CONTRIBUTION TO EPIDEMIOLOGICAL RESEARCH ON THE USE OF HEROIN AND OTHER OPIOID COMPOUNDS

By

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ABSTRACT

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Patterns of heroin use and extra-medical (EM) use of other opioid compounds have re-surfaced as important public health issues in the United States (US) and in many countries. Midway through a 21st century epidemic of death due to heroin overdose in the US, there are many gaps in epidemiological evidence. For example, experts have already have concluded that heroin often becomes an alternative or substitute for other prescription opioids because an unit dose of heroin has become less expensive and now is more readily available than diverted prescription opioids (Cicero et al., 2012; Jones 2013; Muhuri et al., 2013). Nonetheless, the evidence on this issue largely is based on case reports, and provides little basis for causal inference. This problem is compounded by the lack of published population-level estimates on heroin incidence rates, akin to estimates derived by Hunt & Chambers (1976), based upon treatment admissions during the US heroin epidemic of the 1960s and 1970s.

The first aim of this dissertation addresses this incidence rate gap in epidemiological evidence for the US. It seeks to estimate heroin incidence for 1992-2012 using the Hunt-Chambers method based on opioid treatment admissions. The second dissertation aim is concentrated on a causal inference about the process of becoming a newly incident heroin user, and whether this process might be triggered by prior EM use of OxyContin®, a specific prescription opioid. Thus, the second specific aim is to conduct a case-crossover study to investigate a “triggering hypothesis” that links antecedent EM OxyContin® use with later heroin

onset in the US. The third study of this dissertation aims to predict the probability of transitioning from EM prescription pain reliever use to heroin onset using survival analysis models, with attention to hypothesized subgroup variation (i.e., population density).

Based on Hunt's model via re-calibration approaches using Treatment Episode Data Set - Admissions datasets (TEDS-A), heroin onset increased 160% from 2000 to its peak in 2010; the incidence rate in 2012 is similar to the first heroin epidemic in 1969. As for opioids other than heroin (e.g., prescription opioids), the incidence increased more than 250% from 2000 to 2010. The second study investigates whether EM OxyContin® use might have triggered heroin onset among 12-25 year olds in the period of 2004-2014. The excess risk of newly incident heroin use is seen in a four-month interval right after onset of EM OxyContin® use (case-crossover risk ratio = 1.9). Post-estimation exploratory analyses suggest no excess risk for EM users of other prescription pain relievers, and indicate no excess risk correlated with new formulations of OxyContin® per se. In the third study, the peak risk for transitioning from onset of extra-medical prescription pain reliever use (EMPPR) to heroin onset within 10 years emerged at the third year since first EMPPR use. Approximately 5% of participants initiated heroin use in 10 years since EMPPR onset. The estimates of these subgroups remain similar regardless of population density. EMPPR users who are male, White, and with early EMPPR onset have an increased risk of initiating heroin use.

Heroin outbreaks and epidemics revisited the US in the 2010s after the first US heroin epidemic of the 1970s. If successful, this project's new evidence on heroin in the US population in recent epidemic years should improve our understanding of heroin epidemiology, and may be an aid to new public health responses for primary prevention, outreach, and treatment resources with respect to heroin in the current epidemic and during future epidemics.

This dissertation is dedicated to my parents.
Thank you for always believing in me,
always encouraging me,
and loving me unconditionally.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

KEY TO ABBREVIATIONS

CBSA: Core Based Statistical Area

CI: Confidence interval

CSA: Controlled Substances Act

DTSA: Discrete-time survival analysis

DSM: Diagnostic and Statistical Manual

EM: Extra-medical

EMOXY: Extra-medical OxyContin

EMPPR: Extra-medical prescription pain reliever

FDA: Food and Drug Administration

HR: Hazard ratio

IRD: Internationally regulated drugs

LCM: Lag Correction Method

MET: Urban/Metropolis

MSA: Metropolitan Statistical Area

NESARC: National Epidemiologic Survey on Alcohol and Related Conditions

NSDUH: National Survey on Drug Use and Health

RR: Relative risk

SUBRUL: Suburban/Rural

TEDS-A: Treatment Episode Data Set – Admissions

CHAPTER 1

OVERVIEW AND SPECIFIC AIMS

1.1 OVERVIEW

This dissertation focuses on the epidemiology of opioid compounds. As described in Chapter 2.0, the history of human use of opioids dates back to prehistoric times; traces of opium have been found in Paleolithic human settlements. Misuse of opium compounds has been documented since the early 19th century. Morphine and heroin, the two early opium derivatives, were introduced in the mid-to-late 19th century. Later, in the 20th century, semi-synthetic opioids (e.g., hydrocodone, oxycodone) were derived.

Opioid compounds can be conceptualized of as 'an agent' in the general agent-host-environment model of human disease. The range of human disorders resulting from human contact with this 'agent' include opioid overdose (generally with complications such as respiratory depression and cardiac arrest), opioid dependence (as defined by the World Health Organization or the American Psychiatric Association), and infections or other complications associated with injection of opioid compounds (e.g., human immunodeficiency virus (HIV) infection and related opportunistic infections; hepatitis C virus infection; sepsis). There are many unanswered research questions about opioid epidemiology in human populations. This dissertation attempts to answer three specific questions in this domain of opioid epidemiology.

The first question falls under the rubric of 'quantity' within the array of five main rubrics outlined for epidemiology (Anthony & Van Etten, 1998). Namely, 'How many people are becoming heroin users, year by year?' Death statistics for the United States (US) clearly indicate occurrence of a new epidemic of heroin overdose and EMPPR use overdose deaths (Han, Compton, Jones, & Cai, 2015; Paulozzi, Budnitz, & Xi, 2006). Heroin overdoses do not occur

until heroin use occurs. There are several ways to derive estimates of incidence of heroin use; one of the most common approaches is using treatment records on new admissions of people requiring heroin intervention.

The second of the unanswered research questions falls under the rubric of 'causes' within the array of five main rubrics of epidemiology (Anthony & Van Etten, 1998). Of interest is whether the use of sustained release oxycodone (in the formulation known as OxyContin®) triggers or precipitates the onset of heroin use. It is widely believed that the epidemic of OxyContin® use has fueled a current epidemic of heroin use, with newly incident OxyContin® use triggering onset of heroin use that otherwise would not have happened. This 'triggering' hypothesis will be tested using the epidemiological case-crossover approach, and this dissertation includes estimates of the OxyContin®-heroin triggering relationship.

The third research question I am going to address in this dissertation is "in estimating time from extra-medical use of prescription pain reliever (EMPPR) into heroin use, is there hypothesized variation by area characteristics such as population density?" This question falls under the rubric of 'location' within the array of five main rubrics of epidemiology (Anthony & Van Etten, 1998).

1.2 SPECIFIC AIMS

1.2.1 **SPECIFIC AIM 1**: To estimate the incidence of heroin use considering lag-time between onset and admission to a treatment facility, and to compare treatment-based estimates with field survey estimates.

For this specific aim, the treatment admissions data based on Treatment Episode Data Set - Admissions (TEDS-A) is used to estimate the incidence of heroin use with using 'indirect' approaches used to provide projections, forecasts, and steady state descriptions of heroin use incidence when the only available data are from treatment admissions. That is, the comparison of heroin incidence estimates based on treatment admissions data versus estimates based on the field survey data will be informative, irrespective of whether the various methodological approaches yield the same or different estimates of incidence. The expectation is that the treatment admission incidence estimates will not differ from those of the field survey data (i.e., a null hypothesis).

1.2.2 **SPECIFIC AIM 2**: To estimate the triggering effect from OxyContin® use specifically and from prescription opioids generally to heroin use via the case-crossover approach.

This specific aim is to learn whether prior use of OxyContin® might trigger or precipitate onsets of heroin use (e.g., when OxyContin® becomes too expensive or cost-prohibitive and heroin use becomes less cost-prohibitive). The data come from the month and year of onset obtained from recent national surveys. The design involves a case-crossover approach such that there are two estimated quantities of crucial significance: (1) the number of individuals whose onset of heroin use is preceded by OxyContin® onset during a pre-specified 'hazard interval,' and (2) the number of individuals whose onset of heroin use is preceded by OxyContin® onset during a pre-specified 'control interval.' The ratio of these two numbers can be used to derive an evaluation of the degree to which OxyContin® use might be triggering onset of heroin use.

1.2.3 **SPECIFIC AIM 3**: To estimate the probability of transition from extra-medical EMPPR onset to heroin onset with using survival analysis models, with attention to hypothesized subgroup variation in relation to population density and region of the country.

In the second specific aim, the hazard interval is pre-specified from EMPPR onset to heroin onset. To evaluate my hypotheses of the length of time from EMPPR onset to heroin onset, I turn to using survival analysis approaches to study the duration of elapsed time and the factors influencing this duration, with attention to hypothesized subgroup variation in relation to population density and region of the country. The null hypothesis is that the estimated median time from EMPPR onset to heroin onset will not differ by population density.

CHAPTER 2

BACKGROUND AND SIGNIFICANCE

2.1 HEROIN AND OTHER OPIOIDS

2.1.1 Brief introduction of opioids

The focal point of this dissertation is the human use of opioid drug compounds, as studied from an epidemiological perspective. Opioids are prominent as beneficial medicinal compounds and especially respected for their pain relieving effect. However, they also have some toxic consequences, including case fatality when large doses are taken (White & Irvine, 1999). The term 'opioid' refers to derivatives of the opium poppy (e.g., morphine, heroin) or are synthesized (e.g., methadone) compounds such as methadone. As just noted, opioids usually are prescribed for pain relief. In the opium form, opioids have been used as pain relievers for thousands of years (Booth, 1999).

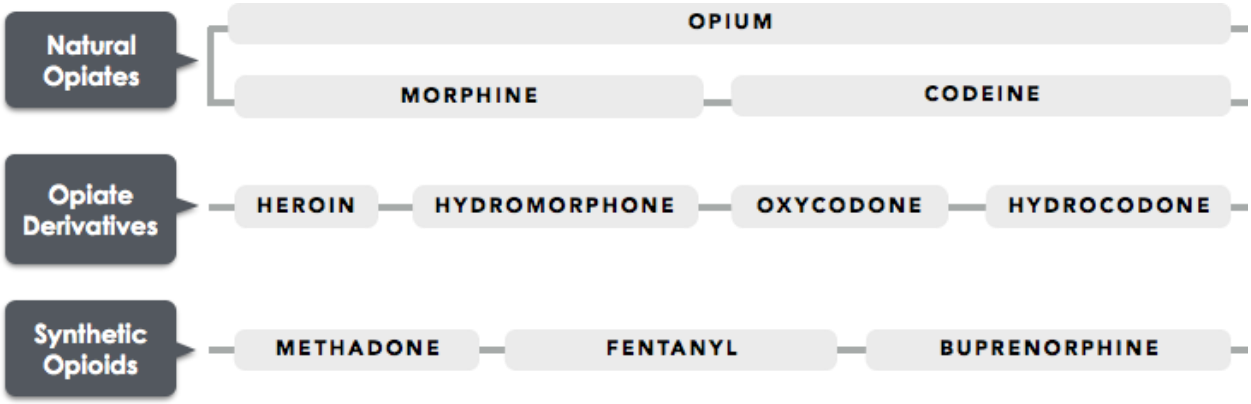
The distinction between opiates and opioids is fairly straightforward. Opiates are essentially the derivatives of opium poppy. Opioids encompass the opiates as well as semi-synthetic and synthetic compounds, some of which can be derived in a laboratory when an opium supply is not present. Methadone is a prototypical opioid. It was developed during the World War II era by chemists in Nazi Germany, when the country became concerned that its access to opium poppy fields might be constrained by wartime blockades, and efficacious opioid pain relief was a pressing need (Defalque & Wright, 2007)**.**

It is possible to discriminate between three types of opioids: 1) Natural Opioids ('opiates'), which are directly created from alkaloids in the opium poppy plant, most often from material in the seedpods; 2) Opioid Derivatives (also called semi-synthetic opiates), which are derived from

natural opioids; 3) Synthetic Opioids, which are manufactured in chemical laboratories to yield similar chemical structures to the truly 'opiate' compounds derived from opium poppy plants.

For clarity, morphine and codeine are classified as natural opiates, whereas heroin is a derivative of morphine, as shown in the accompanying figure.

Figure 2.1.1 Classification of opioid subtypes. (Adapted from Booth, 1999)

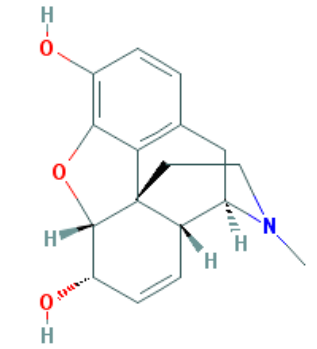
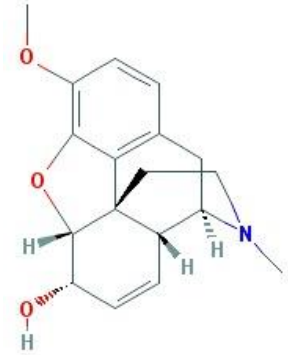
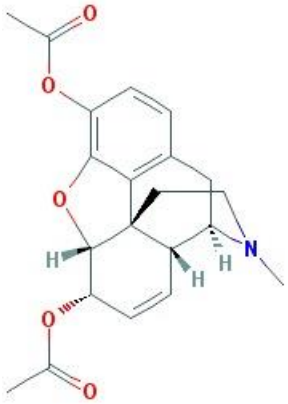
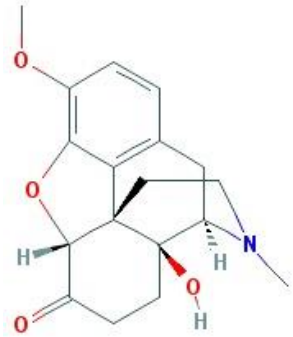
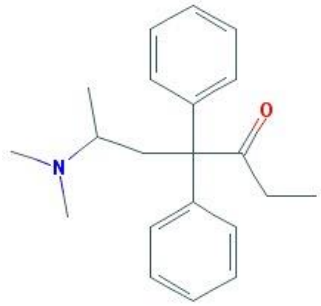
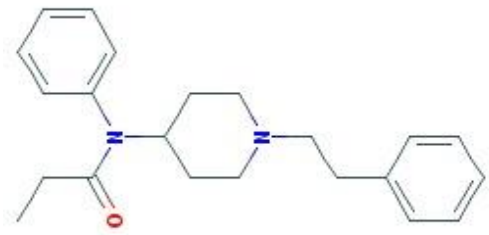


2.1.2 Pharmacology of heroin and other opioids

Opioids work in the body by interacting with proteins called opioid receptors, which can be found in the central nervous system (CNS) and gastrointestinal tract (GI). Opioid receptors are responsible for analgesic effects of opioids in the body. The three main types of opioid receptors are mu (μ), kappa (κ), and delta (δ). For example, when opioid binds to the μ-receptor, it produces the effects of analgesia. Morphine is the first chemical found to bind to the μ-receptor. The κ-receptor is also associated directly with analgesia but not many significant agonists acting on the κ-receptor are known. Morphine and other commonly used opioid analgesics strongly bind to the δ-receptor but the δ-receptor is mostly found in larger cells and plays an important role in spinal analgesia (Jordan, Cvejic, & Devi, 2000).

The chemical structure of a drug determines its affinity and activity for receptors and the ability to elicit a response to the body. Similarity, the affinity and activity of opioid receptors can be determined by its chemical structure (Feinberg, Creese, & Snyder, 1976). The chemical structures of various opioid compounds are displayed in the Figure 2.1.2.

Figure 2.1.2 Chemical structures of examples of six opioids

NATURAL OPIATES	
Morphine Molecular Formula: C17H19NO3 	**Codeine** Molecular Formula: C18H21NO3 
SEMI-SYNTHETIC OPIATES	
Heroin Molecular Formula: C21H23NO5 	**Oxycondone** Molecular Formula: C18H21NO4 
SYNTHETIC OPIATES	
Methadone Molecular Formula: C21H27NO 	**Fentanyl** Molecular Formula: C22H28N2O 

Source: PubChem Substance and PubChem Compound database (https://pubchem.ncbi.nlm.nih.gov/)

2.1.3 History of supply, manufacture, and use

Opium poppy crops are found in many countries. In 1803, morphine was extracted from opium resin for medical treatments. In 1827, Merck pharmaceutical company (Germany) began the manufacture of morphine, after which it was widely prescribed to relieve pain, reduce coughing, or improve sleep. In 1898, heroin was introduced by the Bayer Company in Germany. It was developed chiefly as an alternative to morphine for cough suppressants, and the Bayer Company promoted that heroin did not have morphine's addictive side effects at that time. Later time was found that heroin might be more addictive than morphine (BAYER Pharmaceutical Products, 1901).

Before 1914, laws concerning opiates were strictly imposed only on a local city or state basis in the US. For example, one of the first laws was in San Francisco in 1875; smoking opium became illegal in opium dens. Harrison Narcotics Tax Act was a US federal law approved in 1914. It stated that

> *It is an act to provide for the registration of, with collectors of internal revenue, and to impose a special tax upon all persons who produce, import, manufacture, compound, deal in, dispense, sell, distribute, or give away opium or coca leaves, their salts, derivatives, or preparations, and for other purposes* (Harrison Narcotics Tax Act, 1914).

This law aimed to require professionals who prescribed narcotics (e.g., heroin) to register and pay taxes. Therefore, it helped to manage distribution and sale of narcotics. Harrison's legislation did not prohibit drugs specifically but the prescription of narcotics is only permitted under the course of clinicians' professional practices.

In 1924, US Congress banned the manufacture, importation, and sale of heroin. In 1970, it enacted a Controlled Substance Act (CSA), which involved placing selected drugs into

one of five schedules under existing federal law. Heroin was listed as a Schedule I drug, making it illegal to make or possess. Drugs in this schedule have no currently accepted medical use in the US. The United States government recognized that the epidemiological 'reservoir' for heroin, opioids, and other drugs subject to the Controlled Substances Act of 1970 (CSA1970) often was located outside the US. These 'agents' in the agent-host-environment model might originate in the opium-growing regions of Asia, and for this reason, international regulation was proposed. An international treaty analogy of CSA1970 regulations has been adopted by most countries participating in the United Nations and World Health Organization under the name "Psychotropic Drug Convention," which sets forth its own set of "schedules," many of which are based on CSA1970 specifications. For this reason, and because within-country jurisdictions sometimes depart from the CSA1970 and also from the Psychotropic Drug Conventions, we no longer can declare drug use as 'illegal' or refer to 'illegal drug use' because it might not be illegal in some jurisdictions. (For instance, heroin is used in the practice of medicine in Switzerland; cannabis now is used in the practice of medicine in many of the states of the US, and can be used recreationally in a growing number of states and in many countries.) For this reason, we refer to the drugs regulated under CSA1970 as 'internationally regulated drugs' (IRD) and this designation segregates them from widely used drug compounds that are not internationally regulated at this point (e.g., alcoholic beverages, nicotine and tobacco products; caffeine-containing compounds such as coffee; betel nut) (Blatman, 1971).

Increasing numbers of heroin users in the US reached the level of an epidemic in 1970s; at that time, more than 70% users were African Americans (Boyle & Brunswick, 1980; Clayton & Voss, 1981; DuPont & Greene, 1973; Hunt & Chambers, 1976; O'Donnell, Voss, Clayton, Slatin, & Room, 1976). Injection was the most common method of using heroin.

Celebrities with drug overdose deaths involving heroin or other opioids have raised the visibility of heroin to the public (Just, Bleckwenn, Schnakenberg, Skatulla, & Weckbecker, 2016). Some famous musicians of the era who died at the young age because of drug overdose such as heroin or cocaine. More recently, River Phoenix, a famous American actor and singer, died at the age of 23 in 1993 from heroin and cocaine overdose. Kurt Cobain, the lead singer of the band Nirvana, said "heroin is the only thing that's saving me from blowing my head off right now. I've been to 10 doctors and nothing they can do about it. I've got to do something to stop this pain." Cobain committed suicide while high on heroin and died at the age of 27 in 1994. Prince, a famous American musician, died from an opioid overdose of prescription fentanyl in 2016. A list of musicians of the era who died from heroin or other opioid drugs overdose is shown in Appendix A.

2.2 CLASSIC STUDIES ON HEROIN EPIDEMIOLOGY

This section provides an overview of background information on heroin epidemiology based on historical classics, including the history of heroin epidemics and how it changed over time.

2.2.1 The Road to H (Chein et al., 1964)

The "H" stands for heroin. In the early 1950s, juvenile heroin users often were found in deprived areas of the inner city with a large proportion of disrupted or impoverished families. However, the inter-relationships were not clear. To investigate drugs, delinquency, and impoverishment, Chein and colleagues studied thousands of male adolescents aged 16-20 in New York City (i.e., Manhattan, Bronx, and Brooklyn) and conducted an extensive set of analyses

examining neighborhood influences, psychosocial correlates, family influences, and individual characteristics of young heroin users (Chein, Gerard, Lee, Rosenfeld, & Wilner, 1964).

The authors noted significant neighborhood effects, influencing the probability of becoming a heroin user or addict and found an association with deprived social and economic conditions. In describing the process of becoming addicted to heroin, youth frequently had delinquent attitudes, which influenced their probability of using heroin (Chein et al., 1964).

Most young heroin users got their first heroin from peers. Among heroin addicts, 90% became habituated users within 1-2 years after first use. The epidemic areas were the places where many residents were of low-income status or low educational attainment. The relationship between drug use and crime was found to be complicated; the authors provided an example of financial resource to explain this relationship among young heroin users. The high price of heroin in the 1950s made it difficult to have a regular basis for young habituated users. In order to maintain supplies of heroin, some of them turned to illegal markets to sell narcotics for cash or drugs. In the areas with a high rate of drug use, the moneymaking juvenile crime was increased proportionally by the increasing number of drug use. However, drug use is not the cause of delinquency. The authors mentioned that, the areas of highest incidence of drug use were the areas of high delinquency. However, an area of high delinquency was not necessary to the spread of drug use for this young population. Some areas of high delinquency have low incidence of drug use. In these areas, the delinquency might have come from rape, assault, automobile theft, or disorderly conduct. The authors concluded that the total amount of delinquency is independent of the number of drug users.

The drug use was not evenly distributed in an area. Chein and colleagues identified epidemic areas and non-epidemic areas by the number of drug users. Based on the study areas of

New York City, epidemic areas of Manhattan contributed 84% of the cases in Manhattan; epidemic areas of Bronx contributed 83% of the cases in Bronx; and epidemic areas of Brooklyn contributed 77% of the cases in Brooklyn. On average, epidemic areas had relatively higher percentage of low-income families, low education attainment, crowded housing, and disadvantaged minority groups (e.g., African American, Puerto Rican). As for cultural context, the participants were asked about their point of view on their neighborhoods. In the areas with the highest incidence of drug use and delinquency, the high incidence of juvenile drug use was linked to negativistic aspects and the sense of futility of the delinquent neighborhoods.

The authors then discussed how these young people became addicted to narcotics. There were four stages in the process becoming involved with narcotics use: experimentation, casual use, habitual use, and efforts to break the habits. Most youths who lived in high-drug-use areas heard about heroin or saw people use it at the time they were 15 years old or so, but there was no evidence of pressure to experiment with heroin. Youths at age of 16 or 17 years were more susceptible to using drugs. Their first heroin use was with peers in social or casual occasions. Of those who became habitual users, most of them had taken heroin for occasional use for one or two years already. Once youths became habitual users, they were more likely to be involved in criminal activities to obtain money or drugs.

2.2.2 The Epidemiology of Opiate Addiction in the United States (Ball and Chambers, 1970)

Ball & Chambers collected articles to provide an overview of opiate problems in the United States, emphasizing opiate addicts (1970). According to reports of opiate addicts admitted to two federal hospitals, more than 70% were using heroin (Lexington and Fort Worth hospitals). The data collected from active files of the Federal Bureau of Narcotics in 1963 showed that 80% of people who were addicted to opiates were younger than 40 years old, and the highest

prevalence of opiate addicts was among people ages 20-29. Across all ages, approximately 16-21% of opiate addicts were female. More non-White and Hispanic groups were found to be opiate addicts after World War II, mostly African Americans, Mexicans, and Puerto Ricans. In the 1960s, 48% of opiate addicts were white, and 36% of them were African Americans. Among opioid addicts, the peak ages of opiate use onset were 16-17 years old. More than 60% of addicts started using opiates before age 21.

Comparing drugs used by addicts between the 1930s and 1970s, 51% of addicts used morphine and 43% used heroin in the 1930s. However, by the 1970s, more than 70% of addicts used heroin; only 7% were addicted to morphine. Heroin had become the top drug used by opiate addicts since 1960s. With respect to the variety of drugs being used, only 1% of addicts used drugs other than heroin, morphine, or opium in the 1930s.The use of other synthetic opiates increased over the next 30 years from 1% to 21% by the 1970s. In a comparison of geographic distribution over time, the highest rates of admission for opiate addiction treatment were from southern states such as Louisiana and Texas in the 1930s. However, by the 1970s the patterns had shifted, and the states with the highest admission rates were in Washington DC and northern states such as New York and Illinois. The number of opiate addicts had remarkably increased in New York City and Chicago over these 30 years. A shift in age and race also occurred in the addict population. The median admission age for male addicts decreased by eight years from the 1930s to 1960s (the shift for female was not reported).

Among opiate addicts admitted to hospitals in the 1960s, two different patterns were found. In New York, Illinois, Arizona, New Mexico, and New Jersey, along with Washington DC and Puerto Rico, the principal cause for diagnosis of opiate addiction was the use of heroin. More than 70% of the persons from New York, Washington DC, and Puerto Rico were African

Americans or Puerto Ricans; and the age at admission from these three locations was younger than other places (the range of median age at admission was 24-30 years). Another pattern was found in Alabama, Georgia, and Kentucky. Addicts from these states mostly used opiates other than heroin such as morphine, paregoric, Dilaudid (hydromorphone), or codeine; less than 5% of them had an addiction because of using heroin. Of these persons, more than 90% were white and admitted to hospitals at older ages (i.e., older than 40 years). The length of opiate use since onset of opiate use before admission for addicts was 9.5 years on average. Mexican-Americans had a shorter average time (8.8 years) compared to Whites (9.4 years) and African-Americans (9.9 years). According to data from the 1960s, 85% of addicts voluntarily sought treatment. Of them, Mexican-Americans had the lowest rate (71%) and Puerto Ricans had the highest rate (94%) of seeking treatment voluntarily (Ball & Chambers, 1970).

2.2.3 The heroin epidemics: A study of heroin use in the US (Hunt and Chambers, 1976)

Based on Ball and Chambers (1970), the use of heroin increased remarkably in the US between the 1930s and the 1970s, and it became a serious problem for public health and caused both social and political issues. Drug use, including heroin use, spread. It could have spread from one population to another and/or from one place to another place. Three sections described the US heroin epidemic. The first section described the spread of heroin use; the second one depicted the characteristics of heroin users; and the third section contained comments on treatment and prevention policy for the use of heroin.

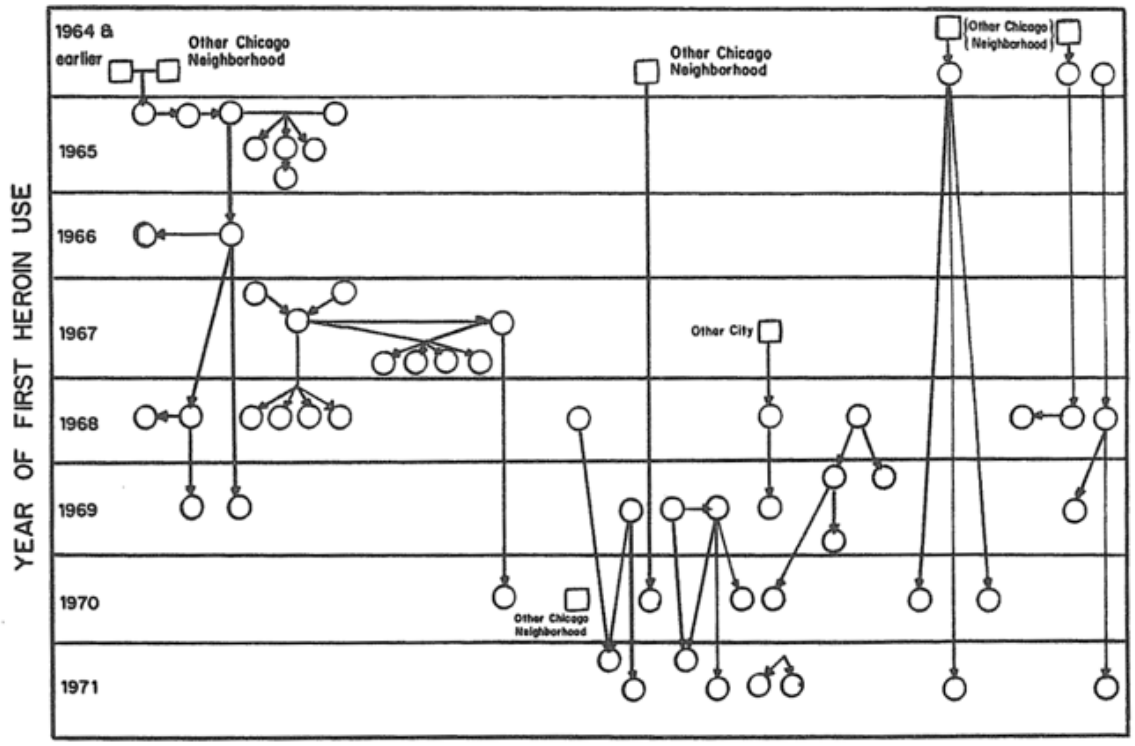
Two models were presented that explained how heroin use spreads: Micro-diffusion and Macro-diffusion. Micro-diffusion, also called Branching process shows how heroin use is spread at a person-to-person level. It suggests that the initial heroin users entered a community and spread the use of heroin to their susceptible friends or peers, and their susceptible friends spread

heroin use to secondary friends or peers, and so on. Based on this Micro-diffusion model, Hunt & Chambers observed that each heroin user spread heroin use to peers only in his/her first year of use, and a community can be completely exposed to heroin in about seven years after the introduction of the first heroin user. This Micro-diffusion model also explained the epidemic of heroin use in Chicago (Hughes, Barker, Crawford, & Jaffe, 1972). Based on this model, the individual of each generation produces a random number of offspring (i.e., newly heroin users). These newly incident heroin users become the successors of the next generation. Figure 2.2.1 shows the process of branching, produced by the probability of distribution, which describes the number of successors of each individual. There are some limitations of this Micro-diffusion model. For example, all successors within the susceptible group are subsumed by the successor in the group. This model assumes that branching process is independent from one group to another group. Therefore, this model might not be a good mathematical model for studying the structure of heroin spreading due to the dependency between groups.

The second model, Macro-diffusion, depicts the use of heroin spread from urban areas with high population densities to suburban and rural areas. For example, the use of heroin began to develop in the 1930s, a time when the majority of illegal heroin was smuggled into the US from other countries (e.g., China). After World War II, the widespread use of heroin was found in large cities (e.g., NYC & Chicago). During the 1960s, most cities and their suburban surroundings were exposed to heroin, and heroin users were increasingly found in these areas. Results showed that new cases of heroin use increased more than ten times during a five-year period (1963-1968). Despite the difficulties of identifying all cases precisely, the rapid increase of heroin users could be described as reaching an epidemic level. In the 1970s, two resources were used for estimating heroin incidence: 1) police arrest data and 2) treatment program data.

However, these two resources were neither comprehensive nor representative of a total population.

Figure 2.2.1 An example of Macro-epidemic process (Hughes P. and Crawford G., Illinois Drug Abuse Program, unpublished, November, 1972)



In the first section of this book, Hunt & Chambers portrayed how fast and how far heroin use spreads (1976). Incidence of heroin use was a measure of spread. The prevalence of active heroin users in a population was surprisingly not well known in 1970s. In their second section, data from different sources produced varying values of heroin use prevalence, and characteristics of heroin users. As aforementioned, treatment programs provided a data source on heroin users, but it includes mostly heavy heroin users. Different characteristics were shown between different treatment programs. For example, methadone treatment programs served principally older, long-addicted, persistently criminal, and non-White heroin users as compared to other treatment programs. A majority of the heroin users arrested for drug law violations or those involved in

other crimes were not the same persons who entered treatment programs. One study showed that only 18% of drug users enrolled in treatment programs had criminal records. Unfortunately, data from a survey of the general population under-estimated the prevalence of heroin use. Another study in New York City showed that a survey of the general population may underestimate the prevalence of heroin use by 50%-400% as compared to other data sources. On the other hand, heroin users in psychiatric hospitals were older and had different patterns of incidence of first use than users from other groups, and of course, all of them had problems of drug addiction and mental illness.

In summary, the challenge in estimating the prevalence of heroin users was counting hidden heroin users regardless of the data source. Hunt projected that 12% of addicts would enter treatment within 1 year, 22% within 2 years, 26% within 2-3 years, 26% within 3-4 years, 6% within 4-5 years, 3% within 5-6 years and 3% within 6-7 years. More than 90% of addicts entered treatment programs within 5-6 years since they first used heroin. Methods from this book (Hunt & Chambers, 1976) will be used in this dissertation for estimating the incidence of heroin from the treatment dataset (TEDS-A). More details will be provided in Chapter 4.

2.3 HEROIN AND OPIOIDS EPIDEMIOLOGY IN THE 21ST CENTURY

2.3.1 The Definition of Abnormal Use of Opioids

Opioids are prescribed for a range of legitimate purposes within medicine. However, there are three types of what might be called abnormal drug use: 1) illegal use, 2) extra-medical (EM) use, and 3) non-medical use, and these categories are not mutually exclusive. In the US, heroin use is illegal. While legal, use of prescription opioids is different and more complicated than the illegal use of heroin. Concerns about the inappropriate use or ‘misuse’ of prescription opioids have been raised in recent years. The definition of what contributes inappropriate use or

prescription misuse has included the following: 1) non-prescribed use, 2) use for recreational purposes, or 3) meeting criteria of the Diagnostic and Statistical Manual (DSM) for opioid dependence (Barrett, Meisner, & Stewart, 2008). In this context, the two types of legal misuse of prescription are included: non-medical use and extra-medical use. Both of them are defined as using prescription drug without a physician's approval. Non-medical prescription opioids use can be described as the act of getting high, however uncertainty about "boundary users." EM prescription opioid use involves use to get high, getting it from someone other than a physician, or using outside the bounds of the prescribed purpose (Anthony, Warner, & Kessler, 1994).

2.3.2 Prevalence of Prescription Opioids and Heroin

Global prevalence of opioid use is about 7 per 1000 people aged 15-64 years, and includes EM prescription opioids and heroin, and roughly half of opioid users are heroin users. In other words, globally, about 31 million people aged 15-64 years had used opioids including heroin and prescription pain relievers. Of that population, approximately 13~21 million people used heroin. Oceania (especially Australia and New Zealand) had the highest prevalence of opioid use (3%), followed by the Americas (2.1%), Europe (0.7%), and Asia (0.4%) and Africa (0.4%). North America has the highest prevalence of opioid use (4%); prevalence of EM prescription opioid use in the United States was 4.3%. Overall, opioids now rank as the world's second most widely used drug after cannabis (3.8%) (United Nations Office on Drugs and Crime 2012).

In the US (2011), an estimated 4.2 million Americans aged 12 or older (1.6 %) had used heroin at least once in their lives, according to a 2012 National Institute on Drug Abuse (NIDA) report (United States. Substance Abuse and Mental Health Services Administration, 2012). About 4-5% of individuals aged 12 years or older used EM prescription opioids in the past year,

and 0.3% used heroin in the past year. Approximately 3.6% of recent extra-medical prescription pain reliever (EMPPR) users had initiated heroin use within 5 years following the first EMPPR use. An estimated 23% of heroin users become dependent (Anthony et al., 1994; Muhuri, Gfroerer, & Davies, 2013).

Heroin use and non-medical opioid use is a significant public health problem in the US. The findings by Grau and colleagues stated that poly-opioid use contributes to quicker transition to heroin and other injection drugs use as compared to single opioid use (Grau, Dasgupta et al. 2007). A 2012 annual report from a national survey presented a finding that approximately 3.6% of recent non-medical opioid users had initiated heroin use within 5 years following first EMPPR use (Muhuri et al., 2013). OxyContin® is one of the most commonly used opioid prescription drugs. In the past, people who used OxyContin® as a means of getting high by crushing the pill so that they could snort the drug. The US Food and Drug Administration (FDA) approved the re-formulated version of OxyContin® in 2010 to prevent users from misusing the drug by snorting or injecting it. Consequently, heroin sometimes became a substitute for OxyContin®. In a qualitative study, an interviewee said: "Most people that I know don't use OxyContin® to get high anymore. They have moved on to heroin [because] it is easier to use, much cheaper, and easily available" (Cicero, Ellis, & Surratt, 2012).

2.3.3 Burden of Disease Attributable to Opioid Use

Approximately 70,000-100,000 people die from opioid overdose each year worldwide, many with drug dependence (UNODC, 2012). In 2010, 20 million DALYs, roughly 0.8% of global all-cause DALYs, have been attributed to drug dependence. Furthermore, among 'scheduled' drugs, it is heroin or other opioid use that often has been followed by appearance of a drug dependence syndrome (e.g., with withdrawal symptoms). This means opioids account for

much of the drug-related DALYs burden, estimated as 9.2 million DALYs in 2010 (Degenhardt et al., 2013).

In the US, the heroin overdose death rate had increased by about 100% over 4 years, from 1 per 100,000 in 2008 to 2.1 per 100,000 in 2012 (Rudd et al., 2014). Data from the National Vital Statistics System showed that the heroin-related overdose deaths nearly tripled over the last decade, from 0.7 per 100,000 in 2000 to 2.7 per 100,000 in 2013. The greatest increase was in the Midwest region (National Vital Statistics System 2014). The growth of overdose deaths due to prescription opioid pain relievers increased faster than overdose deaths of heroin, from 1.5 per 100,000 in 2000 to 5.0 per 100,000 in 2013 (Hedegaard, Chen, & Warner, 2015).

2.3.4 Relationship between prescription opioid (e.g., OxyContin®) and heroin

Both theory and recent empirical evidence from the US support the idea that newly incident heroin use may have been triggered when younger population started to use the original formulated OxyContin® products extra-medically. The origins of theory and conceptual foundations for asking research questions about the suspected EM OxyContin®-heroin triggering hypothesis date back to early general 'steppingstone' and 'gateway' ideas about how use of one drug early in a chain of temporally sequenced events might account for later drug use (Anthony, 2002, 2012; Morral, McCaffrey, & Paddock, 2002). Evidence pertinent to the EM OxyContin®-heroin triggering hypothesis has come largely from clinic-based studies of persons in treatment programs, as well as a mix of field studies with local area recruitment approaches (Carise et al., 2007; Cerda, Santaella, Marshall, Kim, & Martins, 2015; Cicero et al., 2012; Jones, 2013; Mars, Bourgois, Karandinos, Montero, & Ciccarone, 2014; Young & Havens, 2012). Heroin possibly becomes an alternative substitute for OxyContin® because it often has been cheaper and more readily available. In an illustration of evidence from the qualitative research tradition, Cicero and

colleagues provide the following quotation from an EM user, “Most people that I know don't use OxyContin® to get high anymore. They have moved on to heroin [because] it is easier to use, much cleaner, and easily available” (Cicero et al., 2012).

Some clinicians and researchers in this field are skeptical about the suspected EM OxyContin®-heroin triggering hypothesis, noting a basic principle that when Y follows X, it does not mean that Y is caused by X. Indeed, ten years ago, drawing upon this basic principle, estimates published challenged the causal significance of the more general 'gateway' sequence, and advanced an alternative hypothesis that otherwise uncontrolled individual-level underlying predispositions might account for a temporal sequence of passage from EM use of one drug to EM use of another drug. This idea about individual-level underlying susceptibility traits has an analogy in pharmacoepidemiological research in the form of 'confounding by indication', such that it might not be the exposure to a medicine that triggers some unwanted later effect. Rather, the apparent causal linkage from earlier medicine use to a later adversity sometimes might be wholly explained by the underlying medical condition that prompted a clinician to prescribe the medicine in the first place (i.e., the 'indication'). To illustrate, for reasons such as these, one might be hesitant to blame an antidepressant medicine for subsequent suicide outcomes because it truly might be the underlying depression that has prompted both the exposure to the antidepressant medicine and also the later suicide attempt or successful suicide. With respect to EM use of OxyContin® products, it might not be the EM OxyContin® use per se that has been the trigger for new onsets of heroin use. Rather, there might some other shared source or sources of variation accounting for both of these linked behaviors, which might be found anywhere across the range from micro-level domains (e.g., genetic influences) toward macro-level domains (e.g., drug policies).

2.4 RESEARCH GAPS AND SIGNIFICANCE

In the world, and in the US specifically, heroin and extra-medical prescription opioids use has become a significant public health problem. The number of overdose deaths due to heroin or other opioid compounds increased 4~5 times in the past two decades (Cicero, Ellis, Surratt, & Kurtz, 2014; Muhuri et al., 2013). The epidemiology of heroin use and EMPPR use now intersect considerably (Cicero, Ellis, & Harney, 2015; Compton, Jones, & Baldwin, 2016; Jones, 2013; Mars et al., 2014; Young & Havens, 2012). However, there are gaps in epidemiological research, with several important unanswered research questions. For example, concerns about completeness of epidemiological estimates for incidence of heroin use exist. For instance, if heroin users don't participate in field surveys, incidence rates based on treatment admissions might be as good or better estimates. The idea that OxyContin® or other prescription opioids is triggering onset of heroin use has not been examined completely. The current estimates are subject to confounding and other biases that might create spurious associations. Genetic susceptibility traits have not been held constant. Furthermore, more than 80% of heroin users had previous EM prescription opioid use (Muhuri et al., 2013). However, research about environmental factors and individual characteristics that influence probability of transitioning from extra-medical prescription opioid use to heroin use are still limited and unclear.

CHAPTER 3

MATERIALS

3.1 NATIONAL SURVEY ON DRUG USE AND HEALTH (NSDUH)

This dissertation focuses on two U.S. study populations: 1) the general population from an annual nationally representative survey, and 2) persons who entered treatment programs from a national data system of annual admissions to substance abuse treatment facilities. The NSDUH study population was designated to include civilian, non-institutionalized US residents age 12 and older, including residents of households as well as group quarters and homeless shelters. For NSDUH, the national sampling frame and approach is based on lists of residential dwelling units within primary sampling units in all geographic areas annually. Its nationally representative samples are drawn using multi-stage area probability sampling for each of the 50 states in the US and the District of Columbia. The surveys exclude relatively small segments of the current US non-institutionalized population, such as homeless persons who do not reside in shelters, military personnel on active duty; residents of institutional group quarters such as prisons and psychiatric hospitals also are excluded. With the exceptions noted, all community-dwelling civilian residents are eligible to be sampled and to participate as survey respondents. NSDUH seeks large nationally representative community samples of non-institutionalized civilians age 12+ years, generally achieving participation levels at 65%-70%. Repeated annually from 2004 through 2013, the NSDUH research approach involves multi-stage area probability sampling and recruitment according to protocols approved by a cognizant Institutional Review Board. Each year, the NSDUH yields an independent replication in the form of a nationally representative sample of the study population. The “Survey Documentation and Analysis” (SDA) for NSDUH

is a public-use dataset and is available for download on the website (http://www.icpsr.umich.edu/icpsrweb/SAMHDA/sda).

3.2 TREATMENT EPISODE DATA SET - ADMISSIONS (TEDS-A)

In epidemiological concepts, it is seldom possible to study incidence of heroin use directly because many cases are unreported. Besides, the relationship between reported cases and total cases may be unclear. Therefore, the inference of total cases is difficult to make. Nationally representative survey data (e.g., NSDUH) helps in understanding the number of heroin cases in the community by multi-stage sampling approach. However, this number might be underreported from self-reported survey due to social undesirability or stigmatization. Therefore, this dissertation includes an alternative national surveillance dataset collecting cases (i.e., TEDS). Using treatment program dataset to estimate the incidence of heroin use, the lag between heroin onset and the time of entering treatment program must be considered. For heroin users in treatment programs, there are very few users entering treatment program in their first year of use (~12%). Earlier in the U.S., it seemed that more than 90% of users entering treatment program within 5-6 years since they first used heroin (Hunt and Chambers 1976). However, a recent study showed that the lag time now is much longer, and that women have shorter length of time from first use of heroin to treatment admission than men, approximately 17 years for men and 14 years for women (Substance Abuse and Mental Health Services Administration 2011). On the other hand, a large number of heroin users do not become dependent (Anthony, Warner et al. 1994).

TEDS is a national census data system in the US focused on persons aged 12 or older who admitted to or discharged from substance abuse treatment facilities. TEDS-A is a national census system of collecting annual admissions reported by public or private drug use treatment facilities. Unfortunately, not all treatment facilities report their admission or discharge cases to

TEDS system. Only some treatment programs are required to report all of their admissions to their state based on the types of funds they receive (i.e., the facilities that received public funds must report). TEDS-A was collected since 1992, year by year. The most recently available public-use TEDS-A datasets can be downloaded through a SAMHSA website (http://www.icpsr.umich.edu/icpsrweb/SAMHDA/sda).

CHAPTER 4

MANUSCRIPT 1 – EMPIRICAL EVIDENCE ON THE ESTIMATION OF HEROIN INCIDENCE IN THE UNITED STATES: A BACK-CALCULATION APPROACH

4.1 ABSTRACT

Heroin incidence trends in the United States study population are studied using the TEDS-A from 1992 to 2012. Hunt's Lag Correction Method is used to estimate the number of incident heroin cases by adjusting reported numbers of heroin users visiting drug treatment programs for the time lag between first use of heroin and first treatment admission (lag distribution). Initial estimates from the Hunt model 1992–2012 TEDS-A analyses show more than 11 million admissions age 12-to-54-years-old with heroin as primary drug, and clear evidence of two heroin epidemic peaks, in 1969 (5.2 per 10,000) and in 2012 (4.2 per 10,000). Moreover, for the incidence rate of opioids other than heroin, the first peak is observed in 1970 (1.5 per 10,000) and the second peak was in 2010, about 3 times higher than the first peak (3.8 per 10,000). However, the result from treatment data need to be interpreted cautiously, especially in relation to the wider context of underlying trends in the population. Potential biases might derive from underreporting heroin users and from the changes in the proportion of users in treatment programs. This study discloses temporal patterns and relative heroin incidence rates. Whereas the results may not serve as absolute numbers of newly incident cases, they suggest accelerated heroin incidence rates in recent epidemic years. The evidence should improve our understanding of heroin epidemiology, complementing field survey estimates.

4.2 INTRODUCTION

In this study, the main aim is to estimate the annual incidence of heroin use in the US from World War II until 21st century. The first heroin epidemic in the US occurred after World War II. The number of newly incident heroin cases rapidly increased between 1950s and 1970s (DuPont & Greene, 1973; Greene, 1974; Hughes et al., 1972; Hunt & Chambers, 1976). About 30% of the veterans had experience of heroin use while serving in Asian conflicts (e.g., Vietnam War, 1954-1975) and some continued heroin use after return to the U.S. About 20% of Vietnam veterans became dependent (Robins, Davis, & Goodwin, 1974). During the 21st century, a resurgent heroin epidemic in the U.S. has been discussed in the literature (Jones, Logan, Gladden, & Bohm, 2015; Lipari & Hughes, 2015). Heroin overdose deaths have increased five times since 2000 (0.7 to 3.5 per 1000). Heroin users in the 21st century were more likely to start EM prescription opioids use before their first use of heroin (Cicero et al., 2015; Compton et al., 2016; Jones, 2013; Young & Havens, 2012).

During the interval from 1950 through the 2010s, we have no systematic study of heroin incidence estimates (i.e., from World War II until recently), and no way to compare the two US heroin epidemics using the same data source and method. This study fills that gap, and provides national-level estimates of heroin incidence from the 1950s to 2010s.

Identifying the new cases of heroin users from community surveys is difficult because the prevalence of heroin use is relatively low: an estimated 0.1% of people aged 12 or older are current heroin users (United States. Substance Abuse and Mental Health Services Administration, 2014a). Voluntary reporting of illegal drug use may not be as one might hope. In contrast to small number from community surveys, more heroin users can be obtained from treatment program dataset. For example, from the dataset of Treatment Episode Data Set -

Admissions (TEDS-A), heroin as a primary drug accounted for about 13~16% of all treatment admissions (United States. Substance Abuse and Mental Health Services Administration, 2014b). TEDS-A data provide estimates required for Hunt's Lag Correction Method (LCM) in order to estimate heroin incidence, including age of first heroin use. The resulting 'Lag length' is defined as the delayed years between heroin onset and subsequent entry into treatment (Hunt & Chambers, 1976). The retrospective information about lag-time, provided in the treatment data (TEDS-A 1992-2012), allows heroin incidence estimation, 1950 through 2012.

In this research, the most important topic is estimating the annual number of newly incident heroin users and seeing ebb and flow of this public health problem in the U.S. This study provides empirical evidence on the trend of heroin incidence over the span of 60 years in the US. One clear strength and advantage of using treatment data relative to alternative observational national surveys, is that more heroin users can be found in the treatment programs than community or household surveys. The result is more stable estimates for heroin incidence. Another strength of this study's research approach is that it is not restricted to samples of persons in any specific location. Instead, this research takes into account all heroin users irrespective of where they are located in the U.S. as long as their first treatment admission occurred between 1992 and 2012.

However, this study cannot lay claim to provide nationally representative estimates of heroin incidence for the general US population. This study only seeks to estimate the patterns of "relative heroin incidence" over the past 60 years, from one epidemic to the next, occurring more than 100 years after Bayer marketed heroin in 1895, as shown in Table 4.2.1.

Table 4.2.1 A brief summary of the history of opium

Year	Events
1803	Morphine is extracted from opium resin and used for medical treatment of pain and chronic diseases.
1827	Merck pharmaceutical company (Germany) begins the manufacture of morphine.
1895	Heroin was introduced by the Bayer Company in Germany. It was developed chiefly as a morphine substitute for cough suppressants and Bayer Company claimed that it did not have morphine's side-effects of dependence.
1914	*Harrison Narcotics Tax Act in the USA:* To manage the distribution and sale of heroin, along with other opioids, permitted heroin to be prescribed as well as sold for medical reasons.
Post World War II	Widespread use in metropolitan such as Chicago or New York City.
1950s – Early 1960s	New heroin users found in other big cities such as Detroit.
1960s	New heroin users peak in the late 1960s.
1970s	The speed of spread over geographically rises with increased size of the cities (Hunt & Chambers, 1976).
1980s-1990s	Public health concern about emrging drug use including heroin (Courtwright, 1983; Hughes & Rieche, 1995).
2000s	EM use of prescription opioid has emerged as one of main public health problems for the United States (Bohnert et al., 2011; Compton & Volkow, 2006; Paulozzi et al., 2006).

4.3 METHODS

4.3.1 Data source

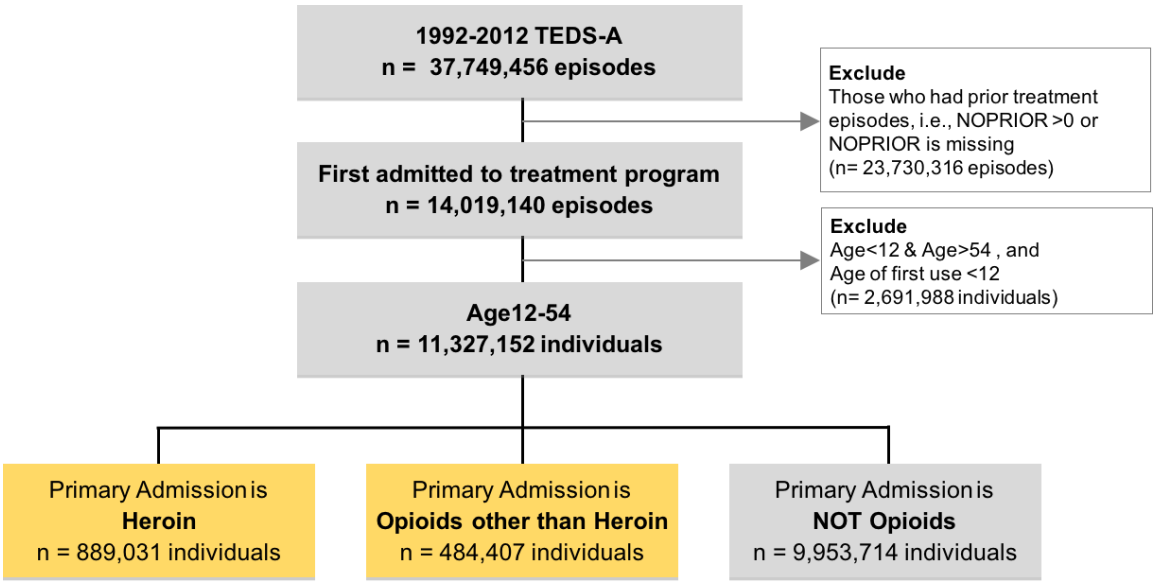
TEDS is a national census data system in the US focused on persons aged 12 or older who admitted to or discharged from drug treatment facilities. As described in Chapter 3, TEDS-A covers a selection of both public and private drug use treatment facilities. Unfortunately, only treatment programs with certain types of funding report their admission and discharge cases to TEDS. Facilities that received public funds must report, but the privately funded treatment facilities report voluntarily. These facilities include early intervention, outpatient treatment, intensive outpatient, hospitalization, detoxification, general hospital, psychiatric hospital, mental health program, and medication assisted therapies. TEDS-A data has been collected since 1992, with results through 2012. The TEDS-A public use datasets are available for download at the following ICPSR URL: http://www.icpsr.umich.edu/icpsrweb/ICPSR/series/56, last accessed on 4th November 2016.

4.3.2 Sample selection

A total number of 37,749,456 episodes of drug admission between 1992 and 2012. Among total episodes, approximately14 million episodes were first admission episodes and the first admission episode from each individual was treated as individual record in this study. For those who were first admitted to the treatment programs, information on the primary drugs for first admission, age of first use of primary drug, age at first admission, were collected from treatment facilities. The flowchart shows the selection of cases of heroin and other opioids with implementing exclusion rules (Figure 4.3.1). A total of 889,031 individuals were identified as heroin users (primary drug of admission: heroin). In the same manner, 484,407 individuals were

identified as users of opioids other than heroin such as non-prescription methadone and other semi-synthetics or synthetics (e.g., codeine, oxycodone, tramadol).

Figure 4.3.1 Flowchart of United States, Treatment Episode Data Set –Admissions (TEDS-A), 1992-2012.



4.3.3 Organizing the case material

Age of first admission and age of first use of heroin were categorized as 12-14, 15-17, 18-20, 21-24, 25-29, 30-34, 35-39, 40-45, 46-49, and 50-54. The tabulated table of these two variables is shown as the Figure 5.3.2. Based on the data structure, the number of individuals in these 55 cells will be calculated separately. Moreover, the data structure of TEDS-A can be used extensively to have one-year period for each cell. The assumption of Uniform Distribution has been made here to break down each cell into multiple one-year period by one-year period cells. That is, the number of individuals in each cell is equally distributed. For example, the assumption is made that the probability of 13-years-old youths having their first heroin use at age

12 is equal to the probability of their first heroin use at age 13. The equation is shown below. One example is presented in the Figure 4.3.3.

Notation and formula

To calculate the number of cases by age of onset and age of first admission

N_k : the number of people in the Cell k, $k = 1, 2, ..., 55$
m_k : the number of smaller cells in the Cell k
p_k : the probability from age at first heroin use to age at first treatment admission in the Cell k
Assume that:

$$p_k \sim Uniform(0, 1)$$

j is the smaller cell in the Cell k, $j = 1, 2, ..., m_k$
n_{jk} : the number of people in the smaller cell j of the Cell k

The assumption of Uniform Distribution made here to break down each cell into multiple one-year period by one-year period cells might not be satisfied and it can be improved through mathematical simulation in the future. However, it is challenging to apply any specific probability distribution on this issue because the mean age of heroin onset was different from time to time or from population to population (Table 4.3.1) (Anglin, Brecht, Woodward, & Bonett, 1986; Bailey, Hser, Hsieh, & Anglin, 1994; Boeri, Sterk, & Elifson, 2008; Carpenter, Chutuape, & Stitzer, 1998; Concool, Smith, & Stimmel, 1979; Hser, Huang, Chou, & Anglin, 2007; Inciardi & Harrison, 1998; Kandel & Yamaguchi, 2002; Kelly, Cornelius, & Clark, 2004; Khantzian & Treece, 1985; Lipari & Hughes, 2015; Lofwall, Brooner, Bigelow, Kindbom, & Strain, 2005; McGlothlin & Anglin, 1981; Neaigus et al., 2006; Neaigus et al., 2001; Nurco, Cisin, & Balter, 1981; O'Driscoll et al., 2001; Ochoa, Hahn, Seal, & Moss, 2001; Pugatch et al., 2001; Rounsaville, Kosten, & Kleber, 1985; Rutherford, Cacciola, & Alterman, 1994; Seal et al., 2001; Vaillant, 1973). Cicero and colleague reported that the age of heroin onset increased about

6 years across 40 years, from 16.5 year in 1960s to 22.9 years in 2000s (Cicero et al., 2014). Advantages of using the uniform distribution includes minimizing the misleading weights in the analysis with the feature of uniformly distributed random elements in each cell.

Table 4.3.1 Literature review of age of first heroin use

Study	**Year of publication**	**Mean age of first heroin use**
Vaillant	1973	23.0
Cooncool et al.	1979	18.2
McGlothlin & Anglin	1981	19.6
Nurco et al.	1981	18.2
Khantzian & Treece	1985	20.0
Rounsaville et al.	1985	20.3
Anglin et al.	1986	18.5
Rutherford et al.	1994	23.2
Bailey et al.	1994	18.1
Inciardi & Harrison	1998	21.0
Capenter et al.	1998	21.1
Neaigus et al.	2001	22.4
O'Driscoll et al.	2001	20.7
Ochoa et al.	2001	18.0
Pugatch et al.	2001	18.2
Seal et al.	2001	20.0
Kandel & Yamaguchi	2002	20.1
Kelly et al.	2004	23.9
Surratt et al.	2004	23.4
Lofwall et al.	2005	19.3
Neaigus et al.	2006	22.3
Hser et al.	2007	17.9
Boeri et al.	2008	19.0
Lipari & Hughes	2015	24.5

Figure 4.3.2 Cross-table of number of individuals per cell by the age of first admission and age of first use (i.e., age of onset)

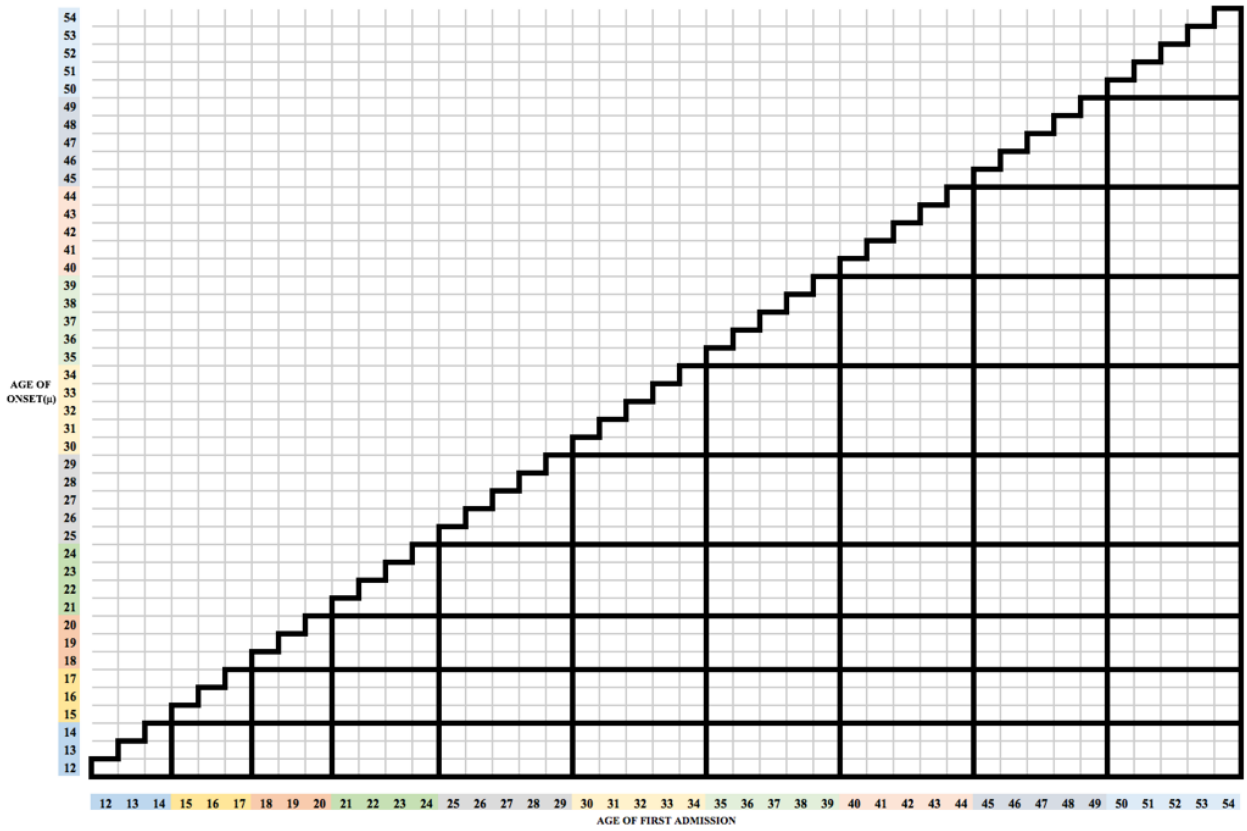
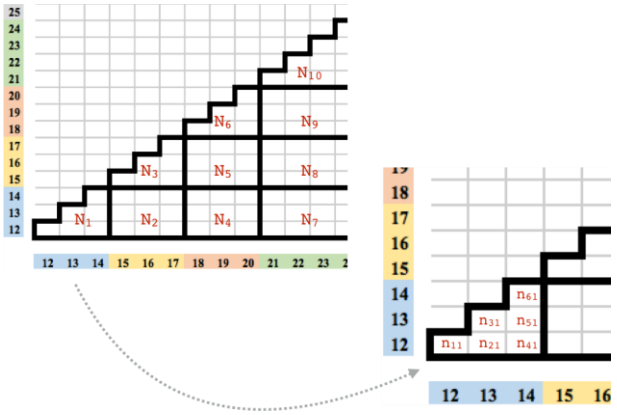


Figure 4.3.3 Uniform Distribution is applied to break down cells into multiple one-year-period cells.



N_k : the number of people in the Cell k, $k = 1, 2, ..., 55$

Take N_1 as an example:

$m_1 = 6$, $p_1 \sim Uniform(0, 1) = \frac{1}{m_1} = \frac{1}{6}$

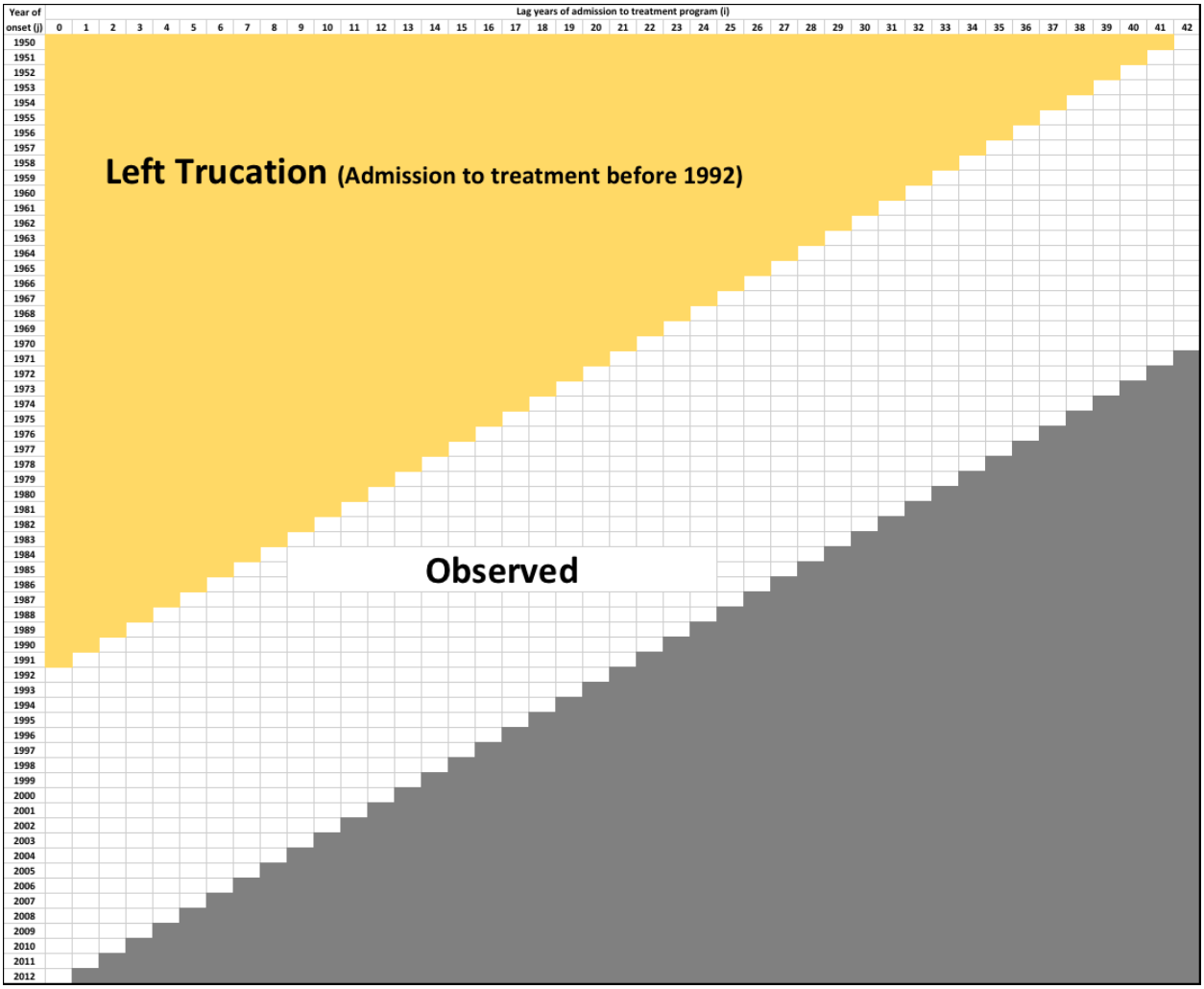
j is the smaller cell in the Cell 1, $j = 1, 2, ..., 6$

$n_{j1} = N_1 \times p_1 = N_1 \times \frac{1}{6} = \frac{N_1}{6}$

4.3.4 Lag Correction Method

After determining twenty-one datasets separately (TEDS-A 1992 to TEDS-A 2012) with their numbers in one-year-period cell shown in Figure 4.3.2, Hunt's method has been applied to estimate the incident heroin cases for each calendar year. The Hunt's LCM, one type of back calculation method, is used to calculate backward. This method provides an estimate of the unknown number of heroin users who were in the treatment program but the data has been truncated (left truncation). That is, Hunt's LCM assumes that heroin users are not always in the treatment data. A lag time distribution is used to work out the number of newly incident heroin users for each calendar year. Hunt's recommendation for estimated 'Lag time' is based on an onset cohort that takes all heroin users who initiated heroin use in a given year and classifies them into subsets by when they entered treatment (i.e., within one year, one to two years, etc.). Hunt's model is based on four assumptions: 1) the probability of admission is the same for persons of specific duration of dependence regardless of year of onset; 2) there is no change on clinical diagnosis of drug dependence; 3) the rate of mortality is constant; 4) and there is a fixed amount of treatment facilities for admitting new persons (Hunt and Chambers 1976). Based on the data TEDS-A 1992-2012, I have been able to carry out the 'Lag time' from 0 to 42 years, specifying year of onset from 1950 to 2012 with left truncation (see Figure 4.3.4).

Figure 4.3.4 Conceptual framework of truncations with lag time, Data from United States, Treatment Episode Data Set –Admissions (TEDS-A), 1992-2012.



Therefore, the lag distribution is estimated from observed admissions for individuals admitted to treatment programs during 1992-2012. The shifts of the lag distributions over calendar time are shown in the Figure 4.3.5.

When admission cohort lag curves are stable for each calendar year, the percentages of each year's admission can be averaged to yield a mean cumulative entry curve, yielding a more robust estimate than any single year provides. The patterns of lag distributions of each admission years are illustrated for heroin and for other opioids in Figure 4.3.6 & Figure 4.3.7, respectively. Lag distribution curves move toward the left from 1992 to 2012, which means that the lag time

from the first use to first admission was getting shorter. For example, the median lag time for heroin is 10 years in 1992 and shifted to shorter lag time of 5 years in 2012. Therefore, the averaged probability of entering treatment by lag time was applied to correct the number of newly incident heroin users. 'Lag' effect can be calculated from the cumulative entry rate by using the number of observed heroin users entering treatment program at onset year. For example, if twenty percent of heroin users were admitted to treatment program in the first year of use, it is assumed that the other eighty percent users of the same onset cohort did not enter program but eventually will. In this manner, an inflation factor can be calculated as 5. Accordingly, the number of newly incident heroin users is calculated from year 1950 to 2012.

Notation and formula

To calculate the number of incidence users for each calendar year based on Hunt's LCM

i : the lag time (year), $i = 0, 1, ..., 43$, $i = 0$ if the year of onset is the year of treatment admission
j : the calendar year of onset, $j = 1950, 1951, ..., 2012$
Ω is the space of heroin users who were admitted to treatment with lag year i

n_{ij} : the number of heroin users in the calendar j with lag year i
n_j : the number of heroin users in the calendar j
$O_{\Omega,j} = \sum_{i=\Omega} n_{ij}$: the number of heroin users who were admitted to treatment in the calendar year j
$P_{\Omega,j}$: The proportion of heroin users entering to the treatment in the calendar year j.

Therefore, $\frac{1}{P_{\Omega,j}}$ is the inflation factor required to adjust reported heroin users for the year j

$\Phi_j = n_j \times \frac{1}{P_{\Omega,j}}$: corrected newly incident heroin users in the calendar year j

Figure 4.3.5 A distribution of lag-years between heroin onset and treatment admission. Data from United States, Treatment Episode Data Set –Admissions (TEDS-A), 1992-2012.

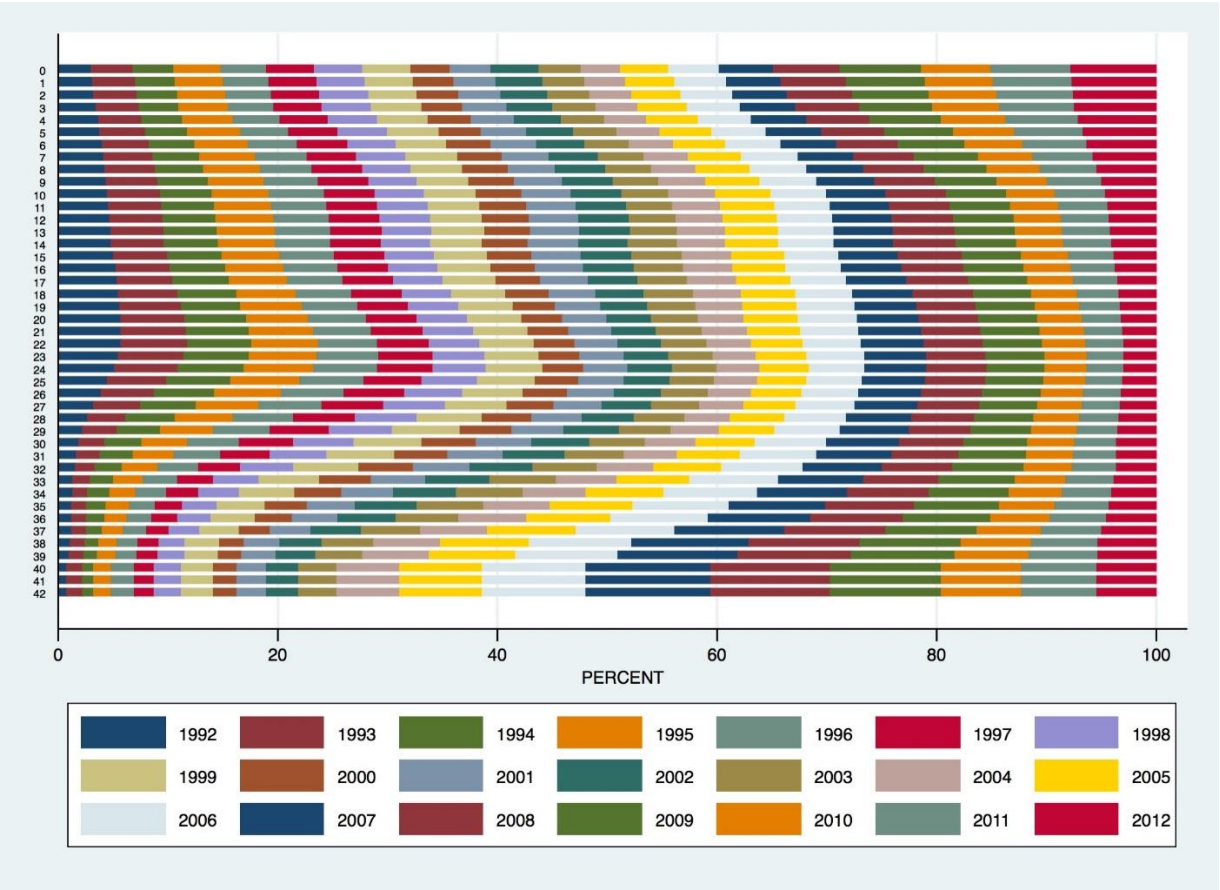


Figure 4.3.6 Heroin lag distribution. Data from United States, Treatment Episode Data Set – Admissions (TEDS-A), 1992-2012.

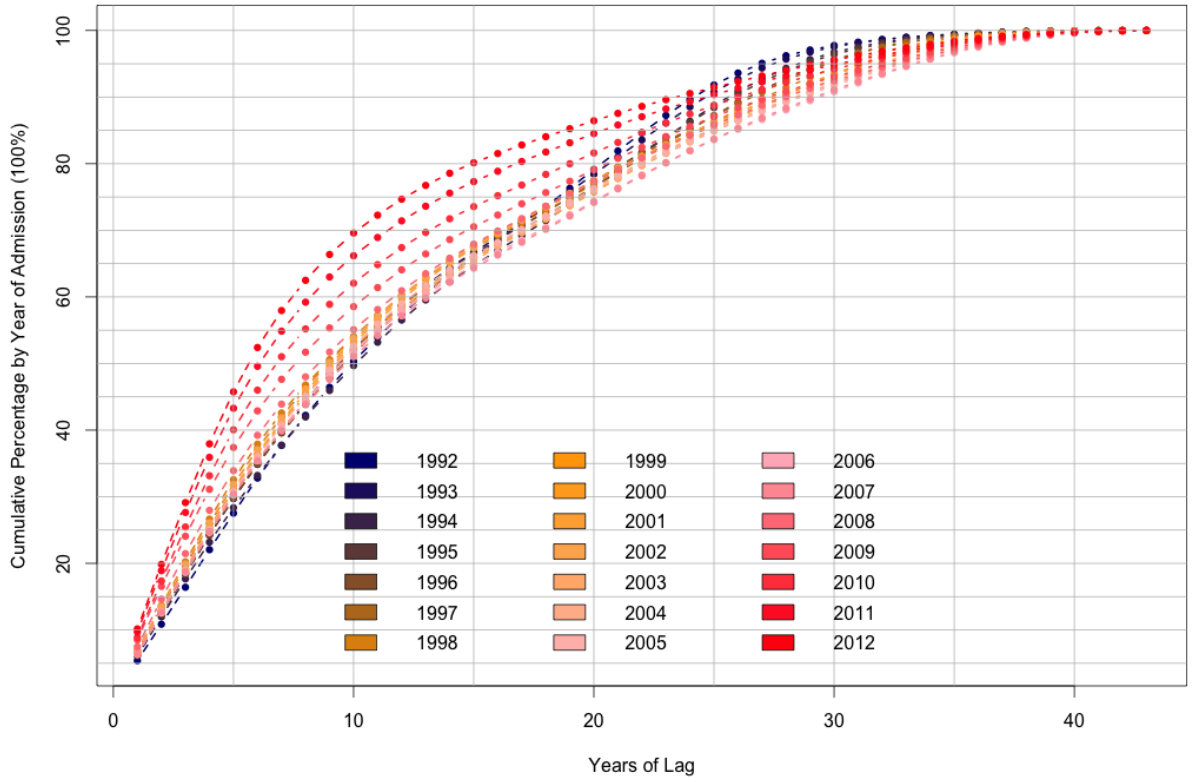
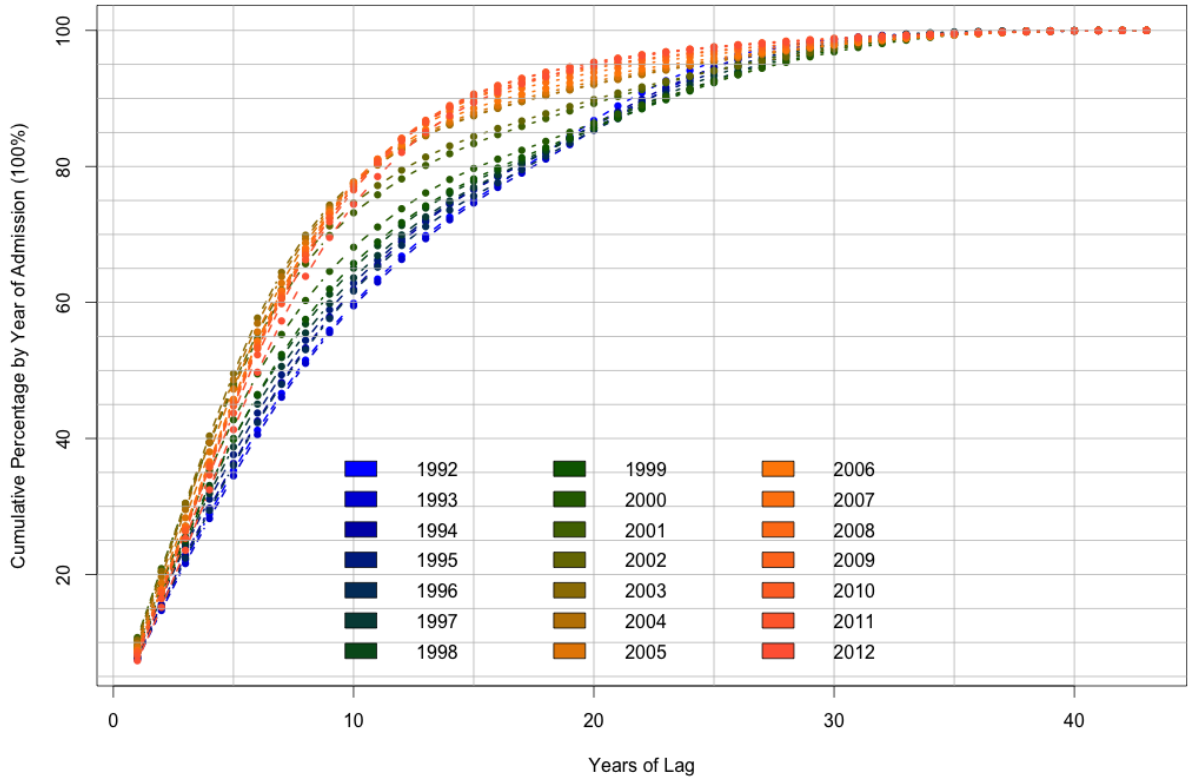


Figure 4.3.7 Other opioids lag distribution. Data from United States, Treatment Episode Data Set –Admissions (TEDS-A), 1992-2012.



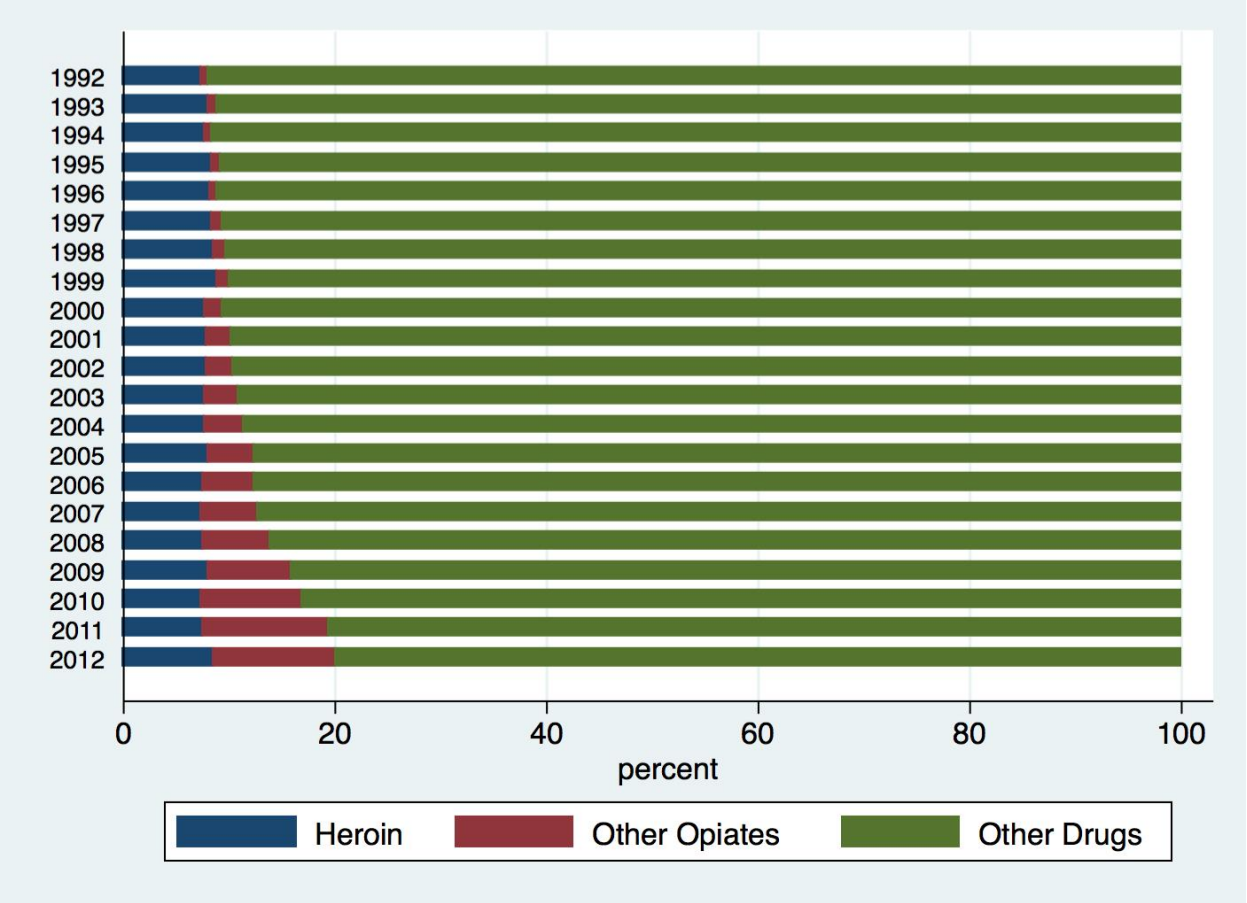
4.4 RESULTS

This study's estimates are from 11,327,152 persons aged 12-54 years -- i.e., those admitted between 1992 and 2012, with an opioid as their primary drug problem as reported by public or private treatment facilities where they were admitted. Among identified persons, 889,031 people (8% of treatment program admissions) had heroin as the primary drug problem prompting treatment. These are the observations used to apply Hunt's back- calculation approach in order to estimate newly incident heroin cases by estimating numbers of being truncated, year by year, based on those actually admitted for treatment, 1950-2012 (Table 4.4.1).

Table 4.4.1 Number of people admitted to the treatment program by the type of primary drug use problem for their first admission. Data from United States, Treatment Episode Data Set – Admissions (TEDS-A), 1992-2012.

Year of Admission	Heroin	Other opiates	Other drugs	Total
1992	35,692	3,399	447,924	487,015
1993	38,703	3,689	439,641	482,033
1994	38,311	3,771	459,142	501,224
1995	43,357	3,884	471,724	518,965
1996	41,214	4,035	464,457	509,706
1997	40,147	4,106	433,425	477,678
1998	40,528	5,082	427,603	473,213
1999	42,355	5,988	432,148	480,491
2000	35,084	7,814	417,633	460,531
2001	37,234	10,701	425,641	473,576
2002	39,329	13,531	455,168	508,028
2003	37,276	15,474	436,764	489,514
2004	36,506	17,378	422,797	476,681
2005	43,079	23,312	473,250	539,641
2006	45,940	28,951	532,511	607,402
2007	48,244	36,133	579,658	664,035
2008	51,470	45,308	597,757	694,535
2009	54,576	53,644	572,065	680,285
2010	44,882	59,552	512,286	616,720
2011	47,263	74,661	505,104	627,028
2012	47,841	63,994	447,016	558,851
Total	889,031	484,407	9,953,714	11,327,152

Figure 4.4.1 The proportion of first treatment admissions of heroin and other opioids changes over time. Data from United States, Treatment Episode Data Set –Admissions (TEDS-A), 1992-2012.



In 1992, there were 35,692 persons (7.3% of the total admissions in 1992) admitted to treatment programs with heroin as a primary drug problem; this number increased to 47,841 in 2012. Among them, those with 'primary heroin' increased from 7.3% in 1992 to 8.6% in 2012. Additionally, the number of persons admitted with 'primarily some other opioid' increased from 3,399 in 1992 to 63,994 in 2012. As a proportion of admissions, the number shifted remarkably from 0.7% of total admissions in 1992 to 11.5% in 2012. People admitted to treatment programs because of their other opioids use increased approximately 16 times over two decades (Table 4.4.1 & Figure 4.4.1).

Table 4.4.2 presents an overview of selected socio-demographic characteristics of 12- to-54-years-old patients by types of drugs (i.e., heroin, other opioids, and other drugs). As shown, the majority of people first admitted to treatment programs are between their early 20s and 40s (i.e., age of 21-40 years). Heroin and other opioid users are older than other drug users. The sex ratio of males to females is 2:1 for heroin users and nearly 1:1 for other opioids. According to region: more than one-third of heroin users are from the treatment facilities in the Northeast (35%), followed by West (25%), South (22%), and Midwest (18%).

Table 4.4.2 Persons age 12-54 years in the treatment programs by the type of drugs on their primary admission, Data from United States, Treatment Episode Data Set –Admissions (TEDS-A), 1992-2012 (n=11,327,152)

		Heroin		Other Opioids		Other Drugs	
		n	%	n	%	n	%
		889,031	100	484,407	100	9,953,714	100
Age							
	12-14	494	0.06	1,242	0.26	216,606	2.18
	15-17	9,469	1.07	9,640	1.99	1,121,941	11.27
	18-20	57,424	6.46	38,263	7.9	919,419	9.24
	21-24	122,444	13.77	91,981	18.99	1,308,734	13.15
	25-29	153,724	17.29	113,011	23.33	1,515,933	15.23
	30-34	145,854	16.41	79,980	16.51	1,413,297	14.2
	35-39	140,117	15.76	55,526	11.46	1,265,207	12.71
	40-44	123,306	13.87	42,746	8.82	1,028,402	10.33
	45-49	86,809	9.76	32,264	6.66	731,288	7.35
	49-54	49,390	5.56	19,754	4.08	432,887	4.35
Sex							
	Male	581,249	65.38	247,562	51.11	6,898,352	69.3
	Female	307,477	34.59	236,718	48.87	3,050,314	30.64
Region							
	Northeast	312,149	35.11	99,781	20.6	1,905,242	19.14
	Midwest	158,757	17.86	86,289	17.81	2,730,888	27.44
	South	194,886	21.92	224,489	46.34	2,824,013	28.37
	West	220,713	24.83	73,834	15.24	2,490,632	25.02

Observations were omitted due to missing values

Based on the TEDS-A 1992-2012, the number of observed newly incident opioids cases increased from 1950 to 2012. Figure 4.4.2 shows observed and corrected number of newly incident heroin cases each year. Differences between observed and corrected numbers are from correction by lag distribution for the truncated information (see Figure 4.3.4 and Figure 4.3.6).

After factoring in population size for each calendar year based on US census (see Figure 4.4.3), the peak of the first heroin epidemic was observed in 1969 (5.2 per 10,000). The second heroin epidemic was first observed in 2000 (2.5 per 10,000), which increased to 4.2 per 10,000 in 2012, but apparently has not yet reached the heroin incidence peak value seen in 1969 (Figure 4.4.4).

As for opioids compounds other than heroin, the observed and corrected number of newly incident cases are shown in the Figure 4.4.5. The incident opioid cases peak in the 1970s (~17,000 incident cases). In the 2000s, the prescription opioids become one of the most popular drugs being used extra-medically such as "to get high." Figure 4.4.5 shows that the incident cases increased from 7,200 in 1990 to 63,500 cases in 2010, dramatically increase in the past two decades. After factoring population size from U.S. census by calendar years, the first peak of incidence rate was observed in 1969 (1.5 per 10,000). After 1969, the incidence rate was gradually decreased until 1990 (0.5 per 10,000). There was a steep rise, starting in 1990 and increasing nearly eight times to 3.8 per 10,000 in 2010 (Figure 4.4.6). The trends of incidence rate over time differ between heroin and other opioids. Heroin has two clear epidemic peaks in1969 and 2010, and these two peaks were nearly reach the same incidence rates (5.2 versus 4.8 per 10,000). Incidence rates for other opioids compounds increased markedly from the late 1990s until 2012. Taking all opioids as a whole (see Figure 4.4.7), the peak incidence is seen in the late 1960s, with slow increases to a large peak in 2010. The estimated opioids incidence rate in 2012 is larger than the peak rate seen in 1969 (6.5 per 10,000 in 1969 versus 7.8 per 10,000 in 2012).

Figure 4.4.2 The observed and estimated number of newly incident heroin users from 1950 to 2012. Data from United States, Treatment Episode Data Set –Admissions (TEDS-A), 1992-2012.

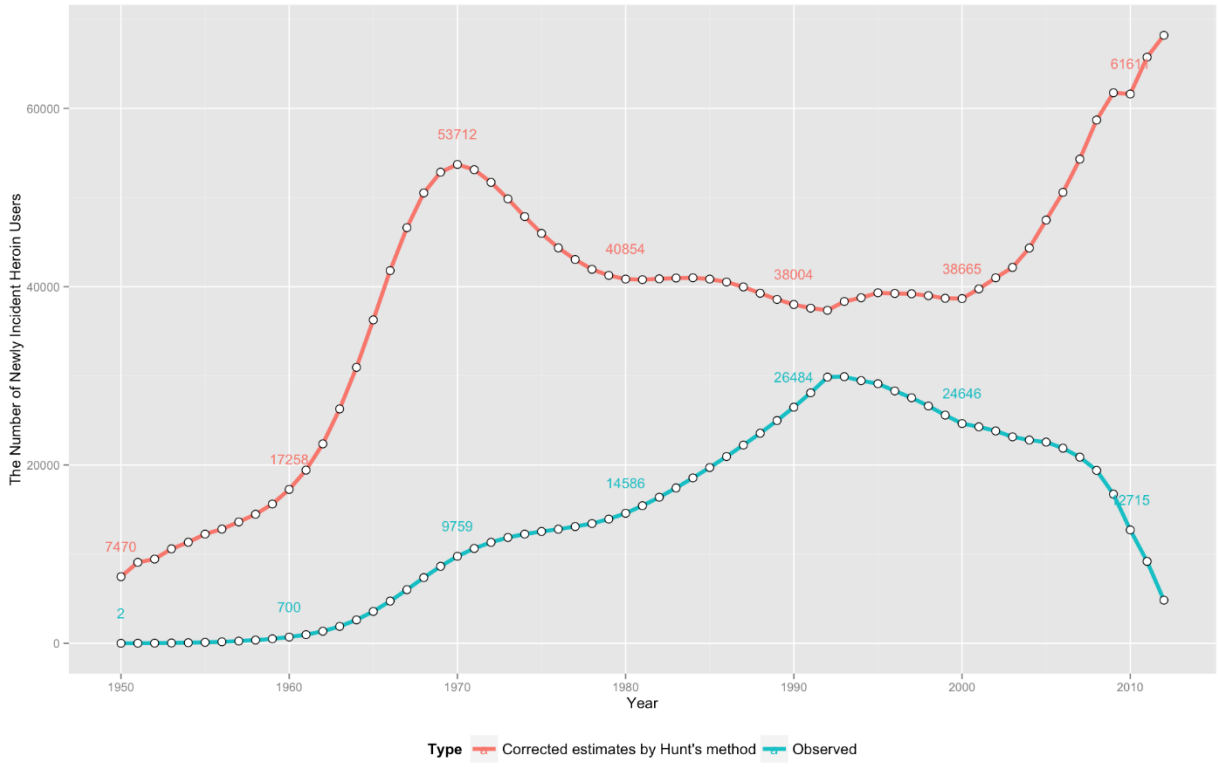


Figure 4.4.3 US population age 12-54 years by year, US census 1950-2010.

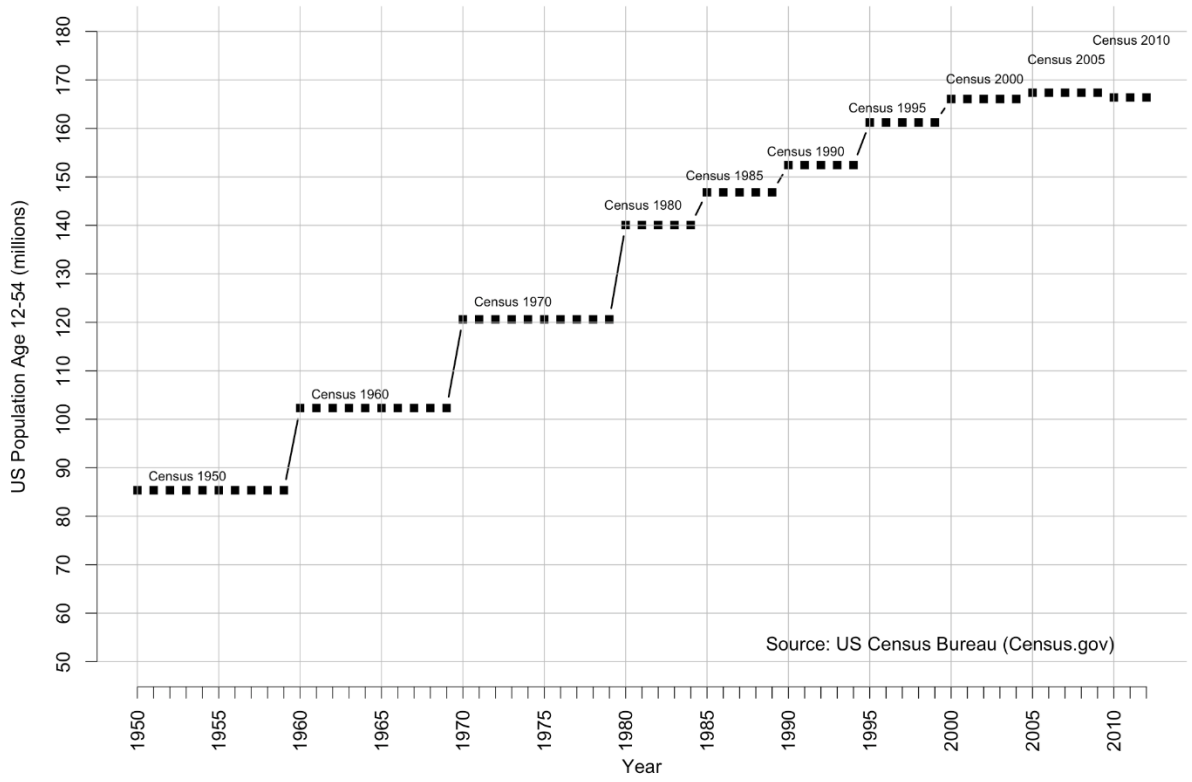


Figure 4.4.4 Heroin incidence rate (per 10,000). Data from United States, Treatment Episode Data Set –Admissions (TEDS-A), 1992-2012.

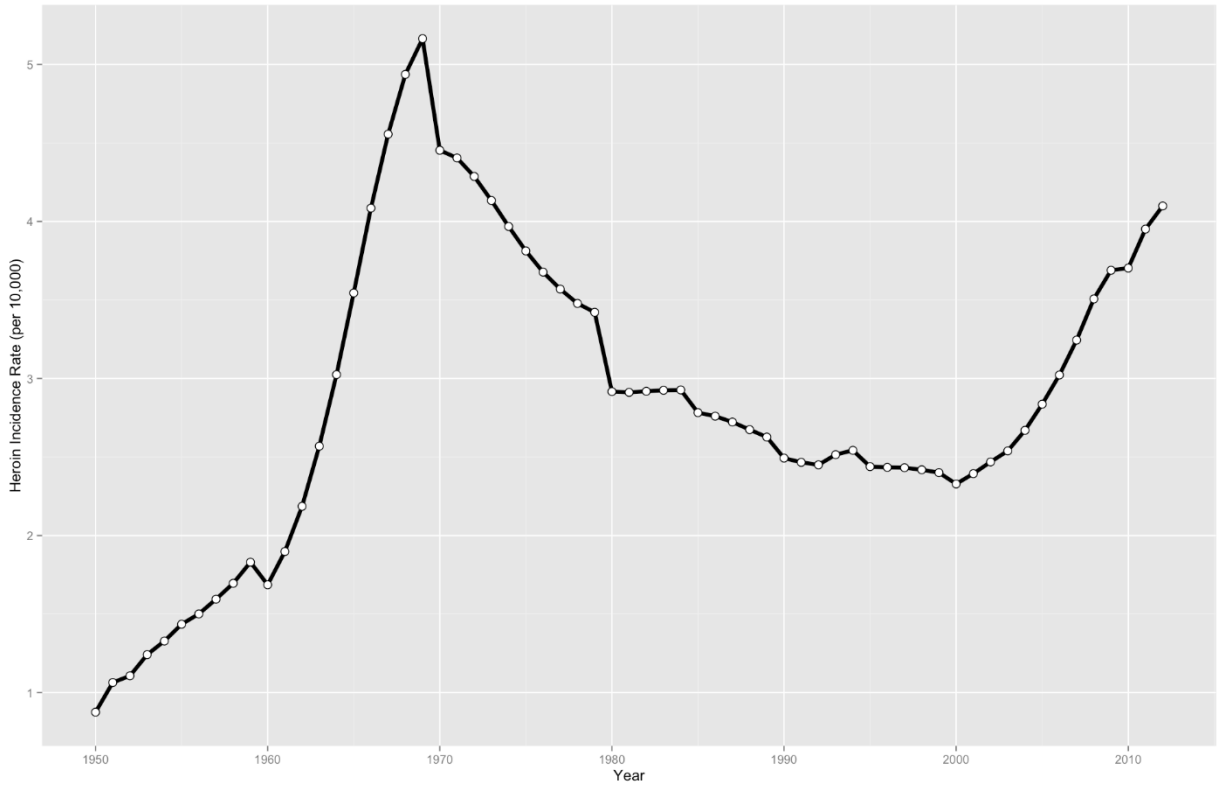


Figure 4.4.5 The observed and estimated number of newly incident users of other opioids from 1950 to 2012. Data from United States, Treatment Episode Data Set –Admissions (TEDS-A), 1992-2012.

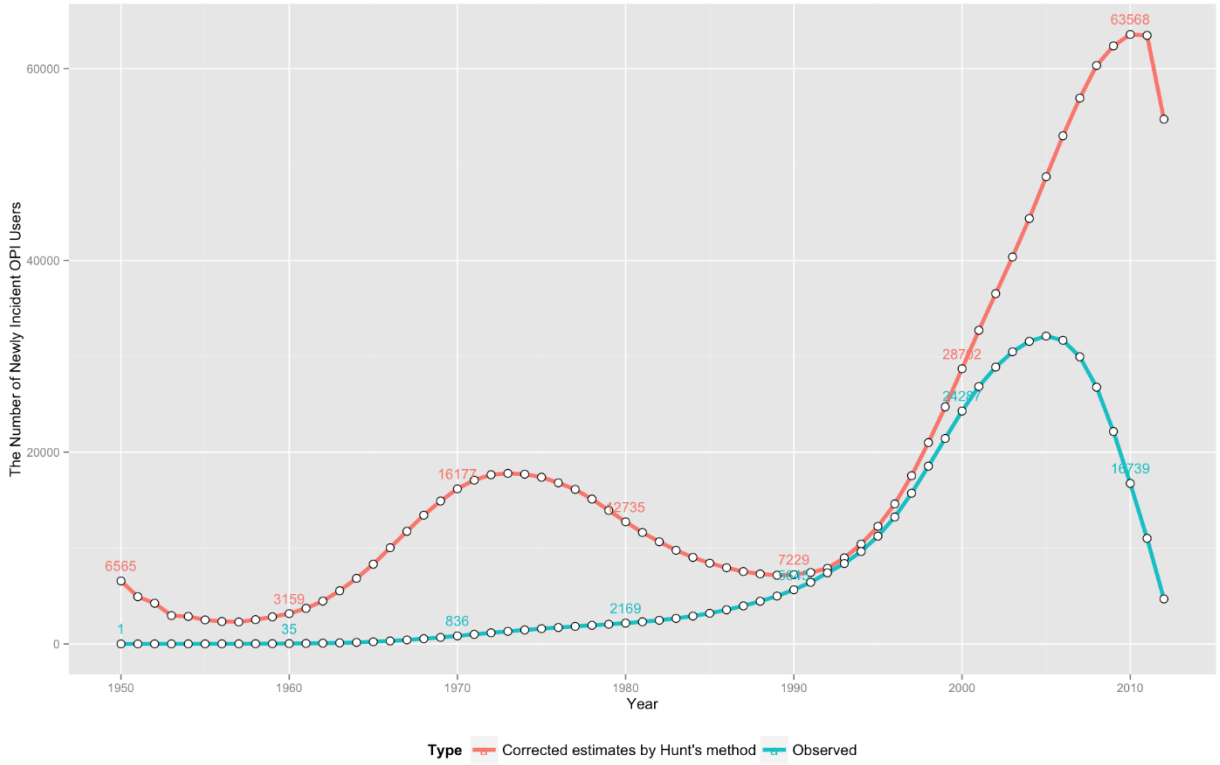


Figure 4.4.6 Incidence rate of opioids other than heroin (per 10,000). Data from United States, Treatment Episode Data Set –Admissions (TEDS-A), 1992-2012.

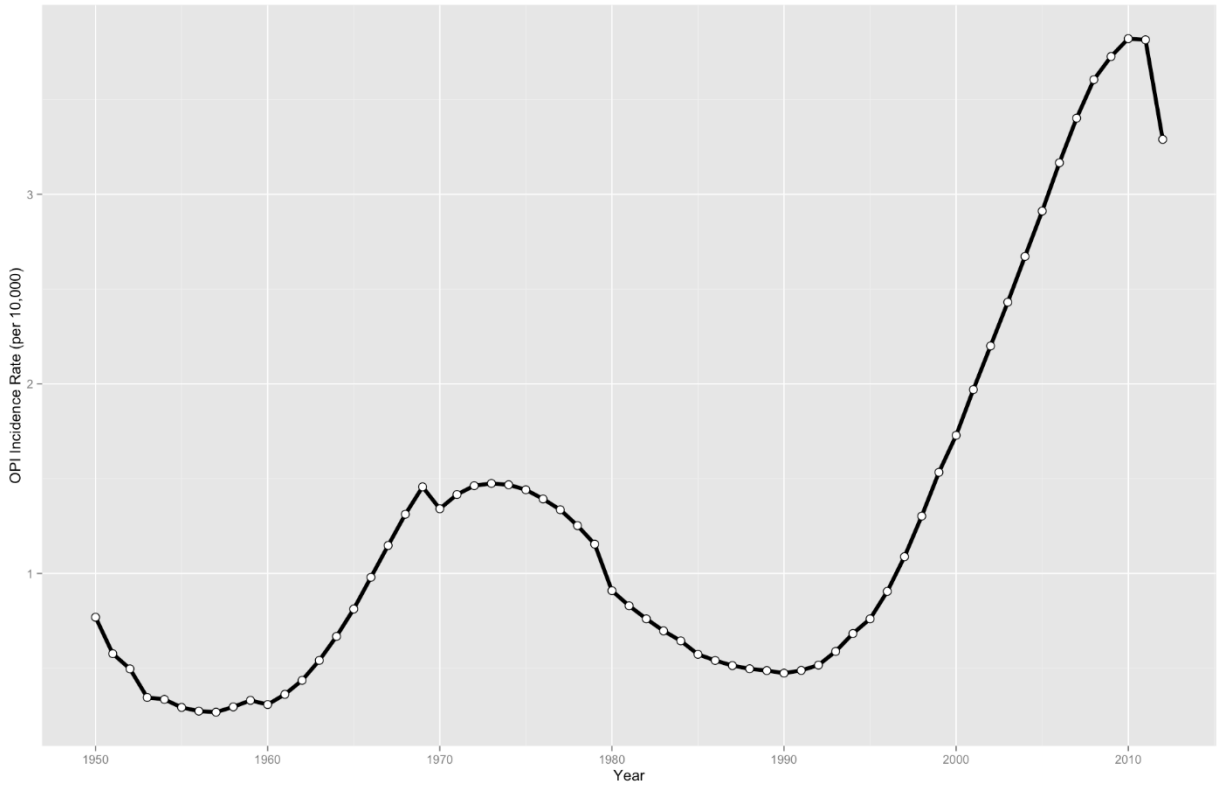
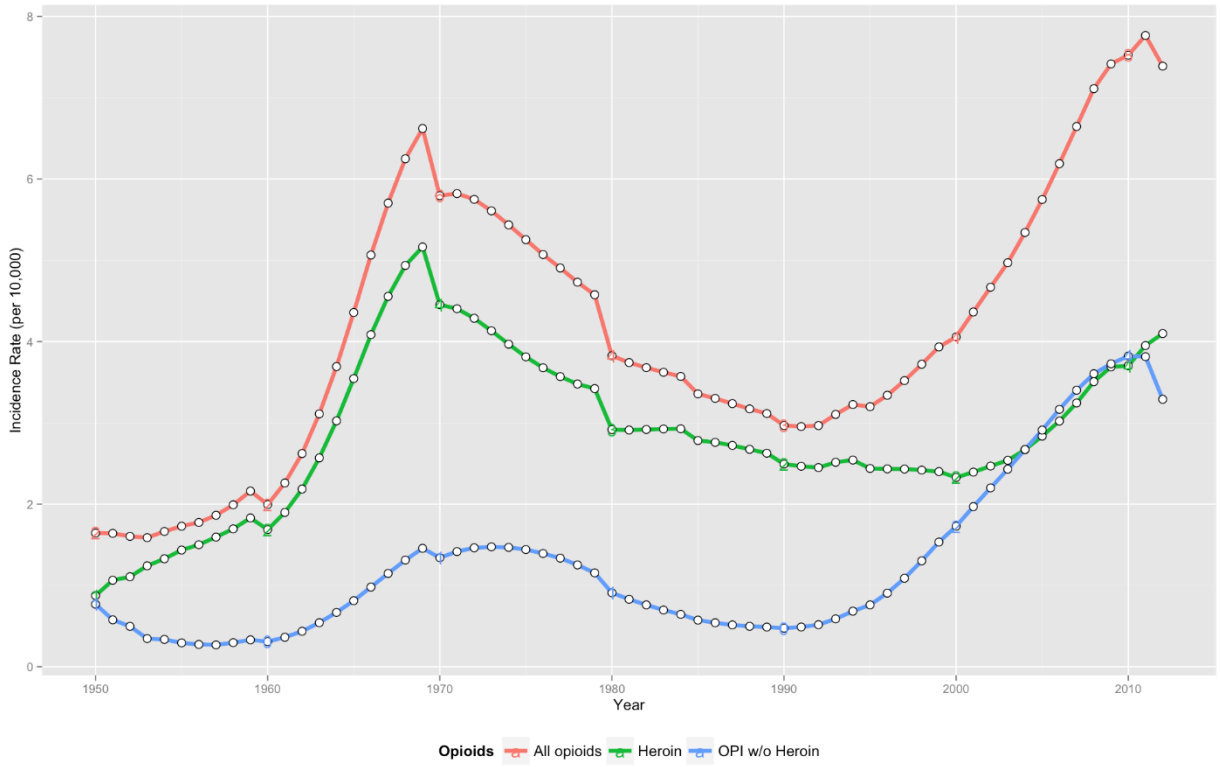


Figure 4.4.7 Incidence rate of all opioid compounds (per 10,000). Data from United States, Treatment Episode Data Set –Admissions (TEDS-A), 1992-2012.



4.5 DISCUSSION

The main findings of this study may be summarized succinctly. First, the number of opioids admissions to treatment programs has increased for heroin and other opioids. Second, the lag time between first opioid use and their first admission for opioid use dropped from 1992 to 2012. Third, according to Hunt's lag distribution approach, two heroin epidemics can be seen to peak in the late 1960s and early 2010s (if no more increase is seen). As for incidence rates for opioids other than heroin, incidence rates increased eightfold from 1995 to 2010.

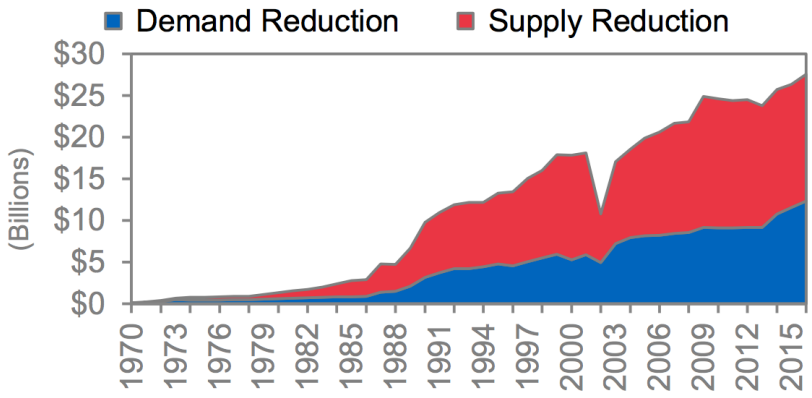
Before detailed discussion of these results, several of the more important study limitations merit attention. Of central concern is how lag distributions changed over time from 1950 to 2012. The lag distribution used in this study was from the averaged values of lag time. The median lag time in this study is 9~10 years for heroin and 7~8 years for other opioid compounds. Similar results have been reported in previous studies. For example, the median lag year was 8 years and the mean was 9~10 years for heroin based on the California treatment program dataset in the 1970s (Judson, Ortiz, Crouse, Carney, & Goldstein, 1980). Krebs et al. reported that the median lag time was 10 years between the first heroin use and first treatment admission based on treatment for opioid use disorder in California from 2006 to 2010 (Krebs et al., 2016). In another study with use of National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), among those who sought treatment, the midpoints in the cumulative probability distributions were 12 years for any drug from the time of first use to first treatment contact (Blanco et al., 2015). According to the previous studies, the lag between first heroin use and first treatment admission was approximately 10 years across the period from 1970s to 2010s. The lag distribution used in this study to correct the number of heroin incident cases might be over- or under-estimated; this is a concern to be investigated in future research.

In addition, there are some limitations with respect to the data source used in this study for the estimates of heroin incidence. TEDS-A is a national census data system of annual admissions to drug treatment facilities in the United States. However, many drug users do not receive treatment (Blanco et al., 2013; Compton, Thomas, Stinson, & Grant, 2007; Edlund, Booth, & Han, 2012; Hasin, Stinson, Ogburn, & Grant, 2007; Kessler et al., 1999; Olfson, Kessler, Berglund, & Lin, 1998; Regier et al., 1993; United States. Substance Abuse and Mental Health Services Administration, 2014a; Wang et al., 2005). The most recent report indicates that only 4.5% of drug users felt they needed the treatment. Among the users who felt they needed, 35% of them did receive the treatment. Overall, only 1.6% of drug users felt they needed and did receive treatment. The main reasons that drug users did not receive treatment: (1) no health coverage and could not afford cost, (2) not ready to quit, (3) did not have knowledge of treatment programs, (4) might have negative effect on job, (5) could deal with the problem by themselves without treatment, and (6) did not feel the need for treatment at the time (United States. Substance Abuse and Mental Health Services Administration, 2014a).

Even with existence of barriers to treatment, the increased number of patients in the treatment programs might not only due to the increase of heroin users but also the increase of capacity of treatment and more options of pharmacological treatments. Methadone is commonly used to treat opioid dependence in the treatment maintenance program in the United States. Methadone was introduced in late 1960s as a maintenance treatment for treating opioid dependence (Dole & Nyswander, 1965). In 2002, buprenorphine was approved by FDA as another medical treatment of heroin dependence other than methadone (https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm191521.htm). Buprenorphine and methadone are the most effective treatment for opioid

dependence according to the World Health Organization (World Health Organization, 2009). Therefore, patients with opioid dependence have more options of treatments since 2002 and this might increase the number of heroin users admitted to treatment programs. Moreover, the federal budget of drug treatment increased from <1 billion US dollars in 1970 to 10 billions in 2015 (Figure 4.5.1). The increased budget might result in the increase of the capacity of drug treatment. These changes in the past decades might influence the proportion of heroin incident cases extracted from TEDS-A database, and then influence the estimates of the heroin incident cases in each calendar year. Moreover, with a very limited literature investigating the difference between opioid users admitted to private and those who admitted to public facilities, the opioid users who admitted to private treatment facilities were more likely to be non-Hispanic White, younger, and both prescription opioid and heroin users. For those who admitted to public treatment facilities have higher likelihood of trading or selling sex (O'Grady, Surratt, Kurtz, & Levi-Minzi, 2014).

Figure 4.5.1 The Federal Drug Control Budget 1970-2015



Link: https://www.drugpolicy.org/sites/default/files/DPA_Fact_sheet_Drug_War_Budget_Feb2015.pdf
Supply Reduction: interdiction, eradication & law enforcement
Demand Reduction: education, prevention & treatment.
Source: White House Office of National Drug Control Policy (ONDCP); Sourcebook of Criminal Justice Statistics.

Notwithstanding limitations such as these, the study findings are of interest because this study has produced heroin incidence rate estimates across 60 years, using Hunt's lag distribution method as applied to TEDS-A admissions data, given us a new view of the ebb and flow of US heroin epidemics. Similar patterns have been seen in prior estimation attempts with more restricted data (i.e., not for 1992-2012), but the sixty-year view has value, and raises questions about whether the current heroin epidemic already has reached its peak.

This study discloses temporal patterns and ‘relative’ heroin incidence. Whereas I do not claim an absolute level of accuracy about numbers of newly incident heroin users, these estimates should prompt new thinking about primary prevention, outreach, and treatment resources for heroin users.

CHAPTER 5

MANUSCRIPT 2 – A TRIGGER FOR NEWLY INCIDENT HEROIN USE? EPIDEMIOLOGICAL EVIDENCE FROM THE UNITED STATES: A CASE-CROSSOVER STUDY DESIGN

5.1 ABSTRACT

The aim of this study is to investigate whether extra-medical (EM) OxyContin® (EMO) use might have triggered heroin onset among 12-25 year olds during 2004-2014, with probes for risk variations across EMO level. A case-crossover study design is used. Setting: United States (US), with community residents 12+ years sampled and recruited for National Surveys on Drug Use and Health (NSDUH), 2004-2014, then assessed using standardized methods. There are 447 newly incident heroin users among participants assessed 2004-2014. Fine-grained self-report month-of-onset data for heroin and EMO use meet temporal sequencing guidelines and help constrain individual-level susceptibilities. The main finding is that excess risk for newly incident heroin use is seen in a four-month interval immediately after onset of EMO use [case-crossover relative risk (RR) = 1.9; 95% confidence interval (CI) = 1.13, 3.10; p = 0.01]. Post-estimation exploratory analyses suggest no excess risk for EM users of other prescription pain relievers, and indicate no excess risk correlated with new formulations of OxyContin®, *per se*. Based on community-dwelling newly incident heroin users ascertained without prejudice, the estimates shed light on previously published but more uncertain evidence on suspected EMO-heroin associations. In conclusion, at least in the United States, the onset of EMO has statistically robust excess risk of triggering heroin use, even if EMO onset, *per se*, is not a cause of heroin use.

5.2 INTRODUCTION

Both theory and recent empirical evidence from the US support the idea that newly incident heroin use might have been triggered when young people started to use other opioid compounds or the originally formulated OxyContin® products extra-medically (Al-Tayyib, Koester, & Riggs, 2017; Banerjee et al., 2016; Carlson, Nahhas, Martins, & Daniulaityte, 2016; Cerda et al., 2015; Cicero et al., 2015; Cicero et al., 2012; Compton et al., 2016; Grau et al., 2007; Jones, 2013; Lankenau et al., 2012; Mars et al., 2014; Martins, Storr, Zhu, & Chilcoat, 2009; Palamar, Shearston, Dawson, Mateu-Gelabert, & Ompad, 2016; Young & Havens, 2012). "Extra-medically" (EM) refers to the use of compounds to get high or for related feelings, and otherwise outside boundaries set by prescribing clinicians as defined by Anthony et al. (Anthony et al., 1994). The origins of theory and conceptual foundations for asking research questions about the suspected EM OxyContin®-heroin triggering hypothesis date back to early general 'steppingstone' and 'gateway' ideas about how the use of one drug early in a chain of temporally sequenced events might account for later drug use (Anthony, 2002, 2012; Morral et al., 2002). Evidence pertinent to the EM OxyContin®-heroin triggering hypothesis has come largely from clinically-based studies of persons in treatment programs, as well as from a mix of field studies with local area recruitment approaches (Cicero et al., 2012; Grau et al., 2007; Martins et al., 2009). Heroin use becomes a possible alternative for OxyContin® because heroin often has been cheaper and more readily available. In an illustration of evidence from the qualitative research tradition, Cicero and colleagues provide the following quotation from an EM user:

> *"Most people that I know don't use OxyContin® to get high anymore. They have moved on to heroin [because] it is easier to use, much cleaner, and easily available" (Cicero et al., 2012).*

With this conceptual framework in mind, we recognized an emergent research opportunity to shed new light and provide more definitive evidence on the idea that extra-medical use of the originally marketed OxyContin® products might have accounted for triggering of onsets of heroin use. We cannot claim that this research opportunity represents the 'perfect' experiment, nor does the opportunity possess all of the advantages of what might be observed in what most likely would be an unethical randomized controlled trial (RCT). Instead, the research approach is completely observational and non-experimental. Randomization is not used to try to bring into balance potentially confounding influences such as might be achieved in an RCT.

Rather, in an important departure from all prior research approaches used to study the hypothesis about EM OxyContin®-heroin triggering (hereinafter abbreviated as 'EMO-heroin' triggering), we try to hold constant underlying individual-level predispositions and other confounding influences by turning to a 'subject-as-own-control' design known as the epidemiologic case-crossover approach. Consider, for example, the idea that an underlying genetic predisposition or susceptibility trait for self-administration of opioid drugs might lead us to make an erroneous conclusion that onset of EMO use has triggered a subsequent onset of newly incident heroin use. That is, it might not be the OxyContin® product, *per se*, that is accounting for any observed excess risk of newly incident heroin use. Instead, it might be an otherwise uncontrolled individual-level predisposition or susceptibility trait.

One clear strength and advantage of the case-crossover 'subject-as-own-control' design, relative to alternative observational research designs, is that it holds constant all of these individual-level or subject-specific predispositions and susceptibility traits up to the time of the suspected causal exposure. This feature of case-crossover research has been explained in recent

research on the cannabis-cocaine association, where interested readers also will find references to the original methodological articles on the epidemiological case-crossover approach (Maclure, 1991; O'Brien, Comment, Liang, & Anthony, 2012).

Another strength of this study's research approach is that we have not restricted the samples to persons attending clinics, nor to users in any specific local area. Instead, we are studying all newly incident heroin users irrespective of where they have been found in recent national surveys of civilians living in US communities, subject to three fairly simple and understandable exclusion rules: (1) all must be residing in non-institutional dwelling units (DU) at the time of the survey, defined to encompass non-household DU such as shelters for homeless persons; (2) the initial heroin use of these individuals must have occurred within 24 months prior to the assessment date and cannot be a thing of the more distant past, in order to minimize any memory and recall errors; (3) among the newly incident heroin users, we must have information based on standardized survey items about what they recall and report about (i) the month and year of the first use of heroin, and (ii) the month and year of the first EMO experience, if and when there has been an EMO onset.

The main value of using case-crossover study design is to deal with the issue of between-subjects confounding, thus avoiding the problems of comparability of control groups with regard to confounding variables such as age and sex. The epidemiological estimates of this association can be seen as a way to prevent heroin initiation among young population.

5.3 METHODS

Before we turn to a more detailed description of methods, there are several important points to be made. First, as noted above, since 2010, the manufacturer has been distributing a new 'abuse deterrent' formulation of OxyContin®, concurrent with efforts to reduce supply of the

original formulations; this study's estimates largely pertain to the original formulations available between 2004 and 2011, and the re-formulations of OxyContin® between 2012 and 2014. We did not exclude 2010-11 from our initial case-crossover estimates for original formulations because it seemed logical that the original OxyContin® formulation might be available for diversion from medicine cabinets, and possibly also within gray or black drug markets as well. Second, with a focus on the basic 'Y after X' relationship, we saw no reason to base this study on any hypothesis or idea about how OxyContin® and heroin might be interacting in a pharmacological or toxicological sense. Third, there is a substantial overlap in US empirical estimates of the correlates of EMO use and the correlates of heroin use, with some noteworthy differences (Cicero et al., 2012; Grau et al., 2007; Martins et al., 2009). Nonetheless, this case-crossover research directly addresses the similarity of all individual-level correlates via its 'subject-as-own-control' nature. Fourth, whereas the NSDUH is designed to yield nationally representative estimates about EM use of heroin and other internationally regulated drugs in the US, we do not claim that this study's estimates should be regarded as 'representative' of this nation as a whole. We judge that the research approach derives some strength because the informative study participants have been sampled, recruited, and assessed 'without prejudice' via a large-scale survey protocol designed to produce national estimates, but we do not ask readers to assume or treat this study's estimates as 'nationally representative' in any sense of that phrase.

5.3.1 Population Under Study and Sampling Approach

The United States National Surveys on Drug Use and Health (NSDUH) seeks large nationally representative community samples of non-institutionalized civilians age 12+ years, generally achieving participation levels at 65%-70%, and with sample coverage of homeless shelters and other non-household dwelling units in the community, as well as household dwelling

units. Repeated annually from 2004 through 2014, the NSDUH research approach involves multi-stage area probability sampling and recruitment according to protocols approved by a cognizant Institutional Review Board (United States. Substance Abuse and Mental Health Services Administration, 2012)

During these years, the number of young people in aggregate NSDUH public use dataset analytic samples (i.e., 12-25 year olds) exceeds 350,000 individuals. By the time this study's exclusion rules are applied with a focus on newly incident heroin users who provided information about month and year of heroin and EMO use, the effective sample size for our case-crossover research is 447 newly incident heroin users. That is, the vast majority of heroin users found in NSDUH surveys started to use heroin in the past, and not within a 24 month interval pre-dated the survey assessment date. For reasons explained in the article's INTRODUCTION, we exclude these past-onset heroin users and focus the estimation task on the 447 newly incident heroin users for whom we have values for month and year of heroin use, and if EMO onset has occurred, for whom we also have values for month and year of EMO onset.

Methodological details of the IRB-approved NSDUH protocol for field survey work are provided in many readily available online reports (e.g. see https://nsduhweb.rti.org/respweb/homepage.cfm, last accessed 19 October 2016). These online reports describe sampling, recruitment, and assessment procedures in great detail, provide codebook documentation of the study variables, and include links to the original interview assessment modules and the standardized items on the topics under study.

5.3.2 Assessment Approach

In brief, with respect to the assessment approach, after sampling and recruitment, each participant completes the NSDUH modularized assessment with coverage of multiple behavior

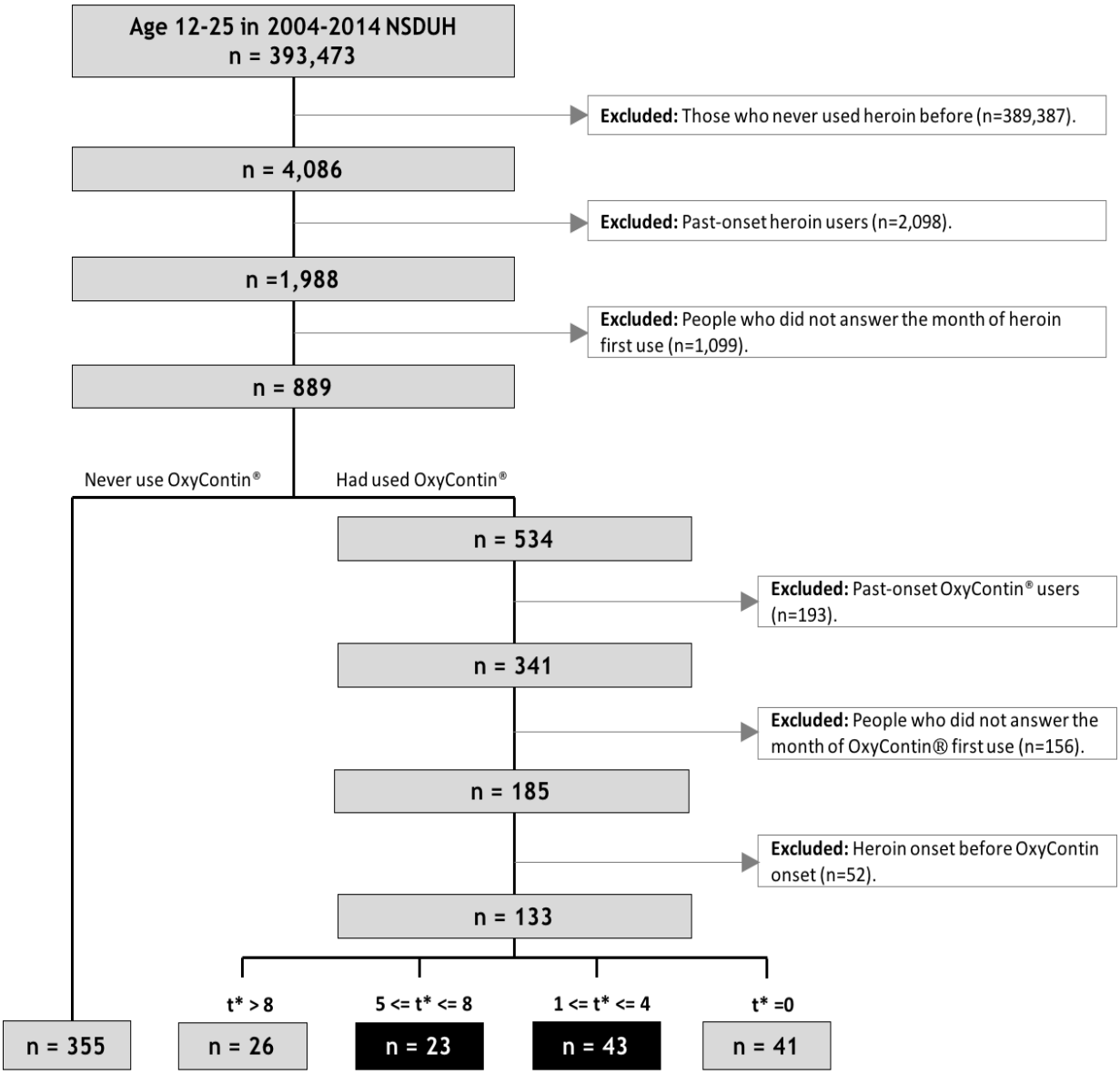
and health domains, including past-onset and newly incident EM drug use for a selection of drugs, including OxyContin® and internationally regulated drugs such as heroin. Almost all NSDUH participants complete confidential computerized self-interviews on the topics under study, with color drug product displays and other aids to enhance response validity, after choice of an English or Spanish language version of the assessment.

Month-of-first-use is assessed for recent-onset newly incident EM users of these drugs, but not for past-onset users (due to anticipated memory errors), with 'newly incident use' made operational as EM use having first occurred within 24 months prior to the date of survey assessment. All users are asked about days of EM use in the 12 months prior to assessment. The exact wording of all NSDUH interview items used in this study is presented in the online methods reports for each year http://www.samhsa.gov/data/population-data-nsduh/reports.

5.3.3 Post-Assessment Inclusions and Exclusions Approach

As shown in Table 6.4.1, a total of 447 newly incident heroin users are included in this study's analytic sample. We have been careful to devise inclusion rules that allow us to consider information from as many newly incident heroin users as is possible, and to implement exclusion rules only to the extent required to create a basic case-crossover analysis of the type shown in the Figure 5.3.1.

Figure 5.3.1 Flow chart illustrates the sample selection of case-crossover study design. Data from 393,473 individuals age 12-25 years of age, United States National Surveys on Drug Use and Health, 2004-2014.



* The month of EM OxyContin® onset before heroin onset

5.3.4 Hazard Interval and Control Interval Specifications

Each epidemiologic case-crossover study requires pre-specification of a 'hazard interval' of a given duration ('d'), as well as a 'control interval' of the same duration. Pre-specification of this 'd' interval during which ‘triggering’ might occur generally involves a synthesis about what is known or judged to be plausible with respect to the hypothesized 'induction' or 'incubation' period after exposure and before a clinically significant event occurs.

Well in advance of the analyses reported here, we studied the available published data, and chose a four-month interval as the duration of the hazard interval. That is, we pre-specified the 'hazard interval' to be the four months just prior to onset of heroin use. For the 'control interval' we specified the four-month interval just prior to the start of the hazard interval (i.e., an equal four-months duration for the hazard interval and for the control interval). As noted previously, when heroin use and EMO use started in the same month, we set aside information about the newly incident heroin users; these individuals contribute no information to the RR estimates of this study because to include them would introduce uncertainty about the temporal sequencing of the two events under study: (1) newly incident heroin use, and (2) newly incident EMO use.

5.3.5 Analyze/Estimate Approach

From the prior sections of this article and prior publications (Maclure, 1991; O'Brien et al., 2012), it can be seen that the relative risk estimate from a case-crossover study uses the 'subject-as-own-control' design to hold constant an array of confounding influences such as individual-level genetic or other susceptibility traits, and produces an RR estimate that conveys the degree to which the evidence favors the suspected triggering hypothesis relative to the evidence favoring the null hypothesis -- i.e., in this study, (a) evidence in favor of EMO-

triggering of heroin onset, expressed as the count of newly incident heroin users who had started EMO use in the four month ‘hazard interval’ just before heroin onset (but not in other months), versus (b) evidence against the triggering hypothesis, expressed as the count of newly incident heroin users who had started EMO use in the four month ‘control interval’.

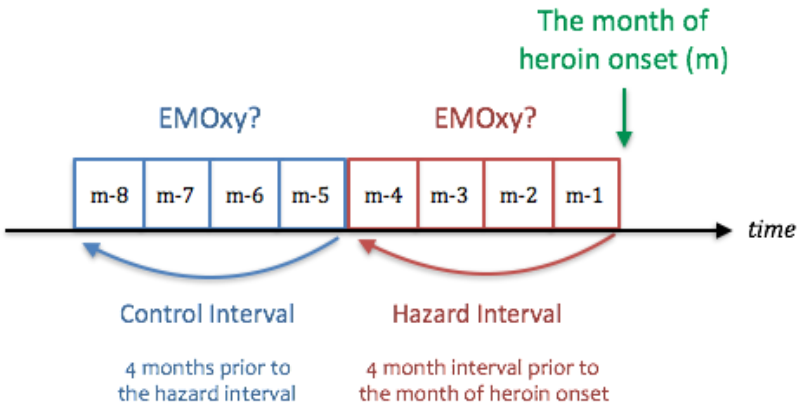
Whereas we had pre-specified the four-month duration of the hazard and control intervals before any data analyses, we decided it would be best to conduct post-estimation exploratory data analyses with other specifications for the 'd' duration value. We describe the estimates from these post-estimation exploratory data analyses in the DISCUSSION section and the first column of Table 5.4.2.

There was another post-estimation exploratory data analysis that we had not planned in advance; it was prompted by comments from anonymous reviewers of our manuscript. Namely, we specified the same four-month duration of the hazard and control intervals, replacing our own suspected causal exposure variable (onset of EMO use) with a different suspected causal exposure variable [onset of any EM use prescription pain reliever (PPR) covered in the NSDUH assessments (e.g., hydrocodone), not counting OxyContin® products]. That is, we shifted the research question from our original hypothesis about OxyContin® products in the direction of a more general hypothesis about prescription opioids and other PPR. For this post-hoc analysis task, we focused on the stratum of newly incident heroin users who had never used OxyContin® products, but we also show estimates based on analyses that include this stratum. The DISCUSSION section describes the estimates of this ancillary analysis; the middle and right-most columns of Table 5.4.2 present the RR estimates and 95% CI.

In the final post-estimation exploration step, we probed into the issues of OxyContin® formulation. We completed another post-estimation exploratory data analysis of risk variations

between original and new formulations of OxyContin® based on the year of EMO onset, i.e., 2004-2011 vs. 2012-2014. The result is shown in the middle and right-most columns of Table 5.4.3.

Figure 5.3.2 Case-Crossover study design



5.4 RESULTS

Among 12-25 year olds at risk for becoming newly incident heroin users during the observation interval of up to 24 months prior to the date of NSDUH assessment, a total of 447 qualified as newly incident heroin users and had non-missing month-of-onset data. The upper right hand cell of Table 5.4.1 shows evidence in favor of EM OxyContin®-triggering of heroin onset -- namely, the 43 exposure-discordant newly incident heroin users who started EM OxyContin® use in the pre-specified 4-month 'hazard interval' just before the month of heroin onset but not in the control interval. Evidence against the triggering hypothesis is in the lower left hand cell of Table 5.4.1 and includes 23 exposure-discordant newly incident heroin users who started EM OxyContin® use in the pre-specified 4-month 'control interval' just prior to the

hazard interval and not in the hazard interval (estimated RR = 43/23 = 1.9; 95% CI = 1.13, 3.10, p = 0.01).

We conducted post-hoc analyses to see what we might have found with different specifications for 'd.' The first column of Table 5.4.2 displays results from this post hoc analysis. If the unethical 'cherry-picking' approach had been used, our research team would have been wise to select d=6, with its much stronger RR estimate of 4.3 and $p < 0.01$ (95% CI = 2.4, 7.7). In truth, our d=4 pre-specification produced one of the smallest of the observed potential RR estimates shown in the first column set of Table 5.4.2; even so, the empirical p = 0.01 for this d=4 pre-specification. The other two sets of columns of Table 5.4.2 show RR estimates from the post hoc analyses that were made to include other prescription opioids in the analyses, which involved re-casting our study focus on OxyContin® products in the direction of a more general triggering hypothesis about EM use of prescription opioids and pain relievers (i.e., not focused on OxyContin® products).

Exclusion of observations from the years after the manufacturer started releasing reformulated 'abuse deterrent' OxyContin® partway through 2011 induced no appreciable attenuation of the triggering effect estimate. The estimated RR for 2004-2011 is 1.8 (95% CI = 1.05, 3.22). We also conducted the analyses to compare with different specifications for 'd' for the periods of before-and-after re-formulations of OxyContin® (see Table 5.4.3).

Table 5.4.1 Data used to estimate case-crossover relative risk in relation to the timing of heroin use in relation to the pre-specified four-month hazard and control intervals prior to the month of newly incident heroin use. Data from 447 newly incident heroin users age 12-25 years of age, United States National Surveys on Drug Use and Health (NSDUH), 2004-2014.

	EM OxyContin® onset: Hazard Interval (Months 1-4 before heroin onset)		
EM OxyContin® onset in Control Interval (Months 5-8 before heroin onset)	**No**	**Yes**	**Total**
No	n=381 [a]	n=43 [b]	
Yes	n=23 [c]	Undefined	447

(Estimated case-crossover RR = b/c = 43/23 = 1.87, 95% CI = 1.13, 3.10, $p = 0.01$).
[a] (85.3% of total n =447); [b] (9.6% of total); [c] (5.1% of total).

Table 5.4.2 Estimates from post-estimation exploratory data analyses to shed light on variations in the study estimates when alternative specifications for the 'd' interval are made, and to illuminate estimates pertinent to more general trigger hypothesis about EM use of prescription opioids and pain relievers. Data from 447 newly incident heroin users age 12-25 years of age, United States, National Surveys on Drug Use and Health (NSDUH), 2004-2014.

	Column Set #1 ("First")				Column Set #2 ("Middle")				Column Set #3 ("Right-most")		
	Hypothesized Triggering Exposure: EM OxyContin® Use.				Hypothesized Triggering Exposure: EM Use of Any Prescription Opioid or Other Prescription Pain Reliever, including EM OxyContin® Users in these estimates.				Hypothesized Triggering Exposure: EM Use of Any Prescription Opioid or Other Prescription Pain Reliever, excluding EM OxyContin® Users from these estimates.		
The 'd' duration of the hazard & control intervals	Estimated RR	Lower 95% CI	Upper 95% CI		Estimated RR	Lower 95% CI	Upper 95% CI		Estimated RR	Lower 95% CI	Upper 95% CI
d=4	**1.87**	**1.13**	**3.10**		1.46	0.91	2.37		1.43	0.72	2.83
d=1	0.71	0.34	1.48		1.15	0.55	2.42		2.50	0.78	7.97
d=2	**2.07**	**1.09**	**3.92**		**2.15**	**1.12**	**4.16**		2.33	0.90	6.07
d=3	1.5	0.89	2.51		1.57	0.93	2.64		1.90	0.88	4.09
d=4	See d=4 in row 1				See d=4 in row 1				See d=4 in row 1		
d=5	**2.65**	**1.58**	**4.43**		**2.36**	**1.44**	**3.89**		**2.50**	**1.20**	**5.21**
d=6	**4.29**	**2.40**	**7.67**		**2.57**	**1.58**	**4.15**		**2.64**	**1.32**	**5.28**
Key: Emboldened text with shading indicates p-value < 0.05											

Table 5.4.3 Estimates from post-estimation exploratory data analyses to shed light on variations in the study estimates before-and-after re-formulation of OxyContin®, and to illuminate estimates pertinent to 2004-2011 and 2012-2014. Data from 335 and 112 newly incident heroin users age 12-25 years of age respectively for 2004-2011 and 2012-2014, United States, National Surveys on Drug Use and Health (NSDUH).

	Column Set #1 ("First")				Column Set #2 ("Middle")				Column Set #3 ("Right-most")		
	Hypothesized Triggering Exposure: EM OxyContin® Use										
	2004-2014				2004-2011 (Before re-formulation)				2012-2014 (After re-formulation)		
The 'd' duration of the hazard & control intervals	Estimated RR	Lower 95% CI	Upper 95% CI		Estimated RR	Lower 95% CI	Upper 95% CI		Estimated RR	Lower 95% CI	Upper 95% CI
d=4	**1.87**	**1.13**	**3.10**		**1.84**	**1.05**	**3.22**		2.00	0.60	6.64
d=1	0.71	0.34	1.48		0.73	0.34	1.6		0.50	0.05	5.51
d=2	**2.07**	**1.09**	**3.92**		**2.89**	**1.35**	**6.16**		0.60	0.14	2.51
d=3	1.50	0.89	2.51		1.58	0.89	2.81		1.20	0.37	3.93
d=4	See d=4 in row 1				See d=4 in row 1				See d=4 in row 1		
d=5	**2.65**	**1.58**	**4.43**		**2.33**	**1.34**	**4.05**		**5.50**	**1.22**	**24.81**
d=6	**4.29**	**2.40**	**7.67**		**4.08**	**2.17**	**7.68**		**5.50**	**1.22**	**24.81**
Key: Emboldened text with shading indicates p-value < 0.05											

5.5 DISCUSSION

Drawing strength from a sample based largely on experiences in US communities before the manufacturer's substitution of an 'abuse deterrent' formulation of OxyContin® products, this study's primary discovery is modest evidence of what might have been a triggering effect of EM OxyContin® use with respect to risk of starting heroin use, as has been hypothesized by prior clinician observers and epidemiologists, estimated here as RR = 1.9 (p = 0.01).

This study's assumptions about independent observations and no appreciable survey design effects are substantiated by the fact that the RR estimate is based on a total of 66 informative newly incident heroin users (summed across the exposure-discordant off-diagonal cells of Table 5.4.1), who qualify as independently observed cases distributed across 11 years of the NSDUH survey interval (2004-2014) and the multiple local sampling strata distributed across the US. Some readers might ask whether the complex multi-stage sampling approach for the NSDUH requires special variance estimation methods as might be needed to take the non-independence of observed cases and survey design effects into account. We reasoned that standard variance estimation for matched pairs RR estimates would suffice, given that the informative cases of newly incident heroin use (i.e., those with exposure-discordant pairs of hazard and control intervals) most likely would arise from completely independent local areas and dwelling units, spread across the independent survey fieldwork conducted from 2004 to 2011. If that is the case, assumptions about independent observations become reasonable, and any survey design effect will be of trivial size. Indeed, an unweighted analysis without attention to multi-stage sampling and non-independence of sampled observations might lead to different variance approximations and perhaps wider confidence intervals as compared to what can be obtained using analysis weights and the calculus methods such as Taylor series linearization that

we often use to handle survey design effects in our epidemiological field studies. In this study, our reasoning was that we could conduct a post-hoc investigation to evaluate whether there might have been an unlikely and generally implausible departure from standard assumptions about rarely occurring events in survey research on newly incident heroin use (e.g., as might be true if there are multiple exposure-discordant newly incident cases from the same sampling stratum in the same survey year). If and when the post hoc investigation might disclose multiple cases arising in the same survey year and within the same local sampling stratum, then it would be possible to turn to approaches that have been used in epidemiological studies of neonates when there are twins or other multiple births. To illustrate, just as investigators often select one of the twins or multiple births at random from the set of liveborn multiple birth neonates, it would be possible to select one newly incident heroin user at random from within any specific local area that gave rise to more than one newly incident heroin user in a given survey year. As it happened, it was unnecessary in this study to take a random draw of one of the exposure-discordant newly incident heroin users from the survey sampling stratum and to re-calculate the matched pairs RR estimator and its 95% confidence intervals (CI).

As for weaknesses of this study, it should be noted that the NSDUH are cross-sectional surveys. In order to simulate a prospective study and to align temporal sequencing correctly, it has been necessary to turn to NSDUH retrospective data about fine-grained autobiographical details such as the month of drug use onset. Memory flaws, confusion, and chronological errors may be present, as suggested elsewhere (Anthony, Neumark, & Van Etten, 2000). In addition, some concurrent EMO-heroin users might fall outside the sampling frame, or decline to participate, as noted in this Chapter's INTRODUCTION, but we do not judge this possibility to be especially compelling with respect to bias in this study's relative risk estimates.

Notwithstanding limitations such as these, we judge that this new evidence on the EMO-heroin triggering hypothesis represents an important contribution and step forward in our understanding of the epidemiology of heroin use in specific and to the epidemiology of prescription pain reliever use in general. As for implications with respect to clinical or public health policy and actions, these findings highlight some potential unintended consequences of sustained release opioid re-formulations in the pharmaceutical research and development process (Jones, Muhuri, & Lurie, 2016), but perhaps it is of most importance that the case-crossover approach rules out predispositions and susceptibility traits that have not been controlled in the prior investigations of this topic, yielding more definitive evidence than has been available from past inquiries. These results tend to confirm the initial EMO-heroin triggering hypothesis articulated by observant clinicians and in anecdotes from heroin users, as well as observations from prior field study investigations without benefit of the case-crossover approach, including those conducted prior to the manufacturer's introduction of the 'abuse deterrent' formulation. If the findings can be confirmed in future replications, the survival analysis estimates may have value in clinical or public health practice. Once the future investigations of case-crossover research on the suspected EMO-heroin triggering hypothesis during the interval 2011 to 2020 are completed, it will be possible to be more confident that the intent of ‘abuse deterrence’ has been achieved (Cicero & Ellis, 2015). Moreover, a better understanding for EMO-heroin triggering would consider a cohort study design, but we are not aware that any cohort study has been published. However, there is an ongoing study in Australia that is evaluating the potential impact of re-formulated OxyContin® via gathering cohort data of regularly opioids misusers (Degenhardt et al., 2015). This prospective cohort study might help future studies to understand how re-formulated OxyContin® correlated with heroin or other opioid use.

CHAPTER 6

MANUSCRIPT 3 – PATTERNS OF DURATION OF ELAPSED TIME FROM EXTRA-MEDICAL PRESCRIPTION PAIN RELIEVER ONSET TO FIRST HEROIN USE: A SURVIVAL ANALYSIS

6.1 ABSTRACT

Population density was associated with heroin use in the 1970s. Heroin incidence peaked earlier in the cities then shifted to smaller cities and rural areas. During the 21st century, many studies have found that prior use of extra-medical prescription pain relievers (EMPPR) is associated with increased risk of heroin use. This study aims to estimate the degree to which living in a metropolitan area is associated with transitioning from 1st EMPPR use to 1st heroin use. Its study population included non-institutionalized United States civilians age 12 years and older. Survival analyses produced time-specific risk estimates of initiating use of heroin among EMPPR users. Estimated peak risk for 1st heroin use was found three years after EMPPR onset. With 10 years of observation, approximately 5% of EMPPR users had initiated heroin use. The corresponding proportion 6% for males as compared to 3% for females. About 7% of EMPPR users who started EMPPR during adolescence initiated heroin use within 10 years. Estimated transition probabilities for these subgroups did not vary with population density. EMPPR users who are male, White, and with early EMPPR onset have increased risk of initiating heroin use. Although the outcome does not support the proposed hypothesis, the findings may also help clinicians to understand a more vulnerable population for heroin use (e.g., early EMPPR onset) and help prevention programs to identify target populations in the clinical setting.

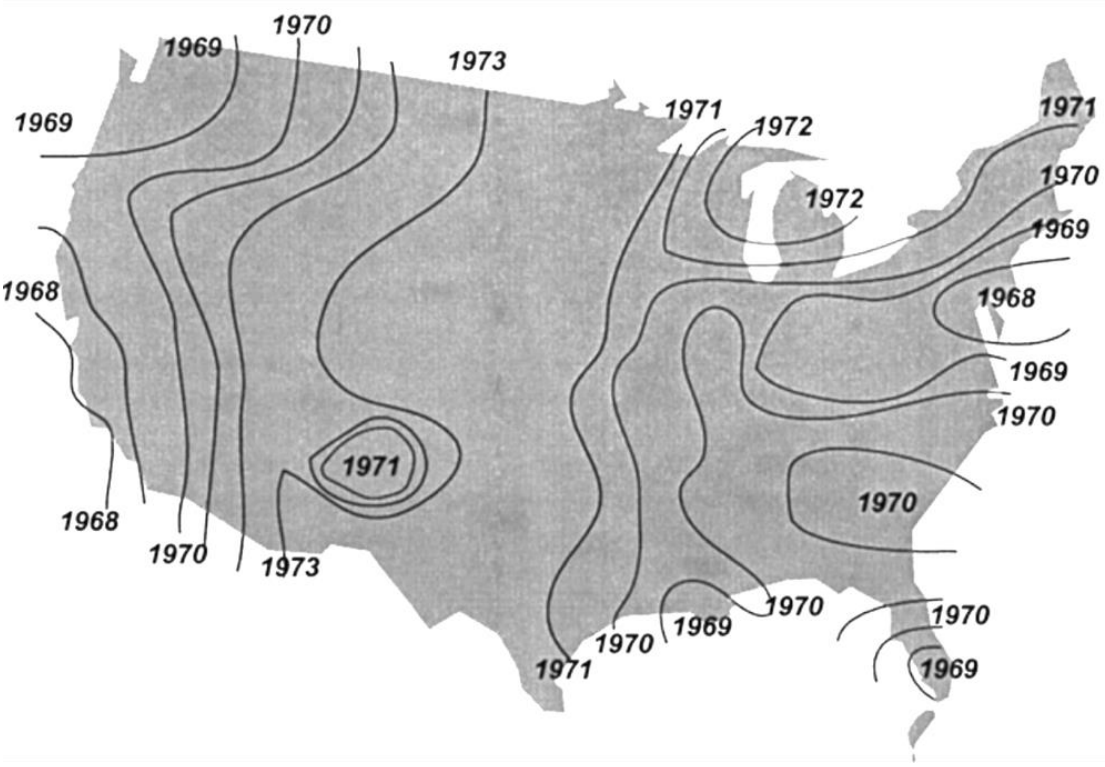
6.2 INTRODUCTION

Heroin use is one of the leading drug use problems in the US. An estimated 4.2 million Americans aged 12 or older (1.6 %) have used heroin at least once in their lives (United States. Substance Abuse and Mental Health Services Administration, 2012), and the prevalence of heroin use increased from 0.33 percent to 1.60 percent in the past decade (Martins et al., 2017). Emerging evidence suggests that prior EM of prescription opioids is associated with heroin use, and the heroin incidence is 19 times greater among those who had prior use of EMPPR. Nearly 80% of heroin users had experienced EMPPR use before initiating heroin use (Compton et al., 2016; Muhuri et al., 2013; Young & Havens, 2012). The transition from prescription opioids to heroin is a growing public health problem in the US though the fraction of prescription opioid users who shifted to use heroin was estimated under 4% (Compton et al., 2016; Jones, 2013; Mars et al., 2014; Muhuri et al., 2013).

Among those people who started using opioid drugs in the 1960s, heroin was the first used. More than 80% were men, nearly equal white to nonwhite ratio, and most heroin users lived in urban or metropolitan areas. Moreover, the emerging heroin users shifted over time from metropolitan cities to smaller cities, and they were not homogeneously distributed in the regions of US. During Post-World War II years, heroin outbreaks first emerged in metropolitan cities especially in the inner cities, such as Chicago and New York City; as time passed the epidemic diffused to smaller cities. The temporal manifestation of peak of heroin incidence in the cities reflected population size in the cities, from densely populated areas to less populated areas (Hughes et al., 1972; Hunt & Chambers, 1976). In Figure 6.2.1, the clear pattern of heroin incidence indicated that heroin spread from higher densely populated states to lower populated states in 1960s. The peak of heroin epidemic began in the East Coast (e.g., New York and

Massachusetts) and West Coast (e.g., California) and shifted to the Midwestern states (e.g., Michigan and Minnesota). In the more recent 21st century heroin epidemic, most people started using heroin after EM use of prescription opioids, female heroin users now are as many as male heroin users, more than 80% are white, and more heroin users are living in non-urban areas (Cicero et al., 2014).

Figure 6.2.1 Hunt's Macro-Diffusion theory



Source: Hunt, L. B., & Chambers, C. D. (1976). The heroin epidemics: a study of heroin use in the U.S., 1965–75. Holliswood, NY: Spectrum, p.48.

It also has been hypothesized that several environmental factors are associated with the transition from EMPPR to heroin, including the easy access to heroin and the cheaper price of heroin, relative to prescription opioids, in the street market may be underlying explanations

(Cicero et al., 2014; Unick, Rosenblum, Mars, & Ciccarone, 2014). Drug use is no longer an urban problem in the US. Some studies report that people who live in the rural areas might have a higher risk of using opioids non-medically because the cost of prescription drugs might be less expensive in smaller towns or rural areas than inner cities, and the increased availability in rural than urban areas (Cicero, Surratt, Inciardi, & Munoz, 2007; Havens, Oser, & Leukefeld, 2007; Keyes, Cerda, Brady, Havens, & Galea, 2014; Paulozzi & Xi, 2008). Young and colleagues also indicated that people who live in rural areas had much higher drug problem severity of nonmedical use of prescription opioid than those who live in urban areas due to the routes of using prescription opioids such as snorting and injection rather than the oral route (Young, Havens, & Leukefeld, 2010). On the other hand, as for the shift of the environment, heroin users have shifted from low-income neighborhood in the cities with majority of African Americans in 1960s to middle-class neighborhood in the suburban and rural areas with primarily White populations in the 21st century. Heroin apparently has become a cheaper and more accessible alternative to prescription opioid in non-urban than in urban areas (Cicero et al., 2014; Cicero & Kuehn, 2014).

The heroin epidemic in 2010s is linked to the shifting of demographic characteristics (e.g., age, sex, race/ethnicity) of heroin users and the areas where people live (e.g., urban vs. rural). Environmental factors (e.g., population density) might play an important role on spreading of drug use (Cicero & Kuehn, 2014; Cooper, Bossak, Tempalski, Des Jarlais, & Friedman, 2009; Dew, Elifson, & Dozier, 2007). However, little is known about the factors influencing heroin spread in relation to environmental conditions and individual characteristics, and whether transitioning from EMPPR use to heroin use is faster in rural areas. The motive of this study is

strongly encouraged by Hunt's micro-diffusion theory (Hunt & Chambers, 1976). The aim of this study is to estimate the probability of transitioning from first EMPPR use to heroin use.

6.3 METHODS

The study population is that of the United States civilians age 12 years and older, 2008-2014, as sampled for the National Surveys on Drug Use and Health (NSDUH), with details provided here: https://www.icpsr.umich.edu/icpsrweb/ICPSR/series/64, and in Chapters 3 and 5, including sampling, recruitment, participation, and assessment plans, as well as sample sizes. The study protocol was reviewed and approved by the cognizant institutional review board for protection of human subjects in research.

The key response of interest in this study is occurrence of heroin use among EMPPR users who had experience of using EMPPR but they did not use heroin previously. The duration of transition from first use of EMPPR to first heroin use was measured through the difference between age of heroin onset and age of EMPPR onset. The suspected causal determinant or covariate of central interest is living area (i.e., metropolis with densely populated areas vs. suburban or rural with less population). The metropolitan area was identified by two variables: population density and metropolis status. Population density was measured via the census on Core Based Statistical Area (CBSA) classifications provided by the Office of Management and Budget. The metropolis status was reported and classified into large metro, small metro, and non-metro. The Urban-Metropolis area (MET) in this study is defined as the large metropolitan area where containing a core urban area of one million or more, versus suburban-rural area (SUBRUL) defined as the small metro or non-metro area with a core area of less than one million populations.

In order to probe more completely into the temporal sequencing issues, the plan for data analysis was organized in relation to standard "explore, analyze, explore" cycles, in which the first exploratory steps involved cross-classifications and Kaplan-Meier curves. Thereafter, the analyze/estimate step involved discrete-time survival analysis (DTSA) via STATA version 13.0 (College Station, TX: StataCorp LP; 2013) software. In this work, the newly incident EMPPR users with 'tied' year of heroin onset are excluded from the analysis due to temporal sequencing concerns. The formula of discrete-time survival analysis is shown below.

Discrete-Time Survival Analysis

$\pi(t)$: the probability of 'heroin onset' in the interval (t, t+1) for the discrete elapsed years

$F(t)$: Cumulative distribution function

$S(t)$: Survival function

$h(t)$: Hazard function

$$F(t) = P(T < t) = \sum_{T \leq t}^{t} \pi(T)$$

$$S(t) = 1 - F(t) = 1 - \sum_{T \leq t}^{t} \pi(T)$$

$$h(t) = P(y_t = 1 | y_{t-1} = 0)$$

y_t indicate whether 'heroin onset' has occurred in the time interval (t, t+1)

Discrete-time logit model

$$log(\frac{h(t)}{1 - h(t)}) = \alpha D_t + \beta X_t$$

α : the coefficient of the cumulative duration
β : the slope coefficient of the covariates
D_t : a vector of the cumulative duration by the interval t
X_t : a vector of covariates (Metropolitan, Sex, Age of EMPPR onset, Race/Ethnicity)

In the initial analysis step, the task was to estimate the probability of transition from first use of EMPPR to time of first heroin use, for which the statistical approach was Kaplan-Meier analysis which provides a visual display of the heroin onset risk experiences of these newly incident EMPPR users, after pre-specified stratification into 'SUBRUL' versus 'MET' of EMPPR users lived when survey was being conducted. In subsequent analysis steps, the statistical approach involved DTSA with logistic model to estimate the risk of heroin initiation among EMPPR users. The outcome of interest was time to onset of heroin use. Each individual's time origin for survival analysis started at the year of first EMPPR use, after which year of heroin onset was ascertained. Right-censoring occurred as heroin onset did not happen until the year of assessment.

The final exploratory analysis steps compared the risks of heroin initiation for metropolis versus non-metropolis (MET vs. SUBRUL) with the stratification of sex (i.e., male vs. female), age of EMPPR onset (i.e., <12, 12-17, 18-25, >25 years), and race/ethnicity (i.e., non-Hispanic White, non-Hispanic Black, Hispanic, and others). In specific, using DTSA models, I traced year-by-year experiences of more than 60,000 aged 12 year or older NSDUH 2008-2014 participants who qualified as EMPPR users and who did not have experience of using heroin before their EMPPR onset which allowed us to deal with temporal sequencing issues. For this research, I stress precision of the study estimates with a focus on 95% confidence intervals; p-values are presented as an aid to interpretation. Cox proposed an extension of the proportional hazards model to discrete time and is used to fit DTSA by working with the conditional odds of heroin use at each time period (Cox, 1972).

6.4 RESULTS

Each Kaplan-Meier survival curve conveys information about the timing of heroin use onsets among the EMPPR users. There are 5% of EMPPR users who began using heroin within 10 years since EMPPR onset (see Figure 6.4.1). With stratification by population density [that is, suburban-rural (SUBRUL) versus urban-metropolis (MET)], an estimated 4.9% of EMPPR users in SUBRUL areas used heroin within 10 years since EMPPR onset, versus 4.6% of EMPPR users in MET areas. There is no clear difference between MSA and non-MSA (p-value=0.15, the log-rank test) (Figure 6.4.2). Male EMPPR users have faster transition from first EMPPR to first heroin use than female EMPPR users (Figure 6.4.3). Age of EMPPR onset during adolescence or young adulthood is associated with faster transition to heroin use, especially for adolescents who age 12-17 years. Approximately 7% of EMPPR adolescents initiated heroin use within 10 years since their first EMPPR use, compared to 3.5% for those started their first EMPPR use during young adulthood (18-25 years old) and 1.5% for those started their first EMPPR use during adulthood (26 years or older). The result is shown in the Figure 6.4.4. Moreover, the corresponding probability of heroin onset is significantly higher for non-Hispanic Whites than other subgroups such as non-Hispanic Black or Hispanic individuals. Approximately 6% of non-Hispanic White EMPPR users had experienced using heroin as compared to 3% for Hispanic and 1% for non-Hispanic Black subgroups, and there is no variation by subgroup with regard to metropolitan or non-metropolitan areas they lived (Figure 6.4.5).

The hazard function describes the instantaneous rate of starting heroin use at specific time points over the observed 10 years and the Figure 6.4.6 is presented as a graphical display to illustrate the risk for heroin onset over time for each subgroup. In other words, the hazard function produced a conditional rate of heroin onset in a specified time interval since first

EMPPR use given that the subject had not used heroin ('at-risk') at each time interval's start. The risk for heroin onset peaks in the third year since EMPPR onset for most EMPPR users. Men have a hazard rate at peak of 0.8%, compared to the peak of 0.5% for women. Non-Hispanic White EMPPR users have a highest hazard rate over time among these race/ethnicity subgroups. They have a hazard rate of heroin onset at peak of 0.8% in the third year since EMPPR onset, compared to the peak of 0.4% for Hispanic individuals and 0.1% for non-Hispanic Black. For adolescents (12-17 years) and young adults (18-25 years), the peak of the risk is on the third year since EMPPR onset (1% for adolescents and 0.5% for young adults). Additionally, for people who started EMPPR younger than 12 years, their risk of heroin onset is increasing from the third year to the sixth year since EMPPR onset. There in no remarkable peak of hazard on heroin onset for those who are older than 25 years.

Under the DTSA with logit model for analysis-weighted data, with Taylor series linearization for variance estimation, unadjusted hazard ratios (HR) and covariate-adjusted hazard ratios (aHR) with their corresponding 95% confidence intervals (CIs) are estimated. The results shown in Table 6.4.1. The risk of heroin onset shows no variation for EMPPR users who lived in MET versus SUBRUL areas. Male EMPPR users are an estimated 1.5 times more likely to become heroin users than female (HR=1.6, 95% CI= 1.4, 1.7). EMPPR users who started EMPPR during adolescence are about five times more likely to initiate heroin use within 10 years since EMPPR onset than those who started EMPPR later in their lives (HR=4.5, 95% CI= 3.7, 5.4). Moreover, non-Hispanic Whites have the highest hazard of the transition from the first EMPPR use to heroin onset among subgroups of race/ethnicity. For example, non-Hispanic White EMPPR users are about six times more likely than non-Hispanic Blacks to start heroin use within 10 years since EMPPR onset (HR=5.8, 95% CI= 4.5, 7.4).

Figure 6.4.1 Kaplan-Meier survival curves for newly incident EMPPR users 12 years or older who started heroin use, plotted in relation to elapsed time (in years) since year of first EMPPR use. Data from the National Surveys on Drug Use and Health (NSDUH), United States, 2008-2014.

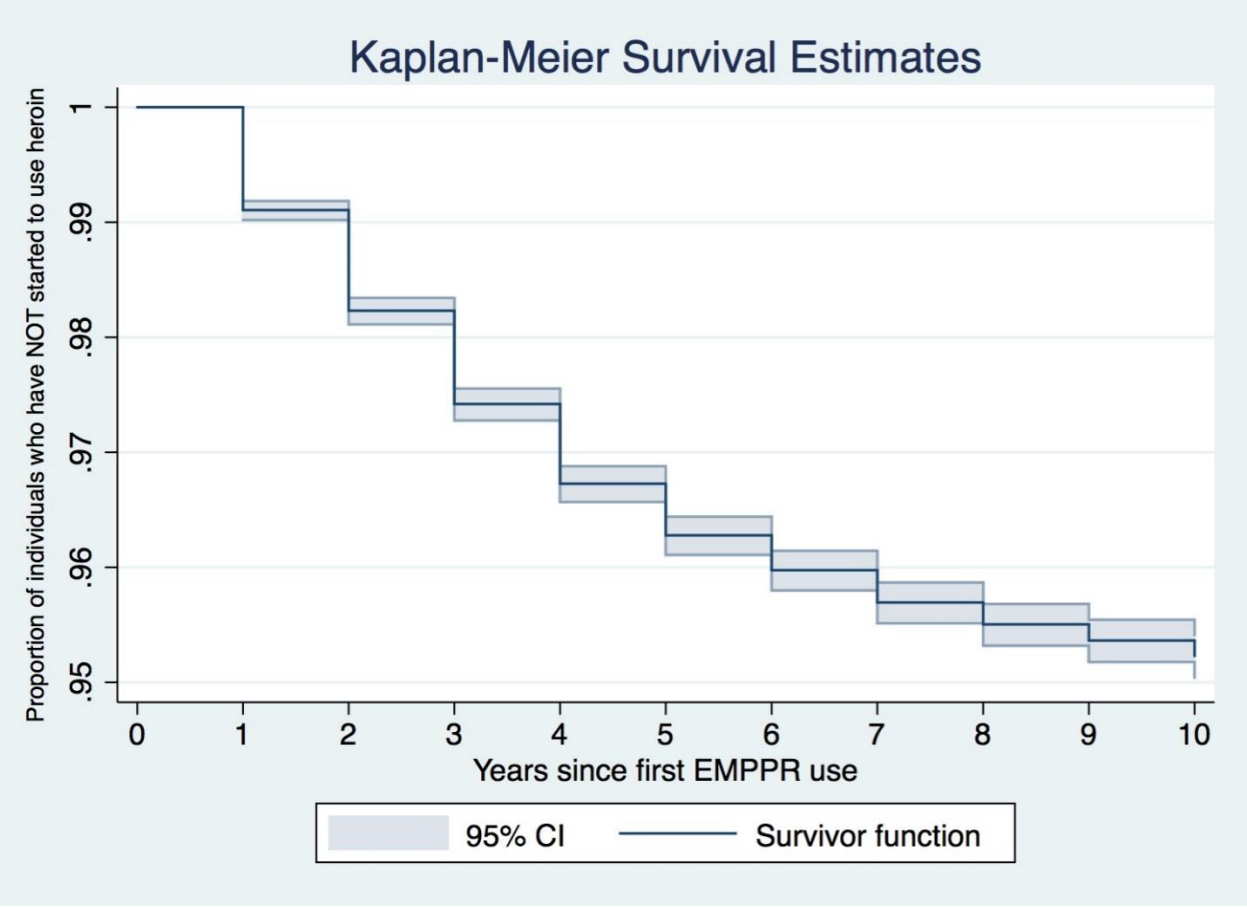


Figure 6.4.2 Kaplan-Meier survival curves for newly incident EMPPR users 12 years or older who started heroin use, plotted in relation to elapsed time (in years) since year of first EMPPR use. Stratified by **MET-SUBRUL**. Data from the National Surveys on Drug Use and Health (NSDUH), United States, 2008-2014.

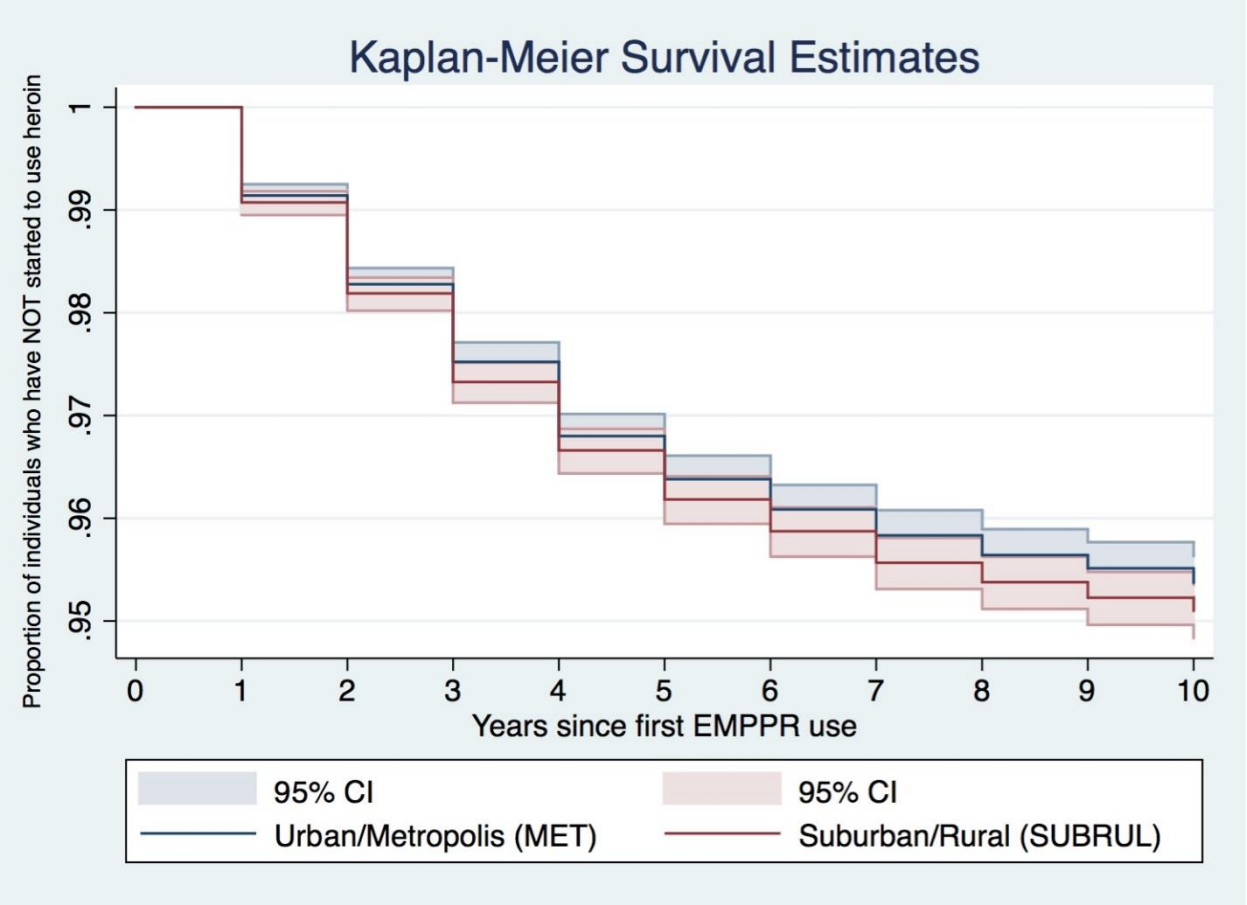


Figure 6.4.3 Kaplan-Meier survival curves for newly incident EMPPR users 12 years or older who started heroin use, plotted in relation to elapsed time (in years) since year of first EMPPR use. Stratified by **Male-Female**. Data from the National Surveys on Drug Use and Health (NSDUH), United States, 2008-2014.

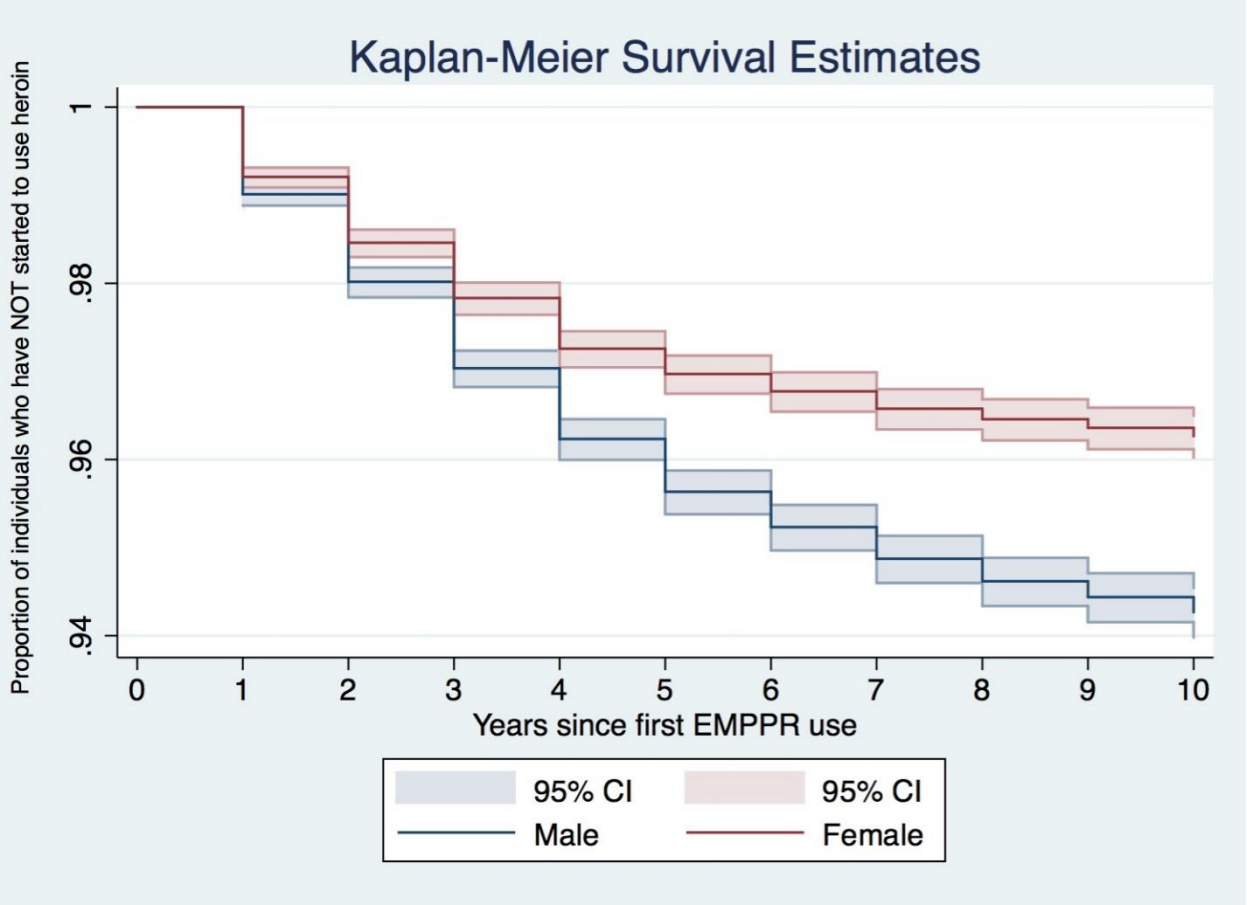


Figure 6.4.4 Kaplan-Meier survival curves for newly incident EMPPR users 12 years or older who started heroin use, plotted in relation to elapsed time (in years) since year of first EMPPR use. Stratified by **Age of EMPPR Onset**. Data from the National Surveys on Drug Use and Health (NSDUH), United States, 2008-2014.

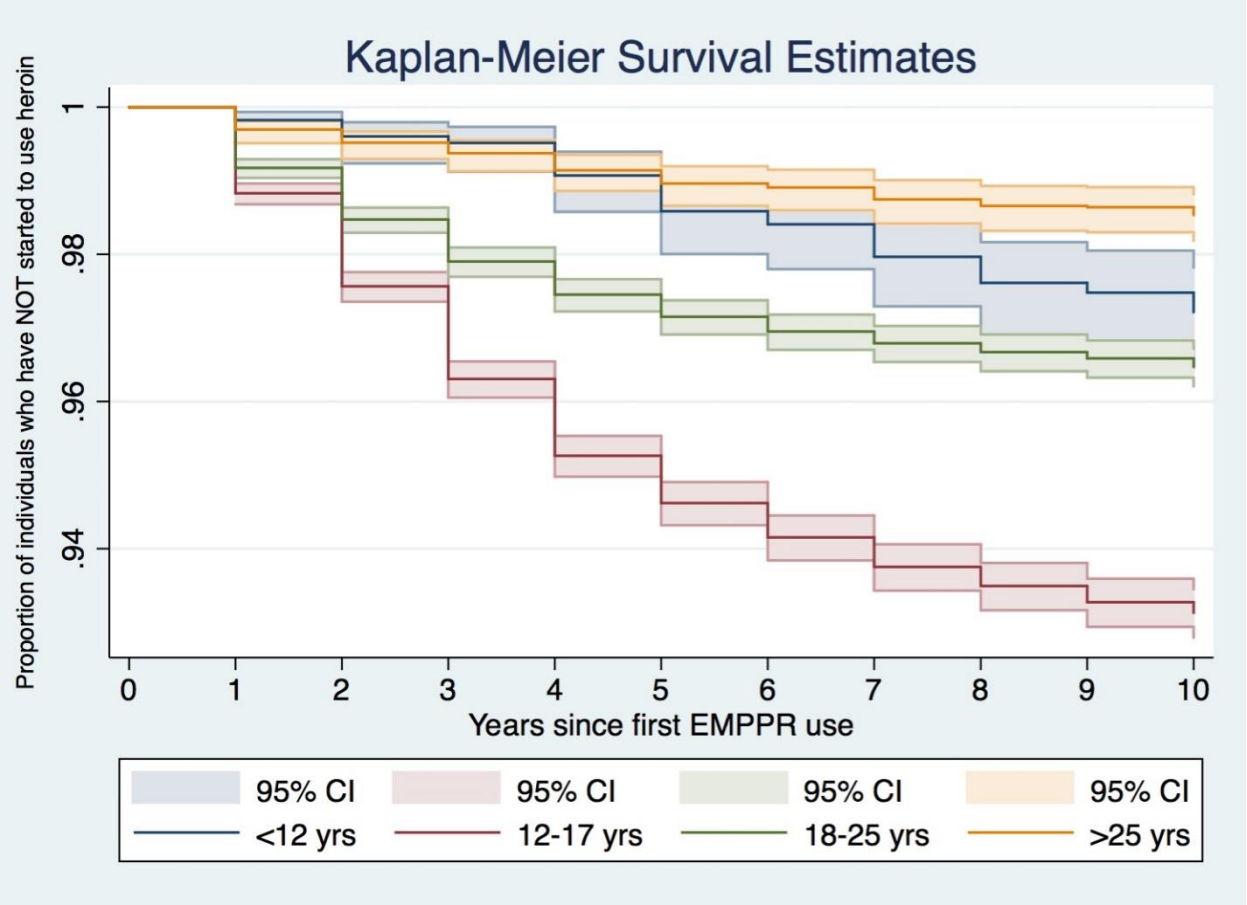


Figure 6.4.5 Kaplan-Meier survival curves for newly incident EMPPR users 12 years or older who started heroin use, plotted in relation to elapsed time (in years) since year of first EMPPR use. Stratified by **Race/Ethnicity**. Data from the National Surveys on Drug Use and Health (NSDUH), United States, 2008-2014.

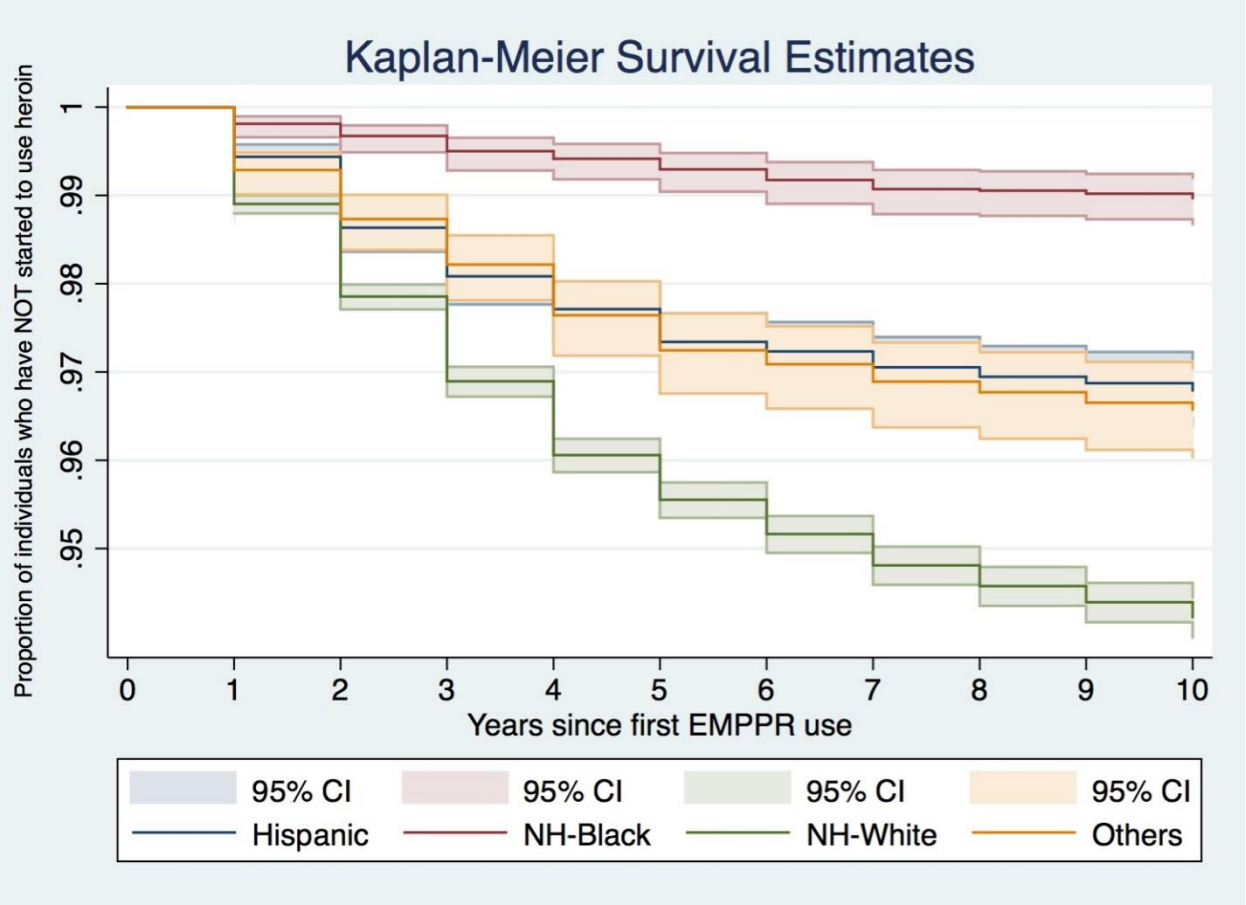


Figure 6.4.6 Estimated hazard functions depict the risk of starting heroin use, plotted in relation to elapsed time (in years) since the year of the first EMPPR use, with contrasts of subgroups (i.e., MET-SUBRUL, sex, age of EMPPR onset, and race/ethnicity). Data from the National Surveys on Drug Use and Health (NSDUH), United States, 2008-2014.

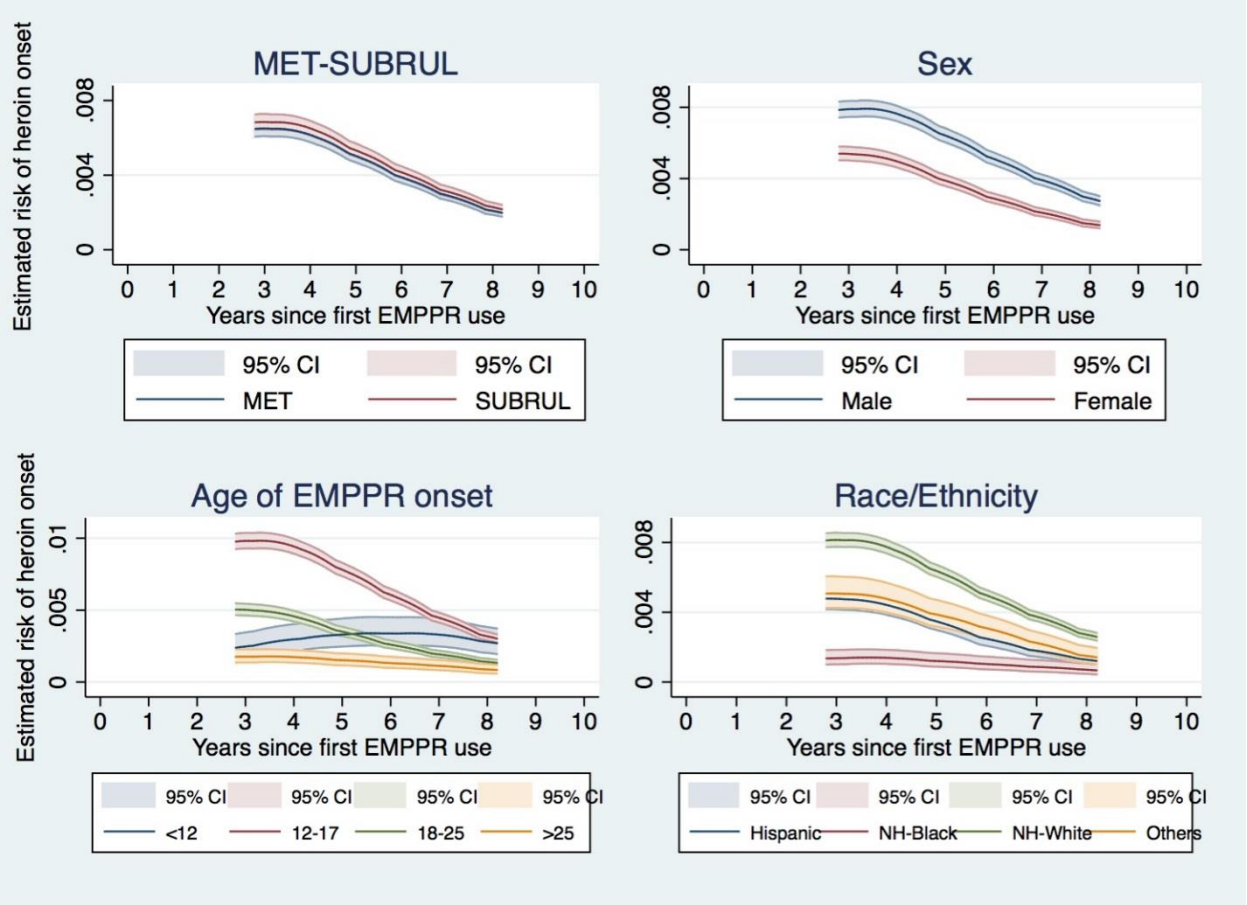


Table 6.4.1 Discrete time data is analyzed in the survival analysis using logic function for each of the time periods. The unadjusted Hazard Ratios (HR) and covariate-adjusted Hazard Ratios (aHR) are estimated with 95% confidence intervals (95% CI). Data from the National Surveys on Drug Use and Health (NSDUH), United States, 2008-2014.

Parameter	Estimates		
	n (%)	HR (95% CI)	aHR (95% CI)
Metropolitan areas [a]			
MET	24,095 (40.07)	Ref.	Ref.
SUBRUL	26,440 (43.97)	1.06 (0.98, 1.15)	0.94 (0.86, 1.02)
Unclassified	9,592 (15.95)	1.03 (0.92, 1.14)	0.89 (0.79, 0.99)
Sex			
Female	28,918 (48.09)	Ref.	Ref.
Male	31,209 (51.91)	1.55 (1.43, 1.67)	1.51 (1.40, 1.63)
Age of EMPPR onset			
<12	2,698 (4.49)	1.74 (1.29, 2.34)	2.08 (1.54, 2.80)
12-17	27,136 (45.13)	4.45 (3.65, 5.42)	4.57 (3.75, 5.56)
18-25	23,661 (39.35)	2.26 (1.84, 2.77)	2.26 (1.84, 2.77)
>26	6,632 (11.03)	Ref.	Ref.
Race/Ethnicity			
Non-Hispanic White	40,922 (68.06)	5.76 (4.45, 7.44)	5.67 (4.39, 7.33)
Non-Hispanic Black	5,811 (9.66)	Ref.	Ref.
Hispanic	8,347 (13.88)	3.15 (2.38, 4.17)	2.93 (2.21, 3.87)
Others	5,047 (8.39)	3.37 (2.51, 4.52)	3.24 (2.42, 4.35)

[a] MET: a metro area contains a core urban area of one million or more populations; SUBRUL: a suburban or rural area contains a core urban area of less than one million populations.

6.5 DISCUSSION

The main findings of this study may be summarized succinctly. Over 10 years, among EMPPR users of age 12 years or older, an estimated 5% initiated heroin use. The peak of the risk of heroin onset is in the third year since first EMPPR use. The population density of the area (MET vs. SUBRUL) is not associated with the transition from EMPPR to heroin use among EMPPR users. However, some factors are associated with heroin onset among EMPPR users such as age of EMPPR onset, sex, and race/ethnicity.

Before detailed discussion of these results, several of the more important study limitations merit attention. This study discloses temporal patterns of heroin onset among EMPPR users. Of central concern is a recall bias in the retrospective self-reported survey between the age of first EMPPR use and age of first heroin use. This bias can be attributed to recall period, age of interview, or other personal characteristics. Memory flaws, confusion, and chronological errors may be present, as suggested elsewhere (Anthony et al., 2000). In this study, the MET-SUBRUL distinction was defined by two variables: (1) Population density identified with CBSA which is a US geographic area defined by the Office of Management and Budget (i.e., Segment in a CBSA with 1 million or more persons, fewer than 1 million, and Segment not in a CBSA), and (2) Urbanicity identified by the categories provided from NSDUH (i.e., large metro, small metro, and non-metro). Therefore, the classification of this variable might not be clear enough to reflect urban or rural areas in the smaller cities or town.

The results of this study from the survival analysis hazard ratio (HR) estimates and survival curves could not help substantiate the idea that population density plays an important role of the transition from first EMPPR use to heroin onset. Hunt's macro-diffusion theory from densely populated areas to less densely populated areas might not work for heroin users in 21st

century who had EMPPR use prior to heroin use (Hunt & Chambers, 1976). The non-significant results of population density might be due to the use of the internet as a source of drugs. Online drug markets and social media are fast-growing trends in contemporary drug consumption. Online drug marketplaces such as 'Silk Road', 'AlphaBay Market' or 'Dream Market' may make drugs more readily available in rural areas (Christin, 2013; Dasgupta et al., 2013; Rhumorbarbe, Staehli, Broseus, Rossy, & Esseiva, 2016; Van Hout & Bingham, 2013; Van Hout & Hearne, 2017). As is the case for social media, internet sources can be used to spread out the information of drug and sale of prescription drugs or illegal drugs as well, such as Craigslist (Tofighi, Perna, Desai, Grov, & Lee, 2016).

However, even though there is no relationship between metropolis status and the shifting from EMPPR to heroin, this study still provides some evidence that characteristics such as non-Hispanic White, male, and early EMPPR onset are associated with the shifting from EMPPR use to heroin onset. These results are convergent with what has been found in previous studies. For example, heroin users have shifted to primarily non-Hispanic White populations (Cicero et al., 2014; Muhuri et al., 2013).

The estimated cumulative probability curves and hazard rate for onset of first heroin use after the year of first EMPPR use may be useful in future investigations of this type because they show a peak of hazard rate of heroin onset at the third year after first EMPPR use. The results may also help clinicians to understand the vulnerable population among EMPPR users, and then helps prevention programs to identify target populations in their primary setting.

CHAPTER 7

FINAL DISCUSSION

7.1 SUMMARY OF FINDINGS

The study in Chapter 4 applies Hunt's back calculation approach to estimate incident cases for heroin and EMPPR use in US. Based on Hunt's model via re-calibration approaches using Treatment Episode Data Set - Admissions datasets (TEDS-A), heroin onset increased 160% from 2000 to its peak in 2010; the incidence rate in 2012 is similar to the first heroin epidemic in 1969. As for opioids other than heroin (e.g., prescription opioids), the incidence increased more than 250% from 2000 to 2010. The study in Chapter 5 investigates whether EM OxyContin® use might have triggered heroin onset among 12-25 year olds between 2004-2014. The excess risk of newly incident heroin use is seen in a four-month interval right after onset of EM OxyContin® use (case-crossover risk ratio = 1.9). Post-estimation exploratory analyses suggest no excess risk for EM users of other prescription pain relievers, and indicate no excess risk correlated with new formulations of OxyContin® per se. In the Chapter 6, the peak risk for transitioning from onset of EMPPR use to heroin onset within 10 years is found at the third year since first EMPPR use. Approximately 5% of participants initiated heroin use in 10 years since EMPPR onset. The estimates of these subgroups remain similar regardless of population density. EM prescription pain reliever users who are male, White, and have early EM prescription pain reliever onset have an increased risk of initiating heroin use.

7.2 LIMITATIONS AND STRENGTHS

In the Chapter 4, Hunt's lag distribution method is used to estimate the incident cases for heroin and EMPPR. However, the change of lag distribution over time from 1950 to 2012 might be a central concern when the averaged value of lag distributions was used to estimate the cases

of truncation. In this study, the median lag year in this study is 9~10 years for heroin and 7~8 years for other opioid compounds and the estimates are similar to other previous studies (Blanco et al., 2015; Judson et al., 1980; Krebs et al., 2016). The lag distribution used in this study to correct the number of heroin incidence cases might be over- or under-estimated; more research is needed on this aspect of the back-calculation. Moreover, there are some limitations with respect to the data source used in this study for the estimates of heroin incidence. TEDS-A is a national census data system of annual admissions to drug treatment facilities in the United States. However, many drug users do not receive treatment (Blanco et al., 2013; Compton et al., 2007; Edlund et al., 2012; Hasin et al., 2007; Kessler et al., 1999; Olfson et al., 1998; Regier et al., 1993; United States. Substance Abuse and Mental Health Services Administration, 2014b; Wang et al., 2005). Based on the dataset of TEDS-A, with only a small proportion of drug users in the treatment program, the numbers of heroin incident cases produced in this study may be under-counts. Even so, the observed patterns of relative heroin incidence over six decades from the first heroin epidemic to the recent heroin epidemic in the 2010s may prove to be valuable evidence and it may help health policy makers planning responses for heroin use in the U.S.

As for weaknesses of using NSDUH datasets in the Chapter 5 and Chapter 6, it should be noted that the NSDUH are cross-sectional surveys. In order to simulate a prospective study and to align temporal sequencing correctly, it has been necessary to turn to NSDUH retrospective data about fine-grained autobiographical details such as the month of drug use onset. Memory flaws, confusion, and chronological errors may be present, as suggested elsewhere (Anthony et al., 2000). Estimates of drug use through national household surveys may involve underreported use because of social pressure or legal consequences of drug use. However, there is evidence on validity and reliability of drug use onset age (United States. Substance Abuse and Mental Health

Services Administration, 2010). Other major advantages from NSDUH are large sample sizes drawn based on a multistage area probability design, and the national representative sample for the entire US civilian population age 12 years and older.

7.3 FUTURE DIRECTIONS AND CONCLUSIONS

The evidence produced in this dissertation research adds to our understanding of heroin epidemiology. It discloses temporal patterns and 'relative' heroin and EMPPR incidence in the past 60 years and it has helped clarify relationships linking EMPPR use with heroin use. The estimates comparing past and recent epidemic years should prompt new thinking about primary prevention, outreach, and treatment resources for heroin users. The results may also help clinicians to understand risks encountered in populations of EMPPR users, which include risks associated with starting heroin use. The results may also help leaders of prevention programs to identify target populations in their primary settings.

CHAPTER 8

CONCLUSIONS

I conclude my doctoral dissertation with a few reflections on this project and what it might mean to future researchers in this area. At the beginning, I concentrated on estimating the incidence of heroin and other opioid compounds to provide empirical evidence on the incidence trend over decades in US history. Factors associated with the transition from extra-medical prescription pain reliever (EMPPR) to heroin use were examined in terms of environmental conditions and individual characteristics thought to be of possible importance for prevention policies or practices, and to future researchers or policy makers in this area.

By the end of the process, I had shifted my attention to the increase of opioid incidence over recent decades for non-heroin opioid compounds such as EMPPR. Moreover, I found the transition probability from EMPPR onset to heroin onset to be greater for some interesting subgroups, especially male EMPPR users and those starting EMPPR use at an earlier age.

For this reason, I will offer no more than a few words about overall conclusions from my research, and the public health challenges faced by anyone who is trying to reduce global health burdens attributed to heroin and other opioids use. First, a recent surge of newly incident opioid users has implications. Considering the lag-time between onset and treatment admission (heroin: 9-10 years; other opioids, 7-8 years), we may face increasing treatment needs. Second, my recommendation is about age of EMPPR onset and risk of 1st heroin use. Here, primary prevention programs are needed, and few prevention researchers now focus specifically on EMPPR use. Finally, I should add that in future research it should become possible to study differences in opioid incidence trends at the state-level or for supra-state geographical regions.

Future research of this type should provide a more a complete understanding of US opioid epidemics of the past and present, setting the stage for better public health work in the future.

APPENDICES

APPENDIX A

THE LIST OF MUSICIANS OF THE ERA WHO DIED FROM HEROIN OR OTHER OPIOID DRUGS OVERDOSE

Table A.1 The list of musicians of the era who died from heroin or other opioid drugs overdose

Musicians	Age of death	Year of death	Overdose drugs
1960s			
Rudy Lewis	27	1964	Heroin
Frankie Lymon	25	1968	Heroin
1970s			
Janis Joplin	27	1970	Heroin
Jim Morrison	27	1971	Suspected heroin
Brian Cole	29	1972	Heroin
Gram Parsons	26	1973	Morphine and alcohol
Zeke Zettner	25	1973	Heroin
Tim Buckley	28	1975	Heroin, morphine, and alcohol
Gary Thain	27	1975	Heroin
Tommy Bolin	25	1976	Heroin, cocaine and alcohol
Elvis Presley	42	1977	Assorted drugs
Gregory Herbert	28	1978	Heroin
Sid Vicious	21	1979	Heroin
Lowell George	34	1979	Heroin
Jimmy McCulloch	26	1979	Morphine
1980s			
Darby Crash	22	1980	Heroin
Tim Hardin	39	1980	Heroin
Mike Bloomfield	37	1981	Heroin
Pete Farndon	30	1983	Heroin
Paul Gardiner	25	1984	Heroin
Gary Holton	33	1985	Morphine and alcohol
Phil Lynott	36	1986	Heroin
Paul Butterfield	44	1987	Heroin
Jesse Ed Davis	43	1988	Heroin

Table A.1 (cont'd)

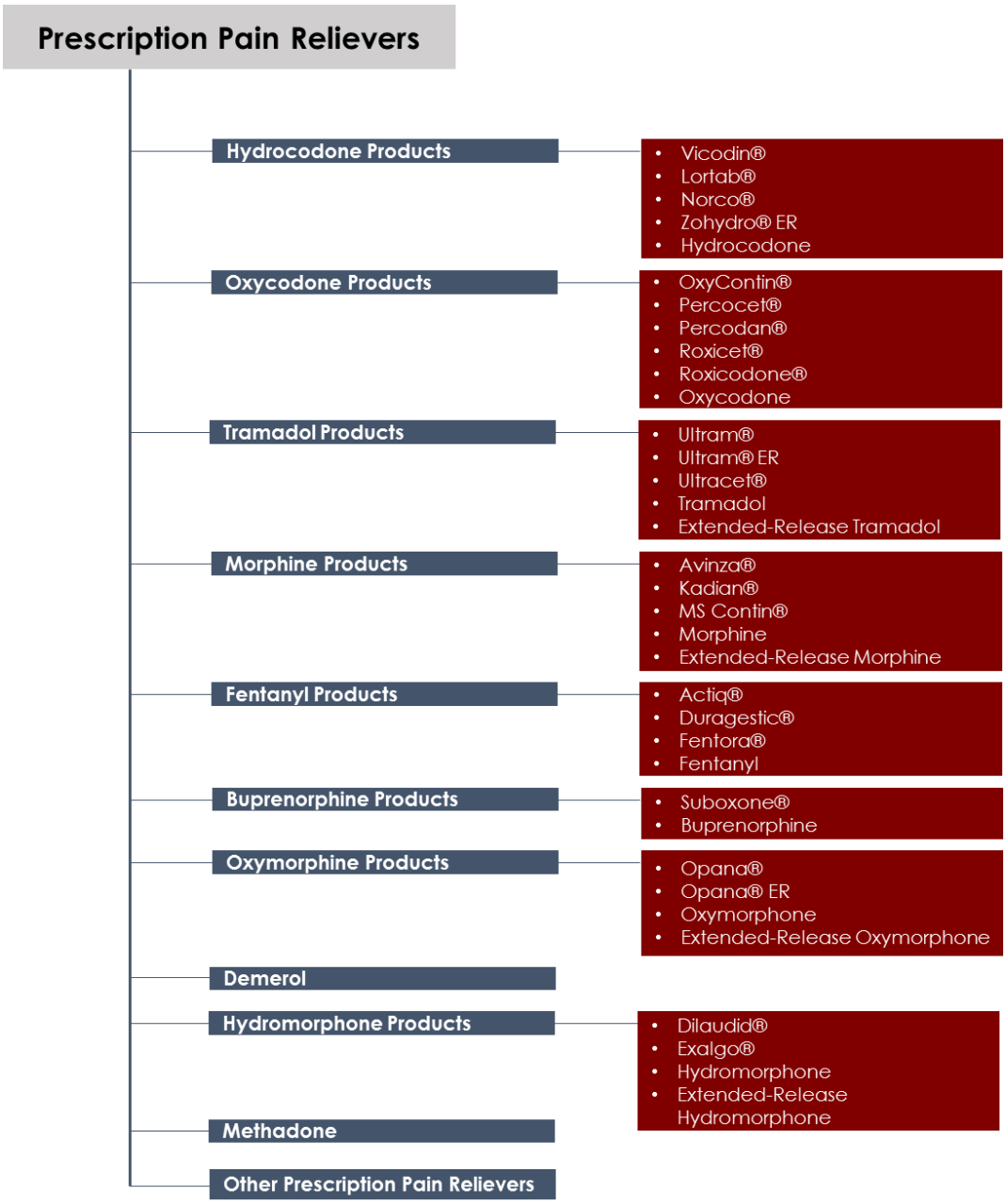
Musicians	Age of death	Year of death	Overdose drugs
1990s			
Andrew Wood	24	1990	Heroin
Iosu Expósito	31	1992	Heroin
River Phoenix	23	1993	Heroin and Cocaine
Dave Rubinstein	29	1993	Heroin
Rob Jones	29	1993	Heroin
Kurt Cobain	27	1994	Suicide while high on heroin
Kristen Pfaff	27	1994	Heroin
Dwayne Goettel	31	1995	Heroin
Bradley Nowell	28	1996	Heroin
John Kahn	48	1996	Heroin
Jonathan Melvoin	34	1996	Heroin
West Arkeen	36	1997	Opiate
Nick Traina	19	1997	Heroin
John Baker Saunders	44	1999	Heroin
David McComb	37	1999	Heroin
2000s			
Allen Woody	44	2000	Heroin
Joachim Nielsen	36	2000	Heroin
Dee Dee Ramone	50	2002	Heroin
Robbin Crosby	42	2002	Heroin
Howie Epstein	47	2003	Heroin
Jeremy Michael Ward	27	2003	Heroin
Tim Hemensley	31	2003	Heroin
Robert Quine	61	2004	Heroin
Gidget Gein	39	2008	Heroin
Jay Bennett	45	2009	Fentanyl
2010s			
Paul Gray	38	2010	Morphine and Fentanyl
Mikey Welsh	40	2011	Heroin
Dave Brockie	50	2014	Heroin
Prince	57	2016	Fentanyl

Source: Wikipedia: List of drug related deaths, accessed on 27 July 2017.
https://en.wikipedia.org/wiki/List_of_deaths_from_drug_overdose_and_intoxication

APPENDIX B

THE LIST OF PRESCRIPTION PAIN RELIEVERS FROM NATIONAL SURVEY ON DRUG USE AND HEALTH (NSDUH)

Figure B.1 The list of prescription pain relievers from NSDUH

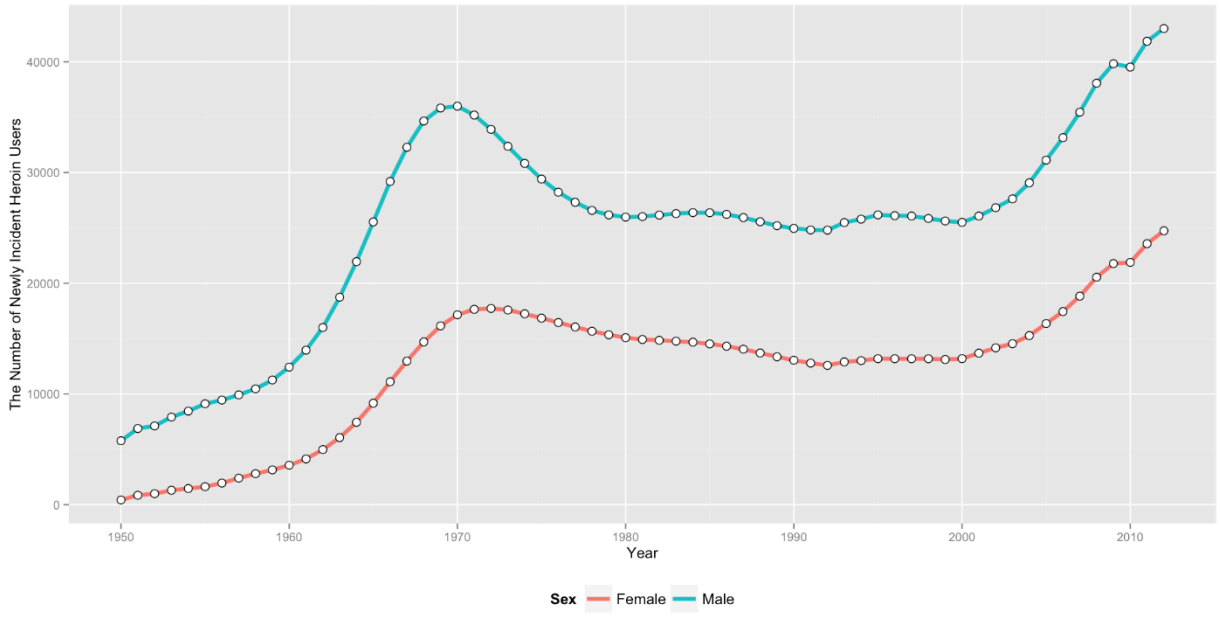


Adapted from Substance Abuse and Mental Health Services Administration (SAMHSA) (https://www.samhsa.gov

APPENDIX C

THE ESTIMATED NUMBERS OF NEWLY INCIDENT HEROIN USERS BY HUNT'S METHOD DURING 1950-2012 FOR MALE AND FEMALE

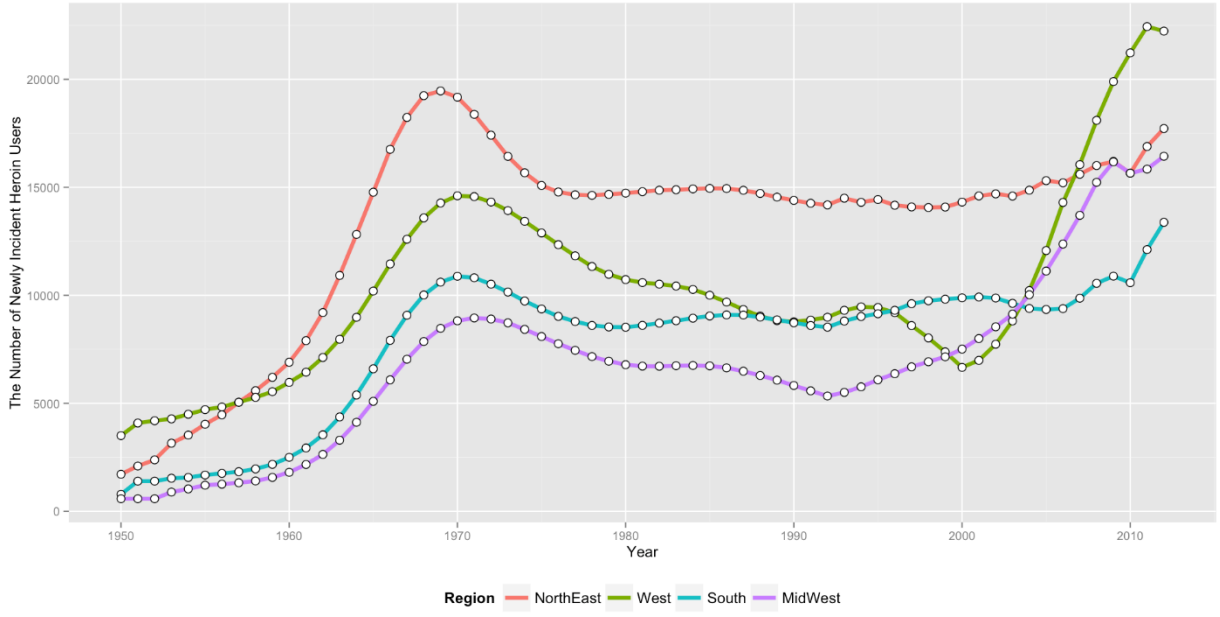
Figure C.1 The estimated numbers of newly incident heroin users by Hunt's method during 1950-2012 for male and female. Data from United States, Treatment Episode Data Set - Admissions, 1992-2012.



APPENDIX D

THE ESTIMATED NUMBERS OF NEWLY INCIDENT HEROIN USERS BY HUNT'S METHOD DURING 1950-2012 FOR FOUR REGIONS (i.e., NORTHEAST, MIDWEST, WEST, SOUTH)

Figure D.1 The estimated numbers of newly incident heroin users by Hunt's method during 1950-2012 for four regions (i.e., Northeast, Midwest, West, South). Data from United States, Treatment Episode Data Set -Admissions, 1992-2012.



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