 million hospital discharges from 2008 through 2014, including 5,538,204 hospital births. This study utilized secondary non-identified information and was, therefore, exempt from review of the Indiana University Institutional Review Board.

4.3.2. Identification of Cases

NAS was defined as having ICD-9 codes of 779.5 (drug withdrawal syndrome in newborn) or 760.72 (narcotics affecting fetus or newborn via placenta or breast milk), or ICD-10 codes of P96.1 (neonatal withdrawal symptoms from maternal use of drugs of addiction), P96.2 (withdrawal symptoms from therapeutic use of drugs in newborn), or P04.49 (newborn affected or suspected to be affected by maternal use of other drugs of addiction) in any of the 15 discharge diagnosis fields.

4.3.3. Personal and Environmental Factors

Personal characteristics of the infant (gender, race) as well as demographic information of the mother (geographic location of residence, household income, and primary insurance type) were available from the NIS datasets and included in the analyses.

Environmental factors included the regional drug overdose fatality rate, which provided a severity indicator of opioid misuse in the geographic region. Mortality rates attributable to drug poisoning (ICD-10: X40-X44, X60-X64, X85 or Y10-Y14) were

aggregated for the nine U.S. Census divisions for each year of the study from 2008 through 2014.[115]

Opioid use among pregnant women was of particular interest since it is the primary risk factor for NAS. Using substance abuse treatment data from the Substance Abuse and Mental Health Services Administration (SAMHSA),[116] annual rates of treatment admissions for opioid misuse in women aged 15 to 44 years were computed. These rates were aggregated for the nine U.S. Census divisions for each year, categorized into quartiles, and then included in the model with a one-year lag; i.e., treatment admission rate quartiles from 2007 were added as independent variables for 2008 NAS outcomes, etc. All women of childbearing age were included, not just pregnant women, in the treatment rate for several reasons. Given that 86% of pregnancies are estimated to be unintended among women who misuse opioids,[117] some women may not be aware of their pregnancy status and, therefore, not report being pregnant at the time of treatment admission. Also, since we included a one-year lag, women who were not pregnant when they entered treatment may have become so within the next year.

4.3.4. Analyses

Individual characteristics and outcomes related to hospital stays for infants with NAS were compared to those without a NAS diagnosis. National NAS incidence rates were calculated for each year by dividing the number of infants with a NAS diagnosis by the total number of hospital births, expressed per 1,000 births. To measure regional variability, NAS incidence rates from 2012 through 2014 were compared among the nine

U.S. Census divisions.

Both bivariate and multivariate logistic regression analyses were performed to test the association between personal and environmental risk factors and the likelihood of an infant being born with neonatal withdrawal as well as to assess NAS trends over time. The multivariate analysis produced adjusted odds ratios, taking potential personal and environmental confounders into account, while the bivariate analyses provided crude or unadjusted odds ratios.

For relevant analyses, weights provided by HCUP were applied to enable nationally representative estimates to be made with confidence. Odds ratios and 95% Wald confidence intervals were computed and included in the results. All analyses were conducted using Statistical Analysis Software SAS® version 9.4 (SAS Institute, Cary, NC). Results with p-values less than 0.05 were deemed significant.

4.4. Results

4.4.1. Description of Study Population

During the study period, 33,230 infants were discharged with a diagnosis of NAS. Compared to all other births, infants with a diagnosis of neonatal withdrawal were more likely to be male, white, from households with lower income, and covered by Medicaid as the primary payer. Most hospital births (NAS and other) occurred in urban, population-dense areas; however, NAS incidence rates were higher in rural areas (Figure 4.1).

During the 7-year period, infants with NAS had significantly longer average length of stays (13.6 days vs. 3.3 days; $p < .01$), higher mean number of comorbid

medical conditions (6.1 vs. 3.0; $p < .01$), and accumulated more average total charges ($50,415 vs. $11,027; $p < .01$) as shown in Table 4.1.

4.4.2. Annual NAS Incidence Rates

The national annual NAS incidence rate nearly tripled from 3.1 (95% CI: 3.0-3.2) per 1,000 births in 2008 to 9.1 (95% CI: 8.8-9.3) per 1,000 births in 2014 (p for trend < .01), as can be seen in Figure 4.2. Rates varied regionally, but the trend pattern remained the same. Particularly high rates and steep increases were seen in the U.S. Census divisions of East South Central (Kentucky, Tennessee, Mississippi, and Alabama) and New England (Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, and Connecticut). The 2014 incidence rates per 1,000 hospital births in these two regions were more than twice as high as the national rate of 9.1, with 20.5 (95% CI: 19.2-21.8) and 18.6 (95% CI: 17.0-20.1) respectively (Table 4.2 and Figure 4.3).

4.4.3. Identification of Personal and Environmental Risk Factors

Table 4.3 shows the findings from the bivariate and multivariate logistic regression analyses. When adjusting for all covariates, the probability of being born with a NAS diagnosis was higher among infants who were male, white, born to families with lower household incomes, covered by Medicaid, and located in urban, population-dense areas. Insurance status (primary payer) had the largest association with the infant being diagnosed with NAS. Being covered by Medicaid, compared to having private insurance, increased the odds of neonatal withdrawal more than eight times (OR: 8.55; 95% CI: 8.41-8.69), and infants without health insurance were nearly 7 times as likely to be

diagnosed with NAS (OR: 6.84; 95% CI: 6.65-7.03), when adjusted for the other covariates.

Infants born to families residing in urban areas was a significant risk factor for NAS in the adjusted model; however, findings based on the bivariate analysis suggested otherwise; i.e., the probability of having a diagnosis of neonatal withdrawal was higher in less population-dense areas. A follow-up analysis (cross-tabulation), which was conducted to identify the drivers of the discrepancy between the adjusted and unadjusted models, indicated that within rural areas there is a large proportion of families in the lowest income quartile, covered by Medicaid, and who are white; all of which are independent risk factors for NAS. The analysis found that as population density decreases, the percentage of patients who are white, poor, and on Medicaid increases (see Figure 4.4).

Among the environmental factors, the previous year's treatment admission rates for opioid misuse in women of childbearing age was associated with the outcome; especially living in a region with treatment rates in the fourth quartile (i.e., highest treatment rate quartile) compared to the first, increased the odds of having an infant born with NAS by 37% (OR: 1.37; 95% CI: 1.31-1.43), when adjusting for the other covariates.

The effect of regional overdose mortality rates was only evident in the bivariate analysis, linking rising overdose death rates to greater odds of infants having a NAS diagnosis. However, after adjusting for all other covariates, the association became insignificant (Table 4.3).

4.5. Discussion

As previous studies have indicated, the national NAS incidence has been on the rise in response to the opioid epidemic [14,15] and the findings from the current study show that this trend continues. More often the infants and families affected were white, in the lowest income quartile, covered by Medicaid, and living in urban areas, when controlling for covariates. Children diagnosed with neonatal withdrawal required longer than average hospital stays, experienced more serious medical conditions, and incurred higher hospitalization charges;[14,118] all of these outcomes put a significant strain on families in terms of costs and suffering. Since Medicaid covered four out of five babies born with NAS, most of the healthcare costs fell on the individual states, making the issue relevant to state Medicaid budgets.

An interesting though unexpected result was the association between NAS and gender. In the adjusted model, the odds for male infants to be diagnosed with NAS were 9% higher than for females - a small, yet significant finding. To our knowledge, few studies have examined sex differences in NAS risk and findings from those who have found inconsistent results. NAS expression and severity have been found to differ among affected infants, though the reasons for this variability are still unknown.[119] Male sex has been linked to a greater vulnerability for developmental deficits throughout infancy and childhood[120] and male infants have displayed poorer levels of neuro-behavioral functioning.[121] Furthermore, a recent large population-based cohort study found that male infants were 18% more likely to suffer from NAS compared to female neonates.[122]

The regional variability in NAS incidence rates highlighted areas in the U.S. that have been affected the most by the NAS problem, primarily East South Central and New England. This points toward a need for targeted policies and additional prevention strategies for women of childbearing age specifically in these regions.

The results of this study found an association between treatment admissions for opioid misuse in women ages 15 to 44 and neonatal withdrawal. Given that most pregnancies in females who misuse opioids are unintended,[117] entering treatment provides an opportunity to counsel women of childbearing age on the risks of delivering a child with NAS and assist them in their family-planning, including access to contraceptives.

4.5.1. Strengths and Limitations

A strength of this study was its large sample size (n=5,538,204 hospital births). Data were obtained through HCUP's NIS, the largest publicly available all-payer inpatient health care database in the nation. NIS allows for national and, since 2012, regional estimates of health conditions with confidence due to its strong scientific design. Furthermore, this study included demographic and environmental (regional) factors in the logistic regression analysis to identify additional risk factors of NAS; an approach that does not appear to have previously been attempted.

Limitations include a growing concern of misclassification bias when using the International Classification of Diseases (ICD) codes compared to using clinical scales to measure neonatal withdrawal, suggesting a possible undercounting of NAS cases.[109] Though it is possible that some of the increase in NAS incidence may be a result of the

attention the syndrome has been receiving in recent years, it is likely that the effect of this artifact was minimal, given the sharp increase and consistent incline in NAS cases over the past years.

4.5.2. Conclusion

National NAS incidence nearly tripled during the 7-year study period ending in 2014, continuing a previously observed upward trend across the country. Rates varied greatly regionally and were highest in the East South Central and New England regions. Healthcare costs associated with a NAS diagnosis can be substantial and the burden falls primarily onto individual states since Medicaid is the primary payer for a large portion of these cases. To reduce NAS, continued public health efforts are needed at the national and state levels to combat the opioid epidemic and implement specific strategies targeting women of childbearing age prior to becoming pregnant as well as during pregnancy for those misusing opioids. Adequate funding to address this problem, particularly in high-risk regions, is crucial.

Table 4.1. Characteristics of U.S. hospital births by NAS status, 2008-2014

	NAS Births (unweighted n=33,230)		All Other Births (unweighted n=5,504,974)	
	Weighted		Weighted	
	Mean	**95% CI**	**Mean**	**95% CI**
Length of stay (days) *	13.6	13.4-13.8	3.3	3.3-3.3
Number of diagnoses *	6.1	6.1-6.2	3.0	3.0-3.0
Total charges ($) *	50,415	49,268-51,562	11,027	10,976-11,078
	Percentage	**95% CI**	**Percentage**	**95% CI**
Male *	53.4	52.9-54.0	51.2	51.1-51.2
Race *				
White	75.5	75.0-76.0	52.3	52.2-52.3
Black	8.9	8.6-9.2	13.9	13.9-14.0
Hispanic	10.1	9.8-10.5	21.3	21.3-21.3
Asian/Pacific Islander	0.6	0.5-0.7	5.3	5.3-5.4
Native American	1.5	1.3-1.6	0.8	0.8-0.9
Other	3.5	3.3-3.7	6.4	6.4-6.4
Income quartile *				
1st quartile (lowest)	36.8	36.3-37.7	27.0	27.0-27.0
2nd quartile	27.3	26.8-27.8	25.4	25.3-25.4
3rd quartile	22.5	22.1-23.0	24.9	24.9-24.9
4th quartile (highest)	13.4	13.0-13.7	22.7	22.7-22.8
Primary payer *				
Medicaid	79.2	78.7-79.6	44.6	44.6-44.7
Private Insurance	13.0	12.7-13.4	47.8	47.8-47.9
Self-Pay	5.5	5.3-5.7	4.5	4.4-4.5

	NAS Births (unweighted n=33,230)		All Other Births (unweighted n=5,504,974)	
	Weighted		Weighted	
Other	2.3	2.1-2.5	3.1	3.1-3.1
Patient location				
Metro county ≥1 million	49.0	48.5-49.6	57.5	57.4-57.5
Metro county ≥250K but <1 million	21.8	21.4-22.3	19.1	19.1-19.1
Metro county ≥50K but <250K	9.4	9.5-10.2	8.9	8.8-8.9
Micropolitan	11.5	11.1-11.8	9.1	9.1-9.2
Not micro or metro	7.8	7.5-8.1	5.5	5.4-5.5

* $p < .0001$

Table 4.2. Annual NAS incidence rate* (95% CI) per 1,000 hospital births, by U.S. census division 2012-2014

	2012	2013	2014
New England	13.2 (11.9-14.5)	16.8 (15.3-18.3)	18.6 (17.0-20.1)
Middle Atlantic	6.9 (6.4-7.5)	7.9 (7.4-8.5)	8.6 (8.0-9.1)
East North Central	7.2 (6.6-7.7)	8.6 (8.0-9.1)	9.8 (9.2-10.4)
West North Central	4.4 (3.8-4.9)	5.6 (5.0-6.2)	5.5 (4.9-6.2)
South Atlantic	7.3 (6.9-7.8)	8.7 (8.2-9.2)	9.4 (8.9-9.9)
East South Central	12.9 (11.8-13.9)	17.7 (16.5-19.0)	20.5 (19.2-21.8)
West South Central	3.3 (2.9-3.6)	3.9 (3.5-4.3)	5.2 (4.8-5.7)
Mountain	7.5 (6.8-8.2)	9.2 (8.4-10.0)	10.0 (9.2-10.8)
Pacific	5.4 (5.0-5.9)	6.4 (6.0-6.9)	6.3 (5.9-6.8)
U.S.	6.8 (6.6-6.9)	8.2 (8.0-8.4)	9.1 (8.8-9.3)

*Weighted

Division 1 (New England): Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut
Division 2 (Mid-Atlantic): New York, Pennsylvania, New Jersey
Division 3 (East North Central): Wisconsin, Michigan, Illinois, Indiana, Ohio
Division 4 (West North Central): Missouri, North Dakota, South Dakota, Nebraska, Kansas, Minnesota, Iowa
Division 5 (South Atlantic): Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida
Division 6 (East South Central) Kentucky, Tennessee, Mississippi, Alabama
Division 7 (West South Central) Oklahoma, Texas, Arkansas, Louisiana
Division 8 (Mountain) Idaho, Montana, Wyoming, Nevada, Utah, Colorado, Arizona, New Mexico
Division 9 (Pacific) Alaska, Washington, Oregon, California, Hawaii

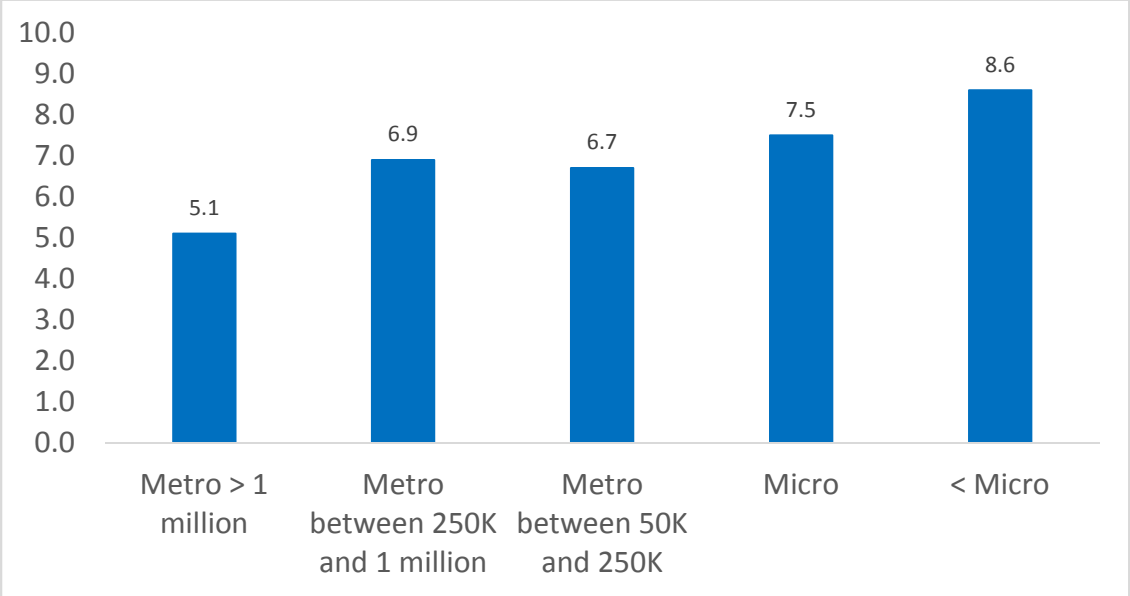
Table 4.3. Personal and environmental risk factors linked to NAS (unadjusted and adjusted odds ratios and 95% confidence intervals)*

	Bivariate (unadjusted)		Multivariable (adjusted)	
Effect	Odds Ratio	95% CI	Odds Ratio	95% CI
Male infants (ref=female)	1.09	1.08-1.11	1.09	1.08-1.10
Race of infant (ref=black)				
White	2.26	2.22-2.31	4.05	3.97-4.13
Hispanic	0.74	0.73-0.76	0.79	0.77-0.81
Asian/Pacific Islander	0.18	0.17-0.19	0.33	0.31-0.35
Native American	2.74	2.62-2.87	3.76	3.57-3.95
Other	0.85	0.82-0.88	1.10	1.06-1.13
Primary payer (ref=private insurance)				
Medicaid	6.51	6.42-6.61	8.55	8.41-8.69
Self-pay	4.52	4.41-4.64	6.84	6.65-7.03
Other	2.71	2.62-2.81	2.73	2.62-2.84
Median household income quartile (ref=4 / highest income quartile)				
1st quartile	2.32	2.29-2.36	1.44	1.41-1.46
2nd quartile	1.83	1.80-1.86	1.19	1.17-1.21
3th quartile	1.54	1.51-1.57	1.13	1.11-1.15
Patient location (ref=1 / metro areas with ≥1 million pop.)				
Metro areas with 250,000-999,999 pop.	1.34	1.32-1.36	0.95	0.94-0.97
metro areas with 50,000-249,999 pop.	1.30	1.28-1.33	0.84	0.82-0.86
Micropolitan areas	1.48	1.45-1.50	0.75	0.73-0.76
Rural (not metro- or micropolitan)	1.68	1.65-1.71	0.74	0.72-0.75

	Bivariate (unadjusted)		Multivariable (adjusted)	
Hospital division (ref=9 / East North Central)				
New England	2.33	2.20-2.29	2.60	2.54-2.68
Middle Atlantic	1.03	1.01-1.05	1.33	1.29-1.36
West North Central	0.63	0.62-0.65	0.91	0.87-0.95
South Atlantic	1.11	1.09-1.12	1.57	1.50-1.63
East South Central	2.24	2.20-2.29	1.55	1.51-1.59
West South Central	0.54	0.53-0.55	0.70	0.67-0.72
Mountain	1.09	1.07-1.12	1.47	1.41-1.53
Pacific	0.81	0.79-0.82	1.69	1.61-1.77
Opioid treatment rate 1-year lag (ref=1 / lowest rate quartile)				
2nd quartile	0.73	0.72-0.74	0.96	0.94-0.98
3rd quartile	0.78	0.76-0.79	1.18	1.14-1.23
4th quartile	1.51	1.50-1.53	1.37	1.31-1.43
Overdose mortality rate	1.14	1.14-1.15	1.01	1.00-1.01
Year	1.18	1.17-1.18	1.14	1.13-1.14

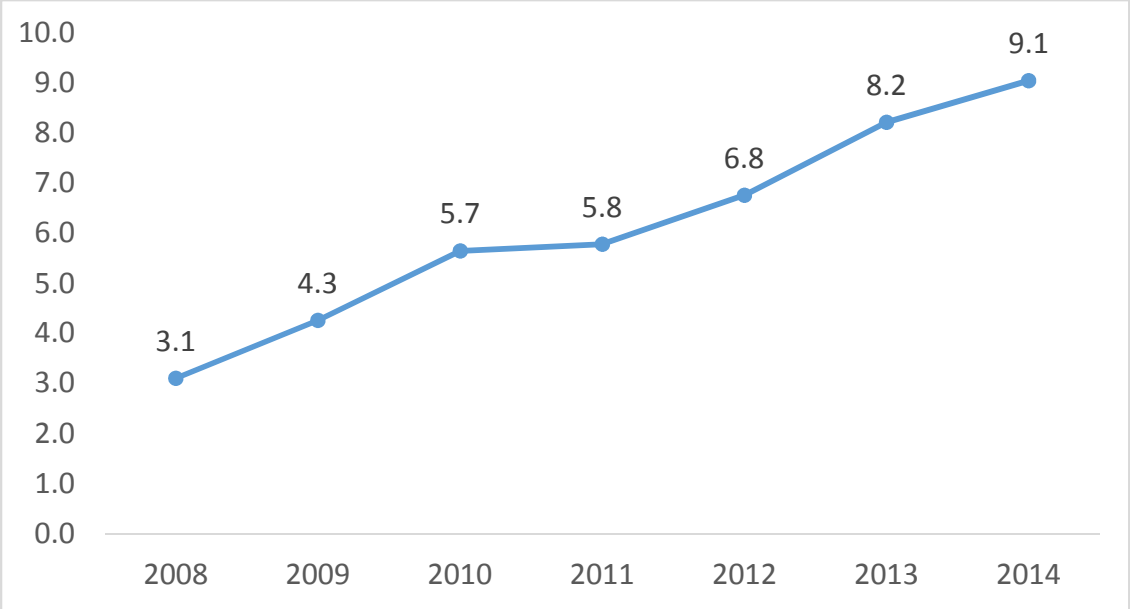
*Weighted

Figure 4.1. Average NAS incidence rate* per 1,000 hospital births by population density of patient location, 2008-2014



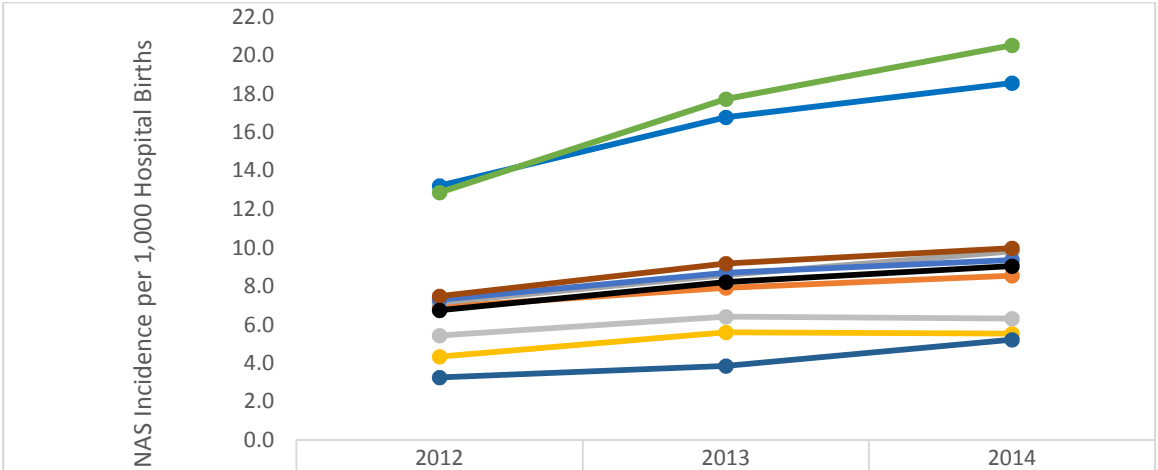
*Weighted as per the National Inpatient Sample instructions

Figure 4.2. Annual NAS incidence rate* per 1,000 hospital births, United States 2008-2014



*Weighted as per the National Inpatient Sample instructions

Figure 4.3. Annual NAS incidence rate* per 1,000 hospital births, by U.S. census division 2012-2014

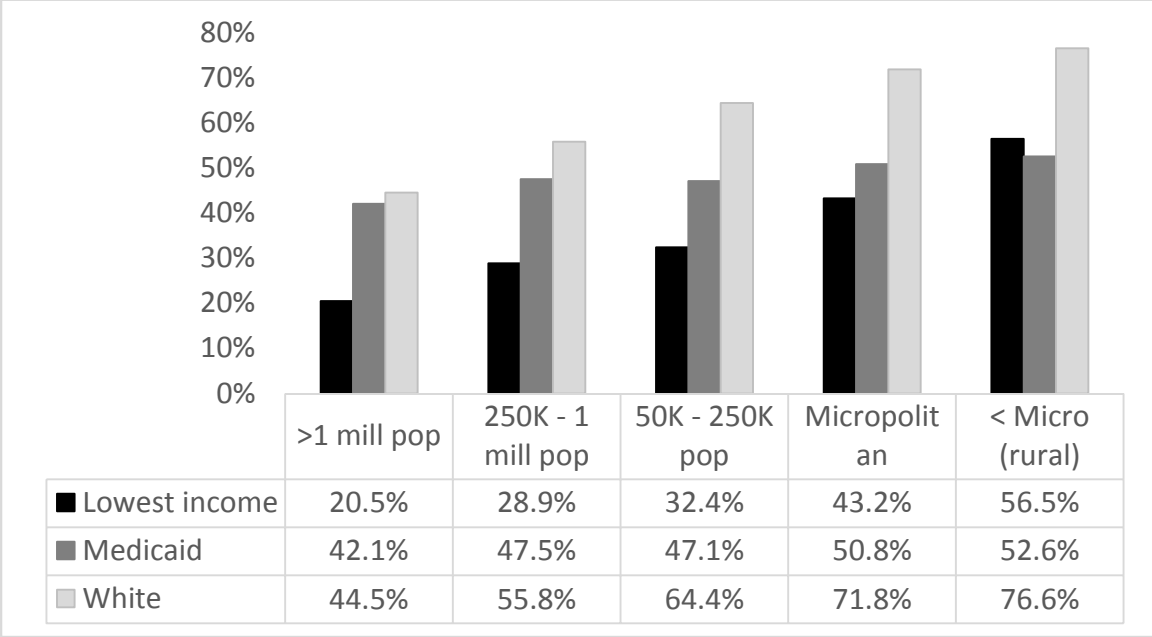


	2012	2013	2014
New England	13.2	16.8	18.6
Middle Atlantic	6.9	7.9	8.6
East North Central	7.2	8.6	9.8
West North Central	4.4	5.6	5.5
South Atlantic	7.3	8.7	9.4
East South Central	12.9	17.7	20.5
West South Central	3.3	3.9	5.2
Mountain	7.5	9.2	10.0
Pacific	5.4	6.4	6.3
U.S.	6.8	8.2	9.1

* Weighted

Division 1 (New England): Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut
Division 2 (Mid-Atlantic): New York, Pennsylvania, New Jersey
Division 3 (East North Central): Wisconsin, Michigan, Illinois, Indiana, Ohio
Division 4 (West North Central): Missouri, North Dakota, South Dakota, Nebraska, Kansas, Minnesota, Iowa
Division 5 (South Atlantic): Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida
Division 6 (East South Central) Kentucky, Tennessee, Mississippi, Alabama
Division 7 (West South Central) Oklahoma, Texas, Arkansas, Louisiana
Division 8 (Mountain) Idaho, Montana, Wyoming, Nevada, Utah, Colorado, Arizona, New Mexico
Division 9 (Pacific) Alaska, Washington, Oregon, California, Hawaii

Figure 4.4. Percentage of patients in the lowest income quartile, covered by Medicaid, and who are white by patient location*



	>1 mill pop	250K - 1 mill pop	50K - 250K pop	Micropolitan	< Micro (rural)
Lowest income	20.5%	28.9%	32.4%	43.2%	56.5%
Medicaid	42.1%	47.5%	47.1%	50.8%	52.6%
White	44.5%	55.8%	64.4%	71.8%	76.6%

*Weighted

CHAPTER 5 Conclusion

In the United States, the misuse of opioids, prescribed or illicit, has risen significantly over the past two decades. This has led to increases in treatment admissions for opioid misuse and addiction (Chapter 2); drug overdoses, many of which resulted in death; and infants born with neonatal abstinence syndrome (Chapter 4). Furthermore, persons addicted to opioids, especially heroin, frequently inject these drugs (Chapter 2). Sharing injection paraphernalia puts users at risk for getting or transmitting infectious diseases such as HIV and Hepatitis C.[123,124] It is estimated that approximately 10 percent of new HIV cases are linked to IDU.[125]

The liberal prescribing of opioids by healthcare professionals in the 1990s and 2000s is believed to have contributed significantly to the epidemic[4] by increasing the availability of prescription opioids in communities[22] and by raising the risk of addiction in patients who receive long-term opioid therapy.[126] However, prescribing practices are changing again and the Centers for Disease Control and Prevention have released opioid prescribing guidelines in 2016 to reduce overprescribing.[31]

5.1. Public Health Recommendations

The overall costs of the opioid epidemic in terms of financial expenditures and human suffering are extremely high.[14,40,52,127] Public health responses at the federal, state, and local levels have been substantial, but these efforts need to be maintained and expanded to successfully curb the problem. Based on findings from these studies (Chapters 2 through 4), the following strategies are recommended:

CHAPTER 2

The percentage of substance use treatment admissions attributable to opioids has increased significantly over the past years, indicating an expanding need for effective programs to treat opioid use disorder. Though not everyone who misuses prescription opioids progresses to heroin, for many in Indiana's treatment population this was the case. Over two-thirds of heroin users in treatment inject the drugs intravenously, which puts them at a high risk for transmitting infectious diseases such as HIV and hepatitis B and C.

1. Provide access to evidence-based treatment services for opioid use disorder (e.g., medication-assisted treatment).
2. Implement programs to reduce transmission of HIV and hepatitis B and C (e.g., syringe exchange programs).

CHAPTER 3

Receiving two or more monthly opioids, on average, and two or more benzodiazepines per year was highly associated with opioid-related risk activities in patients. Healthcare providers who routinely check patients' prescription drug history prior to prescribing a controlled substance may be in a better position to identify those at risk for opioid-related problem behaviors. To help reduce the burden on the healthcare system, integrating PDMP data with electronic health records (EHRs) would save physicians time and effort when accessing patients' charts. Some patients are willing to cross state lines in their pursuit of opioid prescriptions. Data-sharing agreements among PDMPs from multiple states and potentially a national PDMP system would allow for more complete monitoring of problematic behaviors in patients or

prescribers.

3. Encourage healthcare providers to conduct routine PDMP checks prior to prescribing a controlled substance.
4. Integrate PDMP data with EHRs to ease the burden on the healthcare system.
5. Establish PDMP data-sharing protocols across state lines and consider a national PDMP system.

CHAPTER 4

Incidence rates of neonatal abstinence syndrome (NAS) continue to rise across the country; varying greatly among U.S. regions. Healthcare costs associated with the diagnosis can be substantial and fall primarily to individual states by means of Medicaid as the primary payer to a large portion of these cases. Women of childbearing age who are addicted to opioids are the target population for prevention and intervention. Implementing specific strategies prior to these women becoming pregnant as well as during pregnancy is crucial.

6. Counsel women of childbearing age who misuse opioids on the risks of NAS and assist them in family-planning, including access to contraceptives.
7. Provide access to treatment for pregnant women addicted to opioids.

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Role: Principal Investigator

2016-2019 Prescription Drug Overdose Prevention for States. Centers for Disease Control and Prevention (CDC), Award# 1U17CE002721, $891,776, 3/1/2016-8/31/2019.

Role: Co-Investigator

2016-2017 State Epidemiology and Outcomes Workgroup. Indiana Family and Social Services Administration/Division of Mental Health and Addiction and the Substance Abuse and Mental Health Services Administration (SAMHSA), $391,469, 7/1/2016 – 6/30/2017.

Role: Principal Investigator

2016-2017 Indiana Family and Social Services Administration, 7/1/2016 – 6/30/2017. Evaluation contract, $500,000.

Role: Co-Principal Investigator

2016-2018 Indiana MAT-PDOA Grant. Center for Substance Abuse Treatment (CSAT), Substance Abuse and Mental Health Services Administration (SAMHSA), Award #1H79TI026149, $408,756 (subcontract amount), 01/01/2016-07/31/2018.

Role: Research Analyst

2015-2020 Indiana SPF PFS (Strategic Prevention Framework Partnerships for Success). Center for Substance Abuse Treatment (CSAP), Substance Abuse and Mental Health Services Administration (SAMHSA), Award# 1U79SP020788, $750,000, 9/30/2015-9/29/2020.

Role: Research Analyst

2015-2016 State Epidemiology and Outcomes Workgroup. Indiana Family and Social Services Administration/Division of Mental Health and Addiction and the Substance Abuse and Mental Health Services Administration (SAMHSA), $391,468, 7/1/2015-6/30/2016.

Role: Lead Epidemiologist

2014-2017 PEERS-Peer Empowerment Effects Recovery Services. Substance Abuse and Mental Health Services Administration (SAMHSA), Award #1H79TI025460. $50,000 (subcontract amount), 9/30/2014-09/29/2017.

Role: Evaluator

2013-2015 State Epidemiology and Outcomes Workgroup. Indiana Family and Social Services Administration/Division of Mental Health and Addiction and the Substance Abuse and Mental Health Services Administration (SAMHSA), $782,936, 7/1/2013-6/30/2015.

Role: Lead Epidemiologist

2014 Alcohol Retailer Survey. Indiana Coalition to Reduce Underage Drinking, $6,000, 4/1/2014-9/30/2014.

Role: Principal Investigator

2008-2009 Grants to States to Support Oral Health Workforce Activities. Department of Health And Human Services/Health Resources and Services Administration, Award # T12HP10693-01-00, $185,691, 9/1/2008-8/31/2009.

Role: Project Manager (subcontract)

2008 Mental Health and Substance Abuse Needs Assessment in Central Indiana. United Way of Central Indiana, $8,000, 3/3/2008-5/31/2008.

Role: Research Analyst

2006-2007 Mental Health and Addiction Services Needs Assessment. North Central Health Services, $100,000, 7/1/2006-6/30/2007.

Role: Project Manager

Publications (Peer-Reviewed)

2018 Phalen, P, Ray, B, Watson, DP, Huynh, P, & **Greene, MS**. (2018). Fentanyl related overdose in Indianapolis: Estimating trends using multilevel Bayesian models. *Addictive Behaviors*.

2017 **Greene MS**, Chambers RA, Yiannoutsos CT, Wright ER, Steele GK, Zollinger TW. (2017). Assessment of risk behaviors in patients with opioid prescriptions: A study of Indiana's INSPECT data. *The American Journal on Addictions*. 26(8):822-829.

2017 Wright, ER, Kooreman, HE, & **Greene, MS**. (2017). The early impact of the Indiana Scheduled Prescription Electronic Collection and Tracking (INSPECT) program: A potentially effective policy tool for reducing

prescription drug abuse. *Indiana Health Law Review*, 14:112.

2016 Chambers, RA, & **Greene, MS**. (2016). Physician understanding and treatment of addiction: Have 'Pseudoaddiction' and 'Self-Medication' led us astray? *Journal of Addiction and Dependence* 2(3): 1-4, DOI: 10.15436/2471-061X-16-028.

2016 Sajid, A, Whiteman, A, Bell, RL, **Greene, MS**, Engleman, EA, Chambers, RA. (2016). Prescription drug monitoring program data tracking of opioid addiction treatment outcomes in integrated dual diagnosis care involving injectable naltrexone. *American Journal on Addictions,* 25: 557-564, DOI: 10.1111/ajad.12441.

2015 **Greene, MS**, & Chambers, RA. (2015). Pseudoaddiction: Fact or Fiction? An Investigation of the Medical Literature. *Current Addiction Reports*, 1-8.

2014 Hackman, DT, **Greene, MS**, Fernandes, TJ, Brown, AM, Wright, ER, Chambers, RA. (2014). Prescription Drug Monitoring Program Inquiry in Psychiatric Assessment: Detection of High Rates of Opioid Prescribing to a Dual Diagnosis Population. *Journal of Clinical Psychiatry*, 75(7): 750-756.

2014 Wright, ER, Kooreman, HE, **Greene, MS**, Chambers, RA, Banerjee, AB, & Wilson, J. (2014). The iatrogenic epidemic of prescription drug abuse: County-level determinants of opioid availability and abuse. *Drug and Alcohol Dependence*, 138: 209-215.

Teaching Experience

2017 Buzzed and Stoned: The epidemiology of substance abuse

E333. Developed course and instructor on record.

2011 Teaching Aide and co-developer of graduate course “Health Impact Assessment” with Cynthia Stone, DrPH, RN

Professional Membership

American Public Health Association (APHA)

Delta Omega Honorary Society in Public Health