ESSAYS ON THE OPIOID CRISIS

by

Estrella R. Ndrianasy

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor in Philosophy in Economics

Middle Tennessee State University
August 2019

Dissertation Committee:

Dr. Charles L. Baum, II, Chair

Dr. Michael Roach

Dr. Keith J. Gamble

I dedicate this research to my husband, Christopher Shay, my mother, Celestine Nesizafy, my late father, Jackson Ndrianasy, my stepfather Henri Isidore Ratsimbazafy, and my siblings: Loyola, Dianna, Jessica, Anelka, and Mami.

I love you all.

ACKNOWLEDGMENTS

"Ny hazo no vanon-ko lakana, ny tany naniriany no tsara" is a Malagasy proverb meaning an achievement stems from the effort of many.

I humbly and gratefully acknowledge the support and guidance of my family, my professors, and my peers. Without them, I would not have been able to fulfill this dream of mine. First and foremost, I would like to thank my husband, Christopher Shay. Thank you for your sacrifices, your patience, but most of all thank you for believing in me when I did not. I also would like to thank my mother, Celestine Nesizafy, and my father, Jackson Ndrianasy, for your love and your passion for learning. You made me what I am today. Thank you to our families for their unwavering love and support throughout this long and arduous process. I would also like to acknowledge and thank Dr. E. Anthon Eff. Your extensive guidance and ever present words of encouragement were greatly appreciated. You rock, Sir. Thank you, Dr. Bichaka Fayissa, Dr. Mamit Deme, and Dr. Murat Arik for always pushing me beyond my limits.

To my dissertation committee, Dr. Charles L. Baum, Dr. Michael Roach, and Dr. Keith J. Gamble, thank you for guidance and pushing me to finish when it looked like I was not. I am indebted to Dr. Baum for his guidance and patience. Thank you, Dr. Michael Roach, for working through ideas with me and encouraging me to have a passion for research. Thank you, Dr. Keith Gamble for your kind words and help. Finally, I would like to thank the members of the Middle Tennessee State University Economics and Finance department who have been instrumental in making my graduate career possible. Thank you Dr. Adam Rennhoff, Dr. Joachim Zietz, Dr. Mark Owens, Dr. Jason DeBacker, Dr. Karen Mulligan, Dr. Stuart Fowler, Dr. Gassem Homaifar, Dr. Frank Michello, Dr. Aaron Gamino, and Chad Carter. You all made this happen.

ABSTRACT

This dissertation consists of three separate chapters, each providing an empirical analysis on various aspects of the opioid crisis in the United States. Each chapter is a separate article.

The opioid epidemic has claimed tens of thousands of lives across the U.S. since the early 2000s. It is currently the leading cause of drug overdose deaths prompting lawmakers to adopt several opioid-related policies. Chapter I looks at the impact of Naloxone Access Laws on opioid overdose deaths, treatment rehabilitation admissions, and the legal supply of controlled substances. These laws allow a layperson to use Naloxone (Narcan) in the event of an opioid overdose without fear of criminal, civil, or professional immunity prosecution. This study looks at whether the availability of Naloxone and immunity encourages riskier behaviors among addicts. Specifically, the laws may act as a safety net leading to moral hazard. The analysis uses a conditional panel fixed-effects and propensity score matching methods to ascertain the potential for moral hazard. The data used is a combination of panel data aggregated at the state level from the Treatment Episode Data Set, the Multiple Cause of Death, the Automation of Reports and Consolidated Orders System, and the Annual Social and Economic Supplement surveys. The paper finds no evidence for moral hazard stemming from the availability of Naloxone Access Laws on all outcomes of interest. However, concurrent opioid policies such as Prescription Drug Monitoring Programs and Good Samaritans laws are shown to be effective in increasing treatment rehabilitation admissions and reducing overdose deaths.

Chapter II looks at another opioid related policy, the Prescription Drug Monitoring Programs and its mandatory query requirements. Among others, these initiatives

required primarily physicians and pharmacists to query into a patient's health records prior to prescribing and/or dispensing opioids. These laws effectively increased the distribution and availability of prescription opioids. This papers posits such restriction might have the unintended effects of turning opioid abusers to illicit but readily available alternatives such as heroin. The analysis uses a conditional fixed effects logit framework and a simple fixed effect regression model to look at the impact of the queries into opioid overdose deaths from the Multiple Cause of Death data set. States requiring both prescribers and dispenser to query health records see an increase in heroin and methadone deaths but see a decrease in other synthetic narcotics. States with prescribers only requirements see a decrease in heroin deaths and no impact on other types of opioids. Therefore, the study finds mixed evidence on substitution to heroin from prescription opioids due to mandatory query requirements.

Chapter III analyzes the rural-urban difference in the impact of the opioid crisis. Rural areas in the U.S., and particularly in the Appalachian region, are found to be disproportionately affected by the epidemic. The analysis uses the Multiple Cause of Death overdose deaths to compare opioid overdose deaths in a conditional fixed effects model to empirically quantify this phenomenon. It also controls for the OxyContin Reformulation of 2010 which was heavily marketed in rural areas including Appalachia. States located in Appalachia are found to have a significantly higher rate of heroin and methadone mortality whereas the reformulation led to an increase in other opioids and other synthetic narcotics fatalities.

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

CHAPTER I: THE OPIOID CRISIS: NALOXONE ACCESS LAWS AND MORAL HAZARD

CHAPTER II: : PRESCRIPTION DRUG MONITORING PROGRAMS MANDATORY QUERY REQUIREMENTS: OPIOIDS MISUSE AND SUBSTITUTION TO HEROIN

CHAPTER III: OPIOID OVERDOSE DEATHS IN APPALACHIA: A RURAL-URBAN EMPIRICAL ANALYSIS

LIST OF FIGURES

Page

CHAPTER I: THE OPIOID CRISIS: NALOXONE ACCESS LAWS AND MORAL HAZARD

CHAPTER I:

THE OPIOID CRISIS: NALOXONE ACCESS LAWS AND MORAL HAZARD

1 Introduction

The opioid epidemic is prevalent in the U.S. claiming over 60,000 lives in 2016. It is the number one drug killer in the US surpassing cocaine and methamphetamine [Wonder, 2017]. The opioid crisis is fueled by misuse and abuse of prescription pain relievers. Oftentimes, the addiction starts with legitimate needs for pain relievers whose euphoric effects can quickly turn into dependency. Once addicted, the abuser may seek more opioids through "doctor-shopping" wherein they attempt to obtain more of the drugs through multiple prescribers. Diversion of friends and family's non-medical prescription opioids is a common route of obtaining the drugs. Various measures such as Prescription Drug Monitoring Programs, insurance and pharmacy benefit manager strategies, state legislation, clinical guidelines, safe storage and disposal, and naloxone distribution were put in place to prevent doctors from over-prescribing opioids or patients from abusing opioids [Haegerich et al., 2014]. Most of the measures were supply-side interventions with the intent of cutting off an addict's access to the substance, resulting in the substitution to other less restrictive but oftentimes more dangerous alternatives like heroin [Alpert et al., 2017]. Naloxone distribution measures target existing drug consumers, their friends and families, and service providers and educate them overdose risk factors, signs of overdose, appropriate response and administration. The administration of Naloxone Hydrochloride (naloxone) reverses an opioid overdose and can prevent death. Naloxone is an opioid receptor antagonist that can be administered via intramuscular, intravenous, and intranasal routes. It works by displacing opioid agonists, such as heroin or oxycodone, from opioid receptors [Doe-Simkins et al., 2009]. Naloxone is a relatively inexpensive medication with a price tag between $20 to $40 and can also be obtained at no cost from overdose prevention programs in 2016 and works within mere minutes, with prior allergic reaction as the only contraindication [Illinois, 2017]. Most importantly, naloxone has no effect in the absence of opioid consumption. Without any agonist properties, it has no potential for abuse and minimal likelihood for diversion or misuse [Heller and Stancliff, 2007]. Naloxone is a prescription drug, but not a controlled substance, making its prescription legal whereas its dispensing by medical professional at the point of service is subject to varying state rules. As of July 2017, all fifty states and the District of Columbia have a form of NALs to prevent unintentional drug overdose deaths. Generally, NALs remove some form of criminal, civil, and professional liabilities for prescribers, dispensers, and laypersons.

This paper explores naloxone's potential for moral hazard on opioid misuse and abuse. Even when accounting for timing differences in passing NALs, the number of prescription opioids and heroin overdose deaths have increased alarmingly in the past decade and a half lending credibility to the likelihood of riskier drug consumption in the presence of naloxone as a safety net. Plausible unintended effects of NALs are increased consumption of opioids resulting in drug rehabilitation treatments and accidental overdose deaths, or even an increased supply of the substance. Overall, this paper extends the literature by looking at the unintended effects of NALs, a public health effort intended to reduce the effects of the rampant opioid epidemic. The literature hails NALs as successes whereas the evidence suggest an ever increasing trend in opioid deaths, particularly heroin. This study attempts to provide an insight into the crisis while allowing for a national level analysis, and also provide a basis for comparison with the previous community and city level assessments for smaller pilot prevention programs from the early and mid 2000s found in the literature. The paper will be divided into the following sections: literature review, identification strategy, data description, results analysis, and discussion. Overall, the results show no support for the presence of moral hazard with regards to overdose deaths nationally, treatment rehabilitation admissions, and the legal supply of opioids.

2 Literature Review

NALs are widely depicted as successful policies in the fight against the opioid epidemic in the literature. Various pilot programs were implemented in large metropolitan areas in the early 2000s resulting in a reduction of unintended opioid overdose deaths by as much as nine per cent in New York City [Heller and Stancliff, 2007, Worthington et al., 2006] to a high of 20% in Chicago in 2001 [Maxwell et al., 2006]. Other programs such as the Project Lazarus in Wilkes County, North Carolina, led a significant drop of opioid overdose mortality from a high of 46.6 to 29 per 100,000 inhabitants in just one year in 2010 [Albert et al., 2011]. Naloxone distribution programs in other cities such as San Francisco DOPE program in 2010 led to a greater awareness of the benefits provided by NALs [Straus et al., 2013]. The initiative also led to a take-back initiative by the Drug Enforcement Administration in 2012, where 520 tons of unwanted or expired medication were disposed off by the public. The city of Baltimore, Maryland, enacted a similar prevention program called Staying Alive resulting in 22 successful overdose reversals performed by 19 out of 43 individuals recruited through street-based outreach and advertising [Tobin et al., 2009]. Chicago's own program also led to a 20% decrease in heroin overdoses in 2001, followed by a 10% decrease for 2002 and 2003, respectively through the distribution of 3,500 naloxone vials resulting in over 300 overdose reversals [Maxwell et al., 2006]. Overall, naloxone overdose prevention programs have overwhelmingly reported positive outcomes of successful opioid overdose reversals via peer administration of naloxone [Dettmer et al., 2001, Worthington et al., 2006, Maxwell et al., 2006, Sporer and Kral, 2007, Mueller et al., 2015].

There were more than 64,000 drug overdose deaths estimated in 2016, with the largest increase stemming from synthetic opioids such as fentanyl and fentanyl analogs with over 20,000 deaths [Wonder, 2017]. Heroin and natural and semi-synthetic opioids were second and third in number of drug deaths with 15,446 and 14,427 respectively. Another opiate, methadone, was the sixth highest killer with over 3,000 deaths, preceded by cocaine and methamphetamine. In the early 2000s, several studies have documented the effects of NALs on reducing the number of opioid deaths in small pilot programs in large cities in the U.S and the world [Maxwell et al., 2006, Heller and Stancliff, 2007, Kerr et al., 2008, Piper et al., 2008, Tobin et al., 2009, Doe-Simkins et al., 2009, Albert et al., 2011, Wheeler et al., 2012]. The success of NALs is closely tied to a bystander's willingness to intervene and adequacy in the administration of naloxone in the event of an overdose. Overall, participants in NALs training program programs have a positive attitude towards peer administration as they feel empowered to help others by reducing mortality and morbidity in minimizing delays to treatment, feel as they contribute in preserving ambulance services for other medical emergencies, and most of all avoid authority involvement [Kerr et al., 2008]. Nonetheless, some literature has suggested the potential for moral hazard from the NALs due to the reduced expected cost of opioid consumption. The unintended effects range from an increased consumption of non-prescription opioids to the transition to harder drugs such as heroin, cocaine, and methamphetamine [Bachhuber et al., 2014, Seal et al., 2003, 2005]. Others look at competing drug laws, such as Medical Marijuana Laws, and find mixed results in subsequent opioid distribution

[Rees et al., 2017, Powell et al., 2015, DiNardo and Lemieux, 2001]. Moreover, some suggest prescription opioids are potential gateway drugs where misuse is considered a key feature of trajectories into injection drug use such as heroin [Lankenau et al., 2012, Fiellin et al., 2013]. These are attributed to opioid overdose victims continuing or increasing drug abuse to alleviate withdrawal symptoms [Seal et al., 2003, Lagu et al., 2006].

Naloxone then becomes a safety mechanism enabling at risk individuals to consume greater amounts of opioids in the absence of consequences [Albert et al., 2011]. Moral hazard may result in increased opioid addiction and overdose deaths, although the literature is fairly inconclusive. In a survey of injection drug users in San Francisco, 35% felt comfortable using greater amounts of heroin in the presence of naloxone while 46% of overdose victims were planning on using heroin again to alleviate withdrawal symptoms [Seal et al., 2003]. The same authors also found reduced heroin consumption later after adequate education and training in overdose reversal, illustrating the mixed nature of the literature [Seal et al., 2005]. Another naloxone distribution program in Providence, Rhode Island, found rare adverse effects whereby the likelihood of getting addicted on heroin actually increased in opioid addicts when symptoms of withdrawals are precipitated, driving them to seek relief in additional substance abuse [Lagu et al., 2006]. Others highlight the potential for naloxone to increase polysubstance abuse, especially the ascension to harder opiates such as heroin using prescription opioids as gateway drugs [Bachhuber et al., 2014, Sporer and Kral, 2007, Kerr et al., 2008]. Additionally, there has been a significant increase in the amount of substances distributed in the U.S., including methadone, heroin, benzodiazepines and barbiturates, cocaine, other opioids, and their related overdoses [Walley et al., 2013, Rees et al., 2017]. Finally, there is some evidence that competing laws such as Medical Marijuana Laws, could have a reducing effect on prescription opioids misuse through a substitution mechanism [Powell et al., 2015, DiNardo and Lemieux, 2001]. Another example of a measure to combat the prescription opioid overdose deaths but yielded much higher heroin fatalities is the OxyContin Reformulation of 2010, which marked the introduction of an abuse deterrent opioid. The reformulation caused an opioid supply disruption that turned drug addicts to much harder substances such as heroin and fentanyl, illicit and dangerous forms of opiates. The measure marginally decreased prescription painkiller fatalities but significantly increased heroin and synthetic opioid (fentanyl) overdose deaths [Alpert et al., 2017]. Some law enforcement entities also have at best a diverging and at worst a skeptical opinion on the effectiveness of NALs, primarily focusing on their perceived enabling potential, especially with regards to immunity from prosecution [Gaston et al., 2009, Banta-Green et al., 2013].

This paper extends the scarce and mixed literature on the unintended effects of NALs. From an economics perspective, the potential issue of moral hazard is important in order to evaluate the practical costs and benefits associated in the implementation of NALs. The moral hazard itself seems to originate from the sense of safety provided by the presence of naloxone, which may cause an opioid addict to continue misusing at his own and society's cost. This analysis follows the literature by looking at the commonly used substance abuse outcomes: treatment/rehabilitation, unintended overdose deaths, and the amount of opioids distributed for all states. The Treatment Episode Data Set (TEDS), the National Vital Statistics System (NVSS) Multiple Cause of Death Mortality deaths, and Automation of Reports and Consolidated Orders System (ARCOS) will be used to conduct the analysis at the state level. The TEDS and NVSS data are maintained by the CDC by the Substance Abuse and Mental Health Services Administration and National Center for Health Statistics respectively. TEDS reports treatment information on addicts seeking rehabilitation.

NVSS records mortality data and their causes among other things. Finally, the ARCOS data is an automated, comprehensive drug reporting system monitoring the flow of DEA controlled substances from their point of manufacture through commercial distribution channels to point of sale. This paper updates the literature by providing a national level analysis on the effects of NALs since most states passed the measure into law in the early 2010s. Previous work focused on small pilot programs limited with small sample size and weaker power for external validity. Moreover, an extension of the difference-in-difference identification strategy, a fixed effects regression model, as well as a propensity score matching framework will be conducted to analyze the impact of NALs on the opioid overdose epidemic.

3 Data

This analysis combines several data sources to look at various outcomes of the opioid epidemic. The Treatment Episode Data Set (TEDS) provides individual state information on the count of individuals seeking opioid addiction rehabilitation from 2000 to 2014. TEDS removes all identifiable information preventing the analysis from capturing individuals seeking treatment across multiple time periods. Each observation is therefore considered unique. The second outcome of interest is opioid overdose deaths coming from the National Vital Statistics System (NVSS) Multiple Cause of Death Mortality data set. The International Classification of Diseases (ICD-10) is used to identify deaths with external causes of injury related to opioid misuse. The ICD-10 codes used for opioids are X40-X44, X60-X64, X85, and Y10-Y14 from years 2000 to 2014. Although the NVSS put restriction on identifying detailed mortality data since 2005, aggregate information on state death count is still available. Finally, the supply of legal controlled substances is analyzed through the Drug Enforcement Agency's statistical reporting arm, the Automation of Reports and Consolidated Orders System (ARCOS) from 2006 to 2014. The ARCOS data is used to look at trends in the supply of legally sold opioids especially in light of the NALs. Information on commonly distributed opioids such as Codeine, Fentanyl, Hydrocodone, Hydromorphone, Meperidine, Oxycodone, Oxymorphone, and Tapendatol are analyzed at the state and national levels. Data on violent and property crimes are obtained through the Uniform Crime Reporting (UCR) system for all years studied. The UCR data is used as a proxy for the required law enforcement resources per state which may be related to its corresponding opioid abuse levels. State demographics data come from the the Annual Social and Economic Supplement (ASEC) portion of the Current Population Survey and is used to provide a background on overall population characteristics. ASEC observations from 2014 are excluded from the analysis due to the Census Bureau's experimental redesign of health insurance questions that affected approximately 3/8ths of the total sample.

3.1 Summary Statistics

The data in table 1 show an average of over 50,000 grams for the most commonly legally distributed opioids over the between 2006 and 2014 across all states for every 100,000 population. In 2018, the CDC provided guidelines on the lowest effective dosages when prescribing opioids, with thresholds equal or greater to 50 morphine milligrams equivalents (MME) per day needing to be carefully assessed, and titration of dosages greater or equal to 90 MME to be avoided or referred to a pain specialist. For reference a 50 MME/day is equivalent to 50 mg of Hydrocodone (10 tablets of Hydrocodone/acetaminophen 5/300), 33 mg of Oxycodone, or 12 mg of Methadone. At the rate of 50 MME/day, the opioid supply average of 50,000 grams translates to prescriptions of over 1 million MME/day of hydrocodone, more than 1.5 million MME/day of oxycodone, and greater than 4.5 million MME/day of methadone on average per 100,000 population in the US for the time period analyzed.

Second, there were on average a little more than 13 opioid overdose deaths in per 100,000 population nationally from 2000 and 2014, with the number still alarmingly rising. These deaths are categorized in ICD-10 as accidental, intentional self-harm, and events of undetermined intents involving poisoning and exposure to noxious substances such as nonopioid analgesics, antipyretics and antirheumatics; antiepileptic, sedative-hypnotic, antiparkinsonism and psychotic drugs (not elsewhere classified); narcotics and psychodysleptics (hallucinogens), not elsewhere classified; other drugs acting on the autonomic nervous system; other and unspecified drugs, medicaments and biological substances. Furthermore, the TEDS data show an average of above 80 opioid rehabilitation admission per 100,000 population in the US between 2000 to 2014. An opioid rehabilitation admission is defined as one where "opiates and synthetics" were reported at admission regardless of whether such substance was primary, secondary, or tertiary. This definition excludes non-prescription Methadone. Admissions involving "opiates and synthetics" were reported in close to 12% of all drug admissions at a count of about 2.2 million, and accounts for 7% of all primary substance abuse in the time period analyzed.

Overall, the Current Population Survey dataset shows a generally higher proportion of whites at about 79% of all survey respondents whereas 11% are of black descent. There are more females than males at 50% compared to 47% of the entire population, of which close to 3 per cent are unemployed. Educational attainment varies among the population with high school graduates holding the largest share at 22% of the general non-institutionalized population. The age categories show an even distribution with each five year bin ranging from 4.3% to 7.5% of all respondents. A relatively few number of respondents report being in fair or poor health while 2.4% suffer from some physical difficulty. Moreover, close to 13% of the population are under the federal poverty level while households earning less than $5,000 annually represent close to 8%. A significant number of respondents benefits from a limited amount of social security income with 63% of the population receiving less than $5,000 per year. Finally, the Uniform Crime Report dataset shows property crime rate to be an average of 3,200 and violent crime at about 410 per 100,000 population, respectively. Property crimes include burglary, larceny, and motor vehicle theft whereas violent crimes are comprised of murder and non-negligent manslaughter, rape, robbery, and aggravated assault.

3.2 Parallel Trends Assumption

The parallel trend assumption asserts the enactment of a policy should have no effect on the trends of the outcome of interests. Specifically, the adoption of NALs should be completely random as to avoid the issue of selection bias. Per figure 1, it is shown the bulk of states passed the laws between 2013 and 2015. The gap between the first state (New Mexico) passing the laws and the few last ones is about 16 years from 2001 to 2017. There seems to be no pattern as to the timing of the adoption of the law, other than a collective movement from 2013 onward where states from all over the country decided to adopt the law at once.There were no documented federal or state incentives to adopt the laws either to the author's knowledge.Due to data limitation, only states that passed NALs in 2013 and 2014 are aggregated to verify the parallel trends assumption for all three outcomes of interests. In figure 2, the states passing NALs in 2013 seem to have steadily followed an upward trend in opioid rehabilitation admission, regardless of policy adoption. Those adopting NALs in 2014 experienced an immediate sharp decline in rehab admission during the year of its policy adoption which then returns to their previous levels. This patterns violates the common trend assumption but provides insight into the potential spillover effects from other states passing NALs in the previous years.

The picture is much of the same in figure 3 for the opioid overdose deaths with steady decline in both years considered, then a particularly large drop occurs followed by an immediate return to its previous levels. It is important to note the opioid deaths might include heroin deaths. The OxyContin reformulation of 2010 reduced the number of all opioid deaths while simultaneously increasing heroin overdoses due to a substitution effect [Case and Deaton, 2015]. The most recent renewed uptick in opioid overdose deaths might be due to the rapidly increasing impact of the deadly fentanyl. Overall, there seems to be little evidence to suggest a common trend. Finally, the total grams of legally distributed opioids follows a steady trend of declining amount prior and after the adoption of NALs in both years considered, as seen in figure 4. There is generally a decrease in the legal supply of opioid that can be due to physicians prescribing less painkillers due to the various laws restricting their ability to do so, especially the PDMPs. The CDC also advises alternative approaches in treating pain and heavily monitoring the allowable dosage of opioids for treatment to 50 MME or 90 MME/day. In this case, the common trend assumption seems plausible.

4 Identification Strategy

4.1 Fixed Effects Model

A standard difference-in-difference (DID) setup is inadequate for instances where there are multiple time periods and multiple groups. An expansion of the standard DID is possible by including time and individual or group fixed effects. Moreover, the variation in treatment timing is exploited to get a glimpse of the effects of the policy implementation. The expanded regression model is as given below:

$$Y_{st} = year_t + state_s + \beta Naloxone_{st} + \theta X_{st} + \epsilon_{st} \tag{1}$$

where Y_{st} is opioid rehabilitation admissions, overdose deaths, or the legal supply in state s and year t, $year_t$ is the year fixed effect, $state_s$ is the individual state fixed effect, $Naloxone_{st}$ is a dummy equal to one if a state adopted NALs and 0 otherwise, X_{st} is a vector of individual state covariates including other relevant drug related policies, ϵ_{st} is an error term. β is the causal effect of interest and is interpreted as the average treatment effect of the adoption of Naloxone laws. The fixed-effect construct aims to reduce the omitted variable bias unaccounted for within the states such as differing demographics, prevalence of drug consumption, or the existence of pill mills affecting the supply of opioids. The identifying assumption relies on variations in opioid abuse and its corresponding predictors to be time-invariant. Moreover, it is important that changes in within state factors affecting drug abuse are uncorrelated with the state's decision to adopt the Naloxone Access Laws. In other words, the decision to adopt a Naloxone law may be endogenous. The potential for endogeneity is tentatively alleviated through the preliminary fixed-effect model. This preliminary model assumes endogeneity due to omitted variable is removed or at the very least reduced for interpretable results.

4.2 Propensity Score Matching

The interpretation of NALs effect is complicated by the wide variation of states with regards to their characteristics and the timing of the law's adoption. The inherent differences between states, included but not limited to the severity of their opioid epidemic, acts as a critical factor in their decision to adopt NALs and other measure combating the crisis. This introduces biases in the interpretation of law's effect at best and impossible at worst. The core of the issue lies in creating appropriate treatment and control states. Simply put, a state's decision to adopt NALs is endogenous to its specific opioid problem. Assuming that the opioid issue arises from a combination of observable and unobservable factors within the state, a matching method can be utilized to create treatment and control groups by relying not only on the timing of the NALs adoption but on its characteristics. A common method widely used in the literature is propensity score matching where states are matched into control and treatment groups based on their observable characteristics. This method seeks in part to alleviate the issue of common trend when comparing states before and after the adoption of a policy.

Each observation's propensity score derives from the conditional or predicted probability of receiving treatment given pre-treatment characteristics. In this case, each state is given a propensity score on their likelihood to adopt the NALs given their characteristics. States are assigned to control and treatment groups based their population characteristics, adoption of other opioids laws such as PDMPs and GSLs, and crime rates. Following Callaway and Sant'Anna [2018], the standard DID construct with two time periods and no treatment in period 1 is extended to multiple time periods. Let $t = 1, ..., \tau$ represent individual time periods for each year analyzed, NAL_t denotes a binary variable equal to one if a state is treated at year t and zero otherwise. Furthermore, let NAL_g be a binary variable denoting a state that is first treated at year g, while C is a binary variable accounting for states that are never treated at any point in time. Each state will have exactly one of either NAL_g or C equal to one, depending on whether it is receives treatment or not. The generalized propensity score $p_g(X)$ indicates the probability of a state being treated conditional on having covariates X and conditional on being treated or not. Following, the generalized propensity score for multiple time periods and multiple states is defined as:

$$p_g(X) = prob(NAL_g = 1|X,\, NAL_g + C = 1) = \mathbb{E}(NAL_g|X,\, NAL_g + C = 1) \quad (2)$$

The treatment outcomes are defined as $Y_t = \begin{cases} Y_t(1) & \text{if NA}L_t\text{=1} \\ Y_t(0) & \text{otherwise} \end{cases}$

The observed outcome in each year t is $Y_t = NAL_t Y_t(1) + (1 - NAL_t)Y_t(0)$. The actual treatment effect is some part of the previous function as a state cannot be simultaneously a treatment and a control. For a standard DID, the average treatment effect is the difference between treated and control, which becomes a simple t-test between both groups. In the case of multiple group and time periods, the "group average treatment effect" at time t for states first treated at year g is expressed as in Callaway and Sant'Anna [2018] as:

$$ATE(g,t) = \mathbb{E}[Y_t(1) - Y_t(0)|NAL_g = 1] \quad (3)$$

Furthermore, it is assumed that $\{Y_{s1},\, Y_{s2}, ...,\, Y_{s\tau},\, X_s,\, NAL_{s1},\, NAL_{s2}, ...,\, NAL_{s\tau}\}_{s=1}^{n}$ is independently and identically distributed. The outcomes are assumed to be independent of selection into treatment conditional on a state characteristics, i.e. treatment is exogenous. Also, the conditional parallel trend states that control and treatment observations would have followed similar trends in the absence of treatment given state characteristics X. The average outcomes for groups first treated at year g and control observations are assumed to have parallel trends at year g and any other subsequent time periods, conditional on covariates X which will be time specific.

$$\mathbb{E}[Y_t(0) - Y_{t-1}(0)|X,\, NAL_g = 1] = \mathbb{E}[Y_t(0) - Y_{t-1}(0)|X,\, NAL_g = 0]$$

The irreversibility of treatment condition assumes that once treated, a state will be treated in the next time period. That is $NAL_t = 1$implies that $NAL_{t+1} = 1$ for time periods $t = 2, ..., \tau$. The overlap or matching condition assumes that for each value of X, there are both treated and control observations. Specifically, there will be a positive number of observations that will be treated in period g and that there is concurrently a positive probability that an individual is not treated given state covariates X. For all $g = 2, ..., \tau$, it is assumed that $p(NAL_g = 1) > 0$ and $0 < p_g(X) < 1$ states that there is a matched control observation with similar X. Finally, the balancing condition states that assignment to treatment is independent of the X covariates, given the same propensity score between different observations.

5 Results

5.1 Fixed-Effects Regression

The effects of NALs are insignificant with regards to opioids rehabilitation admissions, overdose deaths, and the legal supply available for consumption as seen in . NALs have a negative although insignificant impact on opioid rehabilitation admissions as seen in table 2. This result is consistent across various model specifications. These findings are on par with the literature where various opioid driven policies have no impact on admission into rehabilitation. One plausible explanation is the lack of information on what drives an addict to seek help. The vast majority of patients were admitted through court referrals and thus were involuntary. Second, the limits on Medicaid reimbursements for behavioral health an substance abuse treatment is a deterrent to admitting patients needing help, thus effectively under-reporting the total numbers of addicts impacted by NALs with non-fatal overdoses reversed by Naloxone for instance. Essentially, the data on opioid rehabilitation admissions fails to reflect the actual extent of the epidemics. However, the PDMPs are strongly and positively correlated with opioids treatment admissions. Adopting PDMPs lead to around 13 additional rehabilitation admissions per 100,000 population in the full model and partial model including NALs and PDMPs only.

The results in table 2 also show NALs have no significant effect on opioid overdose deaths. These findings are consistent with the literature which finds unclear results on the impact of policy intervention on prescription opioids abuse outcomes [Meara et al., 2016]. There is some evidence that concurrent laws, such as PDMPs, have a significant and negative effect on opioid overdose deaths. In this analysis, PDMPs significantly reduces the count of opioid overdose deaths by 0.8 per capita. These findings are consistent across different specifications that include other opioid-related policies. Therefore, the fixed-effects findings provide little confirmation on the the hypothesis of moral hazard, here an increase in opioid overdose deaths, due to the implementation of NALs. These results might be due to fatal opioid overdoses being an unsuitable measure for the effectiveness of naloxone given that is is an overdose reversal drug. In fact, an growth in the number of non-fatal opioid overdose deaths would be more appropriate in measuring increased use of naloxone which is the moral hazard issue of interest. Furthermore, the degree of accessibility to naloxone and the general public's ability to effectively use the drug might be factors in NALs being insignificant in the results.

Finally, table 2 illustrates how the implementation of NALs has no impact on the legal supply of opioids. The GSLs however are significant and decrease the legal supply of opioid by an amount of about 3,000 grams to 4,000 grams per 100,000 population. In a scenario of 50 MME/days dosages, NALs resulted in per capital prescriptions of between 60,000 and 80,000 of hydrocodone, between 91,000 and 120,000 of oxycodone, and between 250,000 to over 330,000 of methadone during the time period analyzed.

Year and state fixed effects were used to mitigate issues of linear trends. This decrease might be due to the recent shift away from prescribing precription painkillers in the treatment of pain as was the trend since the mid-nineties. Moreover, competing laws such as Medical Marijuana Laws are causing a shift away from opioids to other substances with far lesser negative effects. More detailed results can be found in table 4 through table 9 located in the appendix.

5.2 Propensity Score Matching

The propensity score results in table 3 match some of the fixed effects regression models although they are of much larger magnitudes. The average treatment effects via various matching techniques are found after randomly assigning treatment and control groups for the states analyzed. The results suggest NALs have a negative but insignificant effect on opioid rehabilitation and fatal overdoses. This could stem from addicts being able to maintain harmful habits by resorting to naloxone injection in the event of an emergency or the laws being ineffective in preventing addictive behaviors. Namely, naloxone is used in lieu of treatment in order to survive an overdose. The matching technique fails to confirm the moral hazard hypothesis. Finally, table 3 also shows NALs having a negative and significant impact on the legal supply of opioid, unlike the previous model.

6 Discussion

There is no evidence of moral hazard stemming from the adoption of Naloxone Access Laws. Various techniques show NALs being of no impact to rehabilitation treatment admissions, overdose deaths, and the legal supply of opioids. The lack of information on the cause for seeking addiction treatment is a data limitation. There are also no information on the degree of access to naloxone for each state, preventing the study from knowing whether an attempt was made to reverse an overdose. Given that the administration of naloxone is a reactionary measure to an overdose, the link between NALs and opioid rehabilitation admission seems therefore unlikely as emergency treatment is the direct response to a non fatal overdose rather than rehabilitation. This issue is further exacerbated by government reimbursement restrictions for substance abuse treatment and the social stigma associated with addiction. A bipartisan bill known as the Medicaid Coverage for Addiction Recovery Expansion Act was introduced in 2017 to ease the restrictions on Medicaid reimbursements for substance use disorder treatment centers with up to 40 beds for stays of up to 60 consecutive days.

The moral hazard hypothesis seems implausible or at least very week. First, the establishment of causality between possession of naloxone and an addict's decision to undertake riskier behavior is impossible to determine without case by case evidence. However, the growing trend of overdose deaths coinciding with the implementation of NALs suggest a strong correlation. This study suggests that amid the broader opioid crisis and its plethora of factors, NALs may regardless carry a non-negligible responsibility in its worsening. Opioids overdose deaths occur in either the absence of naloxone, dangerously high level of opioid consumption, or lack of knowledge on the appropriate use of naloxone. To prevent more deaths, there needs to be more education on the use and limitations of naloxone. Initiatives such as Syringe Services Programs widely known as needle exchange programs (NEPs) providing medically supervised and safer consumption sites are a step in the right direction in empowering people suffering from addiction. The Centers for Disease Control and Prevention also supports such community efforts by providing federal funding to state and local communities via the Consolidated Appropriations Act of 2016.

Finally, the growing supply of legally distributed opioids in relation to the enactment of NALs is cause for concern. The more opioid is available, the more opportunities there are for misuse. The safety net of naloxone might encourage more doctor shopping to increase consumption. Take-back initiatives such as the Drug Enforcement Administration's National Prescription Drug Take Back Day programs to safely dispose of drug are opportunities to reduce the supply of legally available drugs, and hopefully reduce the need for naloxone in the event of a drug overdose. Furthermore, regulations aimed at prescribers to curb over prescription of opioids could greatly impact the epidemic. In the future, research on NALs can be extended by looking separately at the components of the law, specifically the level of liability protection afforded by the law. More insight can be gleaned from understanding the differences in the criminal, civil, or professional immunity the law provide, especially with states varying widely in their restrictions. NALs might have a differential impact on laypersons, prescribers, and dispensers of the opioid antagonist that could paint a very different picture of the opioid epidemic.

References

Albert, Su, Brason, II, Fred, W, Sanford, Catherine K, Dasgupta, Nabarun, Graham, Jim, & Lovette, Beth. 2011. Project Lazarus: Community-based overdose prevention in rural North Carolina. *Pain Medicine*, **12**(s2).

Alpert, Abby, Powell, David, & Pacula, Rosalie Liccardo. 2017. *Supply-side drug policy in the presence of substitutes: Evidence from the introduction of abuse-deterrent opioids*. Tech. rept. National Bureau of Economic Research.

Bachhuber, Marcus A, Saloner, Brendan, Cunningham, Chinazo O, & Barry, Colleen L. 2014. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Internal Medicine*, **174**(10), 1668–1673.

Banta-Green, Caleb J, Beletsky, Leo, Schoeppe, Jennifer A, Coffin, Phillip O, & Kuszler, Patricia C. 2013. Police officers and paramedics experiences with overdose and their knowledge and opinions of Washington state drug overdose-naloxone-Good Samaritan law. *Journal of Urban Health*, **90**(6), 1102–1111.

Callaway, Brantly, & Sant'Anna, Pedro H. C. 2018 (Mar.). *Difference-in-Differences with Multiple Time Periods and an Application on the Minimum Wage and Employment*. DETU Working Papers 1804. Department of Economics, Temple University.

Case, Anne, & Deaton, Angus. 2015. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proceedings of the National Academy of Sciences*, **112**(49), 15078–15083.

Dettmer, Kerstin, Saunders, Bill, & Strang, John. 2001. Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes. *BMJ*, **322**(7291), 895–896.

DiNardo, John, & Lemieux, Thomas. 2001. Alcohol, marijuana, and American youth: the unintended consequences of government regulation. *Journal of Health Economics*, **20**(6), 991–1010.

Doe-Simkins, Maya, Walley, Alexander Y, Epstein, Andy, & Moyer, Peter. 2009. Saved by the nose: bystander-administered intranasal naloxone hydrochloride for opioid overdose. *American Journal of Public Health*, **99**(5), 788–791.

Fiellin, Lynn E, Tetrault, Jeanette M, Becker, William C, Fiellin, David A, & Hoff, Rani A. 2013. Previous use of alcohol, cigarettes, and marijuana and subsequent abuse of prescription opioids in young adults. *Journal of Adolescent Health*, **52**(2), 158–163.

Gaston, Romina Lopez, Best, David, Manning, Victoria, & Day, Ed. 2009. Can we prevent drug related deaths by training opioid users to recognise and manage overdoses? *Harm Reduction Journal*, **6**(1), 26.

Haegerich, Tamara M, Paulozzi, Leonard J, Manns, Brian J, & Jones, Christopher M. 2014. What we know, and donât know, about the impact of state policy and systems-level interventions on prescription drug overdose. *Drug and Alcohol Dependence*, **145**, 34–47.

Heller, Daliah I, & Stancliff, Sharon. 2007. Providing naloxone to substance users for secondary administration to reduce overdose mortality in New York City. *Public Health Reports*, **122**(3), 393–397.

Illinois, Stop Overdose. 2017. *Naloxone Fact Sheet*. `http://stopoverdoseil.org/assets/naloxone-fact-sheet.pdf`. Accessed: 2018-02-11.

Kerr, Debra, Dietze, Paul, Kelly, Anne-Maree, & Jolley, Damien. 2008. Attitudes of Australian heroin users to peer distribution of naloxone for heroin overdose:

perspectives on intranasal administration. *Journal of Urban Health*, **85**(3), 352–360.

Lagu, Tara, Anderson, Bradley J, & Stein, Michael. 2006. Overdoses among friends: drug users are willing to administer naloxone to others. *Journal of Substance Abuse Treatment*, **30**(2), 129–133.

Lankenau, Stephen E, Teti, Michelle, Silva, Karol, Bloom, Jennifer Jackson, Harocopos, Alex, & Treese, Meghan. 2012. Initiation into prescription opioid misuse amongst young injection drug users. *International Journal of Drug Policy*, **23**(1), 37–44.

Maxwell, Sarz, Bigg, Dan, Stanczykiewicz, Karen, & Carlberg-Racich, Suzanne. 2006. Prescribing naloxone to actively injecting heroin users: a program to reduce heroin overdose deaths. *Journal of Addictive Diseases*, **25**(3), 89–96.

Meara, Ellen, Horwitz, Jill R, Powell, Wilson, McClelland, Lynn, Zhou, Weiping, O'Malley, A James, & Morden, Nancy E. 2016. State legal restrictions and prescription-opioid use among disabled adults. *New England Journal of Medicine*, **375**(1), 44–53.

Mueller, Shane R, Walley, Alexander Y, Calcaterra, Susan L, Glanz, Jason M, & Binswanger, Ingrid A. 2015. A review of opioid overdose prevention and naloxone prescribing: Implications for translating community programming into clinical practice. *Substance Abuse*, **36**(2), 240–253.

Piper, Tinka Markham, Stancliff, Sharon, Rudenstine, Sasha, Sherman, Susan, Nandi, Vijay, Clear, Allan, & Galea, Sandro. 2008. Evaluation of a naloxone distribution and administration program in New York City. *Substance Use & Misuse*, **43**(7), 858–870.

Powell, David, Pacula, Rosalie Liccardo, & Jacobson, Mireille. 2015. *Do medical marijuana laws reduce addictions and deaths related to pain killers?* Tech. rept. National Bureau of Economic Research.

Rees, Daniel I, Sabia, Joseph J, Argys, Laura M, Latshaw, Joshua, & Dave, Dhaval. 2017. *With a little help from my friends: The effects of naloxone access and good samaritan laws on opioid-related deaths.* Tech. rept. National Bureau of Economic Research.

Seal, Karen H, Downing, Moher, Kral, Alex H, Singleton-Banks, Shannon, Hammond, Jon-Paul, Lorvick, Jennifer, Ciccarone, Dan, & Edlin, Brian R. 2003. Attitudes about prescribing take-home naloxone to injection drug users for the management of heroin overdose: a survey of street-recruited injectors in the San Francisco Bay Area. *Journal of Urban Health*, **80**(2), 291–301.

Seal, Karen H, Thawley, Robert, Gee, Lauren, Bamberger, Joshua, Kral, Alex H, Ciccarone, Dan, Downing, Moher, & Edlin, Brian R. 2005. Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: a pilot intervention study. *Journal of Urban Health*, **82**(2), 303–311.

Sporer, Karl A, & Kral, Alex H. 2007. Prescription naloxone: a novel approach to heroin overdose prevention. *Annals of Emergency Medicine*, **49**(2), 172–177.

Straus, Michele M, Ghitza, Udi E, & Tai, Betty. 2013. Preventing deaths from rising opioid overdose in the US–the promise of naloxone antidote in community-based naloxone take-home programs. *Substance Abuse and Rehabilitation*, **4**, 65.

Tobin, Karin E, Sherman, Susan G, Beilenson, Peter, Welsh, Christopher, & Latkin, Carl A. 2009. Evaluation of the Staying Alive programme: training injection drug users to properly administer naloxone and save lives. *International Journal of Drug Policy*, **20**(2), 131–136.

Walley, Alexander Y, Doe-Simkins, Maya, Quinn, Emily, Pierce, Courtney, Xuan, Ziming, & Ozonoff, Al. 2013. Opioid overdose prevention with intranasal naloxone among people who take methadone. *Journal of Substance Abuse Treatment*, **44**(2), 241–247.

Wheeler, Eliza, Davidson, Peter J, Jones, T Stephen, & Irwin, Kevin S. 2012. Community-based opioid overdose prevention programs providing naloxoneâUnited States, 2010. *MMWR. Morbidity and Mortality Weekly Report*, **61**(6), 101.

Wonder, CDC. 2017. *Overdose Death Rates*. `https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates`. Accessed: 2018-02-05.

Worthington, Nancy, Piper, Tinka Markham, Galea, Sandro, & Rosenthal, David. 2006. Opiate users' knowledge about overdose prevention and naloxone in New York City: a focus group study. *Harm Reduction Journal*, **3**(1), 19.

APPENDIX A: CHAPTER I TABLES

Table 1: Summary Statistics of Selected Variables

Variables*	***N***	**Mean**	**Std. Dev.**	**Minimum**	**Maximum**
***Opioids Outcomes* (per 100,000 population)**					
Total Grams of Opioids	510	51,584.41	16,844.77	18,281.19	118,645.26
Opioid Overdose Deaths	769	13.55	6.13	3.25	53.14
Opioids Rehabilitation Admissions	571	81.40	87.37	0.43	624.29
Demographic Characteristics (%)					
White	819	78.85	13.29	15.52	98.78
Black	819	10.98	10.19	0.08	44.49
Hispanic	819	12.53	11.83	0.55	53.73
Male	819	47.66	1.29	43.87	51.73
Female	819	50.50	1.04	45.98	54.10
Married	819	40.70	1.91	34.41	47.66
Unemployed	819	2.95	1.02	0.79	7.48
Veteran Status	819	6.77	1.43	2.96	11.86
Income (%)					
Family Income $50,000-$60,000	819	7.89	1.26	4.50	12.91
Social Security Income <$5,000	819	63.25	2.06	57.75	68.75
Below Federal Poverty Level	819	12.56	3.44	4.47	23.84
Education Level (%)					
Less than High School	819	14.67	2.74	8.45	22.48
High School	819	21.96	2.99	15.38	32.94
Some College	819	13.42	1.68	8.85	18.52
Bachelor's	819	11.97	2.35	5.92	18.56
Age (%)					
15 to 19	819	7.76	0.75	2.03	10.04
20 to 24	819	5.63	0.67	3.71	8.29
25 to 29	819	5.89	0.78	2.88	8.76
30 to 34	819	6.61	0.71	4.86	9.04
35 to 39	819	7.11	0.84	4.91	10.25
40 to 44	819	7.51	0.99	4.90	10.55
15 to 49	819	7.22	0.83	4.49	9.88
50 to 54	819	6.47	0.78	3.79	9.14
55 to 59	819	5.34	0.93	2.77	8.21
60 to 64	819	4.28	0.99	1.91	7.57
Over 65	819	10.64	2.10	4.62	18.14
Health Status (%)					
Fair Health	819	7.33	1.64	3.96	13.99
Poor Health	819	3.11	1.20	1.21	8.66
Physical Difficulty	819	2.39	2.61	0.00	8.92
Mobility Difficulty	819	1.38	1.51	0.00	5.21
Crime Rate (%)					
Property Crime	714	0.41	0.22	0.08	1.64
Violent Crime	714	3.24	0.83	1.72	6.41

**Expressed in percentages unless otherwise specified*

Table 2: Fixed Effect-Regression Results

Outcomes (per 100,000 population)	***Policies***	***(1) NAX***	***(2) GSL***	***(3) PDMP***	***(4) Full Model***
Opioid Rehabilitation Admission	**NAX**	-13.41	-14.61	-13.98	-13.37
		(7.704)	(8.140)	(7.660)	(9.224)
	GSL		3.680		4.652
			(8.021)		(9.992)
	PDMP			13.35*	13.22*
				(5.205)	(5.224)
	All Policies				-4.239
					(12.77)
Number of Observations		*531*	*531*	*531*	*531*
Overall R-Squared		*0.0210*	*0.0233*	*0.0232*	*0.0213*
Opioid Overdose Deaths	**NAX**	-0.284	-0.291	-0.254	-0.825
		(0.451)	(0.474)	(0.448)	(0.525)
	GSL		0.0223		-0.772
			(0.475)		(0.600)
	PDMP			-0.839**	-0.831**
				(0.284)	(0.284)
	All Policies				1.743*
					(0.755)
Number of Observations		*669*	*669*	*669*	*669*
Overall R-Squared		*0.257*	*0.288*	*0.289*	*0.262*
Total Grams of Opioid Drugs	**NAX**	406.0	1584.0	322.1	934.0
		(1500.7)	(1589.0)	(1496.2)	(1691.4)
	GSL		-3361.3*		-4428.6*
			(1561.2)		(2095.2)
	PDMP			-1937.0	-1817.4
				(1093.2)	(1090.5)
	All Policies				2290.8
					(2599.6)
Number of Observations		*392*	*392*	*392*	*392*
Overall R-Squared		*0.177*	*0.178*	*0.181*	*0.174*

*Standard Errors in parentheses, * $p<0.05$, ** $p<0.01$, *** $p<0.001$*

Table 3: Propensity Score Matching Average Treatment Effects

Outcomes (per 100,000 population)	***Nearest Neighbor Matching***	***Kernel Matching***	***Stratification Matching***
Opioid Rehabilitation Admission	-37.22 (26.47)	-27.97 (22.62)	-27.70 (22.05)
Opioid Overdose Deaths	-0.140 (1.535)	0.183 (1.270)	-0.295 (1.061)
Total Grams of Opioid Drugs	-10843.2 (5803.8)	-9155.1* (4488.2)	-11164.5* (4354.8)

*Standard Errors in parentheses, * p<0.05, ** p<0.01, *** p<0.001*

Table 4: Opioid Rehabilitation Admission Fixed Effects Results

Variables	**(1)** **NAX**	**(2)** **GSL**	**(3)** **PDMP**	**(4)** **Full Model**
NAX	-13.41 (7.704)	-14.61 (8.140)	-13.98 (7.660)	-13.37 (9.224)
GSL		3.680 (8.021)		4.652 (9.992)
PDMP			13.35* (5.205)	13.22* (5.224)
NAX*GSL*PDMP				-4.239 (12.77)
White	0.227 (1.285)	0.236 (1.286)	-0.0128 (1.281)	-0.0125 (1.284)
Black	0.754 (1.760)	0.714 (1.764)	0.525 (1.752)	0.517 (1.758)
Male	6.895** (2.120)	6.964** (2.128)	6.898** (2.107)	6.959** (2.117)
Less than High School	-1.451 (3.070)	-1.232 (3.109)	-2.358 (3.071)	-2.237 (3.119)
High School Degree	-6.185* (2.759)	-5.977* (2.799)	-6.496* (2.745)	-6.443* (2.804)
Some College	-2.102 (3.357)	-1.939 (3.379)	-3.031 (3.356)	-3.011 (3.398)
Associate Degree	-5.200 (3.891)	-5.005 (3.918)	-5.240 (3.867)	-5.339 (3.965)
Bachelor's Degree	-5.456 (3.574)	-5.191 (3.624)	-6.246 (3.566)	-6.152 (3.635)
Veteran Status	-9.848* (3.854)	-9.661* (3.879)	-9.202* (3.839)	-9.108* (3.868)
Physical Difficulty	4.702 (3.411)	4.644 (3.416)	4.333 (3.393)	4.384 (3.413)
Year Fixed-Effects	Yes	Yes	Yes	Yes
No. of Observations	531	531	531	531
Overall R-Squared	0.0233	0.0232	0.0213	0.0210

*Standard errors in parentheses, * p<0.05, ** p<0.01, *** p<0.001*

Table 5: Continued Opioid Rehabilitation Admission Fixed Effects Results

Variables	**(1)** **NAX**	**(2)** **GSL**	**(3)** **PDMP**	**(4)** **Full Model**
Age 20 to 24	3.934	3.979	5.162	5.154
	(4.612)	(4.617)	(4.608)	(4.619)
Age 25 to 29	2.062	2.057	3.158	3.151
	(4.084)	(4.087)	(4.081)	(4.089)
Age 30 to 34	-2.953	-2.937	-2.282	-2.233
	(4.218)	(4.222)	(4.200)	(4.210)
Age 35 to 39	-1.505	-1.404	-1.283	-1.110
	(4.258)	(4.267)	(4.233)	(4.257)
Age 40 to 44	-0.996	-0.879	0.324	0.502
	(4.580)	(4.591)	(4.581)	(4.606)
Age 45 to 49	2.250	2.326	3.600	3.632
	(4.692)	(4.699)	(4.692)	(4.704)
Age 50 to 54	0.113	0.222	0.392	0.494
	(4.328)	(4.338)	(4.302)	(4.318)
Age 55 to 59	2.992	2.900	2.960	2.925
	(4.428)	(4.437)	(4.401)	(4.415)
Age 60 to 64	15.73***	15.80***	15.80***	15.75***
	(4.389)	(4.395)	(4.362)	(4.384)
Over 65	7.253*	6.982*	8.228*	8.138*
	(3.313)	(3.368)	(3.314)	(3.393)
Family Income < $10,000	-5.682**	-5.614**	-5.084**	-5.105**
	(1.864)	(1.871)	(1.867)	(1.886)
Social Security Income <	5.699	5.675	5.615	5.522
$5,000	(4.441)	(4.446)	(4.414)	(4.429)
Poor Health Status	1.269	1.163	0.486	0.430
	(4.218)	(4.228)	(4.203)	(4.217)
Medicaid Recipients	-2.814**	-2.813**	-2.718**	-2.746**
	(1.041)	(1.042)	(1.036)	(1.041)
Medicare Recipients	-3.985	-4.249	-3.773	-3.800
	(4.846)	(4.884)	(4.817)	(4.886)
Property Crime	51.13***	51.51***	52.44***	52.95***
	(6.455)	(6.514)	(6.436)	(6.538)
Year Fixed-Effects	Yes	Yes	Yes	Yes
No. of Observations	531	531	531	531
Overall R-Squared	0.0233	0.0232	0.0213	0.0210

*Standard errors in parentheses, * p<0.05, ** p<0.01, *** p<0.001*

Table 6: Opioid Overdose Deaths Fixed Effects Results

Variables	**(1)** **NAX**	**(2)** **GSL**	**(3)** **PDMP**	**(4)** **Full Model**
NAX	-0.284	-0.291	-0.254	-0.825
	(0.451)	(0.474)	(0.448)	(0.525)
GSL		0.0223		-0.772
		(0.475)		(0.600)
PDMP			-0.839**	-0.831**
			(0.284)	(0.284)
NAX*GSL*PDMP				1.743*
				(0.755)
White	0.0144	0.0144	0.0370	0.0385
	(0.0673)	(0.0674)	(0.0673)	(0.0671)
Black	0.0519	0.0518	0.0805	0.0739
	(0.0892)	(0.0893)	(0.0891)	(0.0889)
Male	-0.0227	-0.0224	-0.0245	-0.0299
	(0.113)	(0.113)	(0.112)	(0.112)
Less than High School	0.200	0.202	0.268	0.286
	(0.167)	(0.168)	(0.167)	(0.168)
High School Degree	0.359*	0.360*	0.388**	0.425**
	(0.151)	(0.152)	(0.150)	(0.152)
Some College	0.159	0.160	0.224	0.265
	(0.183)	(0.184)	(0.183)	(0.184)
Associate Degree	0.325	0.326	0.328	0.402
	(0.207)	(0.207)	(0.205)	(0.208)
Bachelor's Degree	0.0729	0.0742	0.107	0.147
	(0.195)	(0.198)	(0.194)	(0.196)
Veteran Status	0.116	0.117	0.0687	0.0785
	(0.202)	(0.203)	(0.201)	(0.201)
Physical Difficulty	0.580***	0.580***	0.594***	0.583***
	(0.139)	(0.140)	(0.139)	(0.139)
Year Fixed-Effects	Yes	Yes	Yes	Yes
No. of Observations	669	669	669	669
Overall R-Squared	0.288	0.289	0.262	0.257

*Standard errors in parentheses, * p<0.05, ** p<0.01, *** p<0.001*

Table 7: Continued Opioid Overdose Deaths Fixed Effects Results

Variables	**(1)** **NAX**	**(2)** **GSL**	**(3)** **PDMP**	**(4)** **Full Model**
Age 20 to 24	-0.398	-0.398	-0.444	-0.434
	(0.240)	(0.241)	(0.239)	(0.239)
Age 25 to 29	-0.0954	-0.0956	-0.139	-0.150
	(0.216)	(0.216)	(0.215)	(0.214)
Age 30 to 34	0.0718	0.0721	0.0340	0.0348
	(0.226)	(0.227)	(0.225)	(0.225)
Age 35 to 39	0.0481	0.0485	0.0420	0.0106
	(0.228)	(0.229)	(0.227)	(0.227)
Age 40 to 44	-0.0162	-0.0157	-0.0812	-0.101
	(0.240)	(0.240)	(0.239)	(0.239)
Age 45 to 49	0.0188	0.0190	-0.0640	-0.0734
	(0.244)	(0.244)	(0.244)	(0.243)
Age 50 to 54	0.0150	0.0154	0.0158	0.00773
	(0.236)	(0.237)	(0.235)	(0.234)
Age 55 to 59	0.0363	0.0358	0.0512	0.0456
	(0.235)	(0.236)	(0.234)	(0.233)
Age 60 to 64	-0.479*	-0.479*	-0.467*	-0.448*
	(0.228)	(0.228)	(0.226)	(0.226)
Over 65	-0.413*	-0.415*	-0.454**	-0.497**
	(0.176)	(0.178)	(0.175)	(0.178)
Family Income $<$ $10,000	0.145	0.146	0.116	0.136
	(0.0967)	(0.0971)	(0.0965)	(0.0969)
Social Security Income $<$	-0.511*	-0.511*	-0.536*	-0.524*
$5,000	(0.226)	(0.226)	(0.224)	(0.224)
Poor Health Status	-0.275	-0.275	-0.265	-0.264
	(0.199)	(0.199)	(0.198)	(0.197)
Medicaid Recipients	0.00302	0.00306	-0.00222	0.00553
	(0.0567)	(0.0567)	(0.0563)	(0.0563)
Medicare Recipients	0.194	0.193	0.195	0.150
	(0.252)	(0.254)	(0.250)	(0.252)
Property Crime	0.954**	0.956**	0.900*	0.829*
	(0.355)	(0.357)	(0.353)	(0.355)
Year Fixed-Effects	Yes	Yes	Yes	Yes
No. of Observations	669	669	669	669
Overall R-Squared	0.288	0.289	0.262	0.257

*Standard errors in parentheses, * p<0.05, ** p<0.01, *** p<0.001*

Table 8: Legal Supply of Opioids Fixed Effects Results

Variables	**(1) NAX**	**(2) GSL**	**(3) PDMP**	**(4) Full Model**
NAX	406.0	1584.0	322.1	934.0
	(1500.7)	(1589.0)	(1496.2)	(1691.4)
GSL		-3361.3*		-4428.6*
		(1561.2)		(2095.2)
PDMP			-1937.0	-1817.4
			(1093.2)	(1090.5)
NAX*GSL*PDMP				2290.8
				(2599.6)
White	358.0	287.2	372.3	302.5
	(313.4)	(313.3)	(312.4)	(312.7)
Black	-512.8	-523.7	-470.5	-469.4
	(396.5)	(394.2)	(395.8)	(394.3)
Male	-295.7	-324.6	-314.7	-368.3
	(423.5)	(421.2)	(422.2)	(421.5)
Less than High School	-468.3	-592.3	-308.4	-409.2
	(653.3)	(652.0)	(657.3)	(658.0)
High School Degree	-62.72	-194.7	-12.74	-84.80
	(595.0)	(594.7)	(593.6)	(597.6)
Some College	601.6	427.8	727.1	620.1
	(695.4)	(696.0)	(696.6)	(702.6)
Associate Degree	70.56	-86.44	113.6	80.67
	(802.6)	(801.2)	(800.2)	(811.2)
Bachelor's Degree	-237.2	-404.4	-106.7	-217.7
	(687.2)	(687.6)	(688.8)	(693.5)
Veteran Status	-173.3	-340.2	-314.7	-372.0
	(798.8)	(797.9)	(800.0)	(806.1)
Physical Difficulty	1107.5*	1075.4*	1088.2*	1043.8*
	(456.9)	(454.4)	(455.4)	(453.8)
Year Fixed-Effects	Yes	Yes	Yes	Yes
No. of Observations	392	392	392	392
Overall R-Squared	0.178	0.181	0.174	0.177

*Standard errors in parentheses, * $p<0.05$, ** $p<0.01$, *** $p<0.001$*

Table 9: Continued Legal Supply of Opioids Fixed Effects Results

Variables	**(1)** **NAX**	**(2)** **GSL**	**(3)** **PDMP**	**(4)** **Full Model**
Age 20 to 24	-1067.0	-1081.2	-1183.2	-1196.8
	(904.5)	(899.2)	(903.7)	(899.4)
Age 25 to 29	-255.7	-213.5	-326.9	-270.4
	(824.0)	(819.4)	(822.1)	(818.6)
Age 30 to 34	-975.2	-1067.2	-951.4	-988.2
	(908.5)	(904.1)	(905.4)	(904.1)
Age 35 to 39	-105.5	-115.8	-184.3	-220.0
	(859.2)	(854.2)	(857.4)	(854.0)
Age 40 to 44	-1255.0	-1424.2	-1431.6	-1585.2
	(857.8)	(856.3)	(860.6)	(859.5)
Age 45 to 49	321.8	307.9	46.05	57.98
	(921.6)	(916.2)	(931.5)	(927.0)
Age 50 to 54	-712.6	-799.1	-682.2	-799.8
	(838.2)	(834.3)	(835.5)	(833.3)
Age 55 to 59	1181.8	1174.9	1213.0	1201.7
	(857.1)	(852.1)	(854.3)	(850.2)
Age 60 to 64	242.8	245.6	312.4	293.8
	(839.4)	(834.5)	(837.4)	(833.6)
Over 65	-260.9	-1.702	-314.9	-98.19
	(656.8)	(663.9)	(655.2)	(664.5)
Family Income < \$10,000	-131.2	-229.8	-185.3	-241.1
	(373.5)	(374.2)	(373.5)	(376.3)
Social Security Income <	-525.8	-424.4	-422.5	-356.0
\$5,000	(882.2)	(878.3)	(881.1)	(878.3)
Poor Health Status	-1452.6	-1248.1	-1356.7	-1181.0
	(4820.5)	(4793.2)	(4804.1)	(4781.9)
Medicaid Recipients	57.05	15.12	56.41	12.47
	(217.8)	(217.4)	(217.0)	(216.9)
Medicare Recipients	702.0	842.7	531.1	661.9
	(942.0)	(938.8)	(943.7)	(942.0)
Property Crime	5401.3**	4742.7*	4978.3**	4230.6*
	(1875.4)	(1889.4)	(1884.1)	(1905.3)
Year Fixed-Effects	Yes	Yes	Yes	Yes
No. of Observations	392	392	392	392
Overall R-Squared	0.178	0.181	0.174	0.177

*Standard errors in parentheses, * p<0.05, ** p<0.01, *** p<0.001*

APPENDIX B: CHAPTER I FIGURES

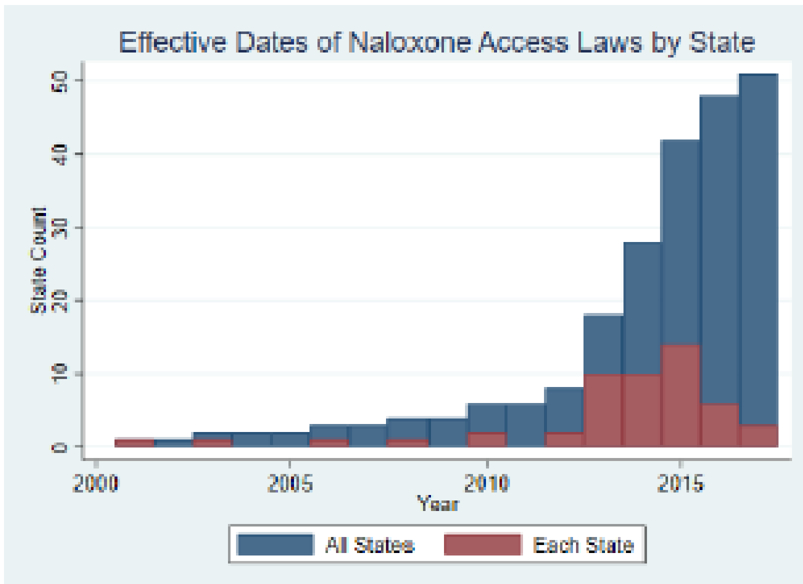

Figure 1: Naloxone Access Laws Effective Dates

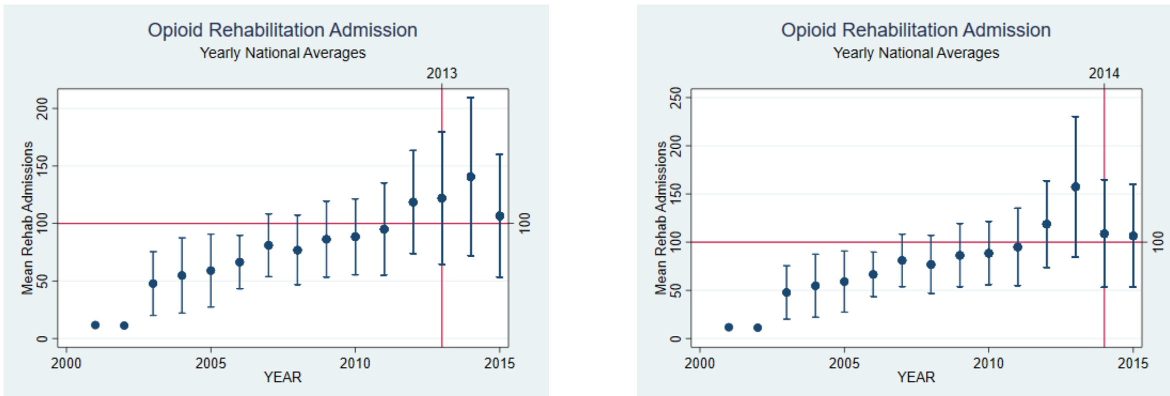

Figure 2: Opioid Rehabilitation Admissions

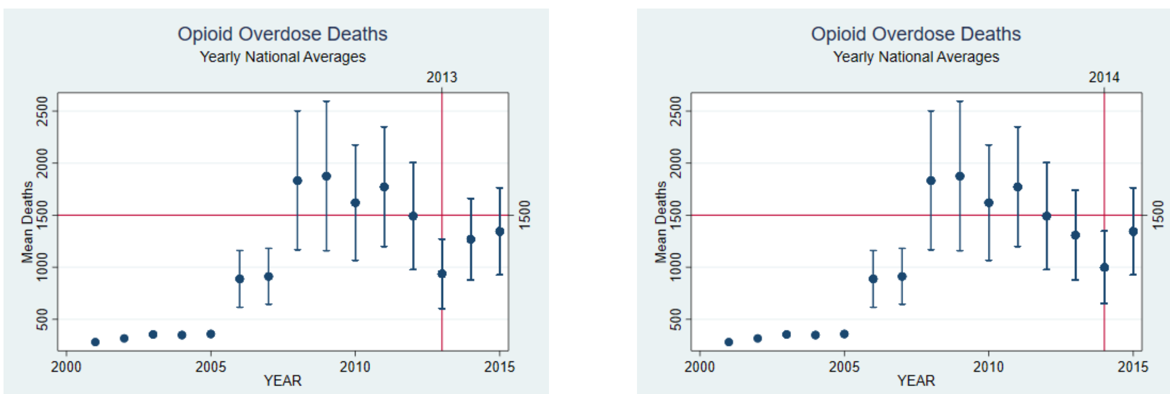

Figure 3: Opioids Overdose Deaths

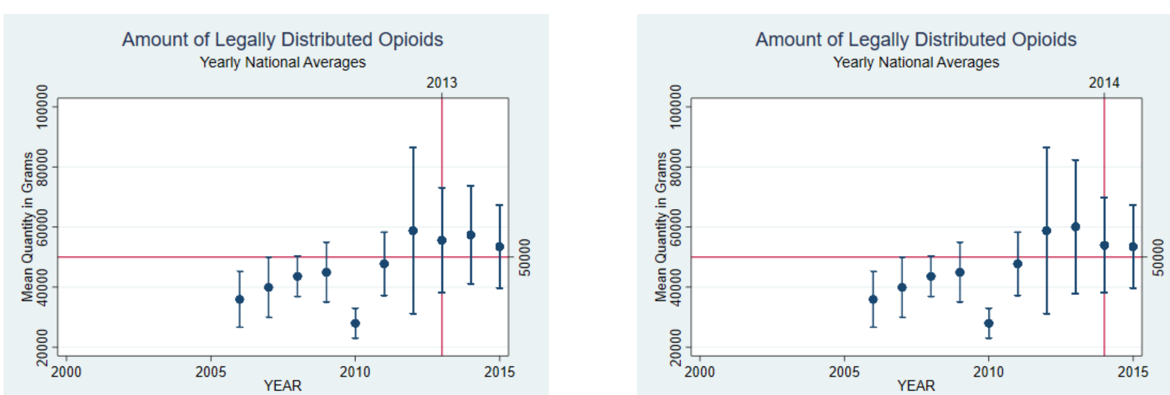

Figure 4: Total Grams of Legally Distributed Opioids

CHAPTER II:

PRESCRIPTION DRUG MONITORING PROGRAMS MANDATORY QUERY REQUIREMENTS: OPIOIDS MISUSE AND SUBSTITUTION TO HEROIN

1 Introduction

This paper looks at the impact of Prescription Drug Monitoring Programs (PDMPs) mandatory query requirements on the likelihood of transition to heroin from prescription opioids misuse. Per the literature, opioid abuse is a risk factor in heroin abuse given they are both opioids. There is also a perception that prescription opioids misuse is relatively "safer" and opens the door to more dangerous substance abuse. Heroin may be the natural progression for an opioid addict in search of a harder drug that is less regulated. This study attempts to answer whether opioid abusers eventually turn to heroin, and looks at the impact of mandatory query requirements on such transition.

Mandatory query requirements are an important piece of PDMPs. Those are state level interventions to improve opioid prescribing, inform clinical practice, and protect patients at risk. Typically, PDMPs are an electronic database that tracks controlled substance prescription in a state. Their main purpose is to provide timely information to health authorities about prescribing and patient behaviors that contribute to the worsening of the opioid crisis. Each state varies on whom is allowed access into PDMPs depending on their type of mandatory query requirements. Authorized users generally include prescribers, dispensers, law enforcement, medical licensing and regulatory boards, or state Medicaid programs. The transition to heroin is measured by comparing its rate of overdose deaths with those other different categories of opioids including other opioids, methadone, other synthetic narcotics, and other and unspecified narcotics. A progression to heroin is confirmed is its per capita overdose death rates is greater than any of the opioid categories.

The widespread abuse of prescription opioid is the leading cause for overdose deaths in the US, claiming over 64,000 lives in 2016 [Wonder, 2017]. Heroin, natural and semi-synthetic opioids followed with a combined 30,000 overdose fatalities, relegating cocaine and methamphetamine to fourth and fifth places respectively. A preferred method for treating chronic pain, prescription opioids are widely available to the general public where diversion and abuse are prevalent, and evidence of doctor-shopping behavior is abundant [Phillips, 2000, Goodwin and Hasin, 2002]. The burden of the opioid crisis falls on a segment of the population that is middle aged and white, residing in rural areas, relatively uneducated, lower income, in chronic and acute pain, and suffering from substance use disorders and other psychiatric diagnoses [Goodwin and Hasin, 2002, Bohnert et al., 2011, Rigg et al., 2012, Han et al., 2015]. Individuals in chronic and acute pain are considered at high risk for prescription opioids misuse, specifically women, the elderly, and addicts with concomitant sedative use disorders which is associated with greater levels of psychopathology and suicide risk [Goodwin and Hasin, 2002, Simoni-Wastila and Strickler, 2004, Bohnert et al., 2011, Han et al., 2015, Kolodny et al., 2015, Kandel et al., 2017]. Non-medical prescription opioids abusers oftentimes engage in multiple substance use including sedatives, cocaine, methamphetamine, psychostimulant, and most commonly heroin [Becker et al., 2008, Calcaterra et al., 2013, Le Lait et al., 2014]. The epidemic is exacerbated by the increase in the amount of opioids dispensed to pain patients, with average milligrams of morphine prescribed per year growing by over 600% between 1997 and 2007 leading to a four fold jump in overdose deaths [Calcaterra et al., 2013].

This paper contributes to the literature by looking at the gateway hypothesis between heroin and prescription opioids. To the best of the author's knowledge, this paper is one of the few to specifically look at the opioids as a gateway drug to opioids by looking at mandatory query requirements and using logistic modeling techniques. The paper is structured as follows: literature review, data review, methodology, results analysis, and discussion. Overall, the study shows the PDMPs mandatory query laws significantly act as deterrents to heroin substitution.

2 Literature Review

Heroin is a type of natural opioid derived from morphine and is consumed through injection, sniffing or snorting, and smoking. It binds to opioid receptors on brain cells involved in feelings of pain and pleasure and in controlling heart rate, sleeping, and breathing [NIDA, 2018]. Prescription opioids such as OxyContin and Vicodin are reported to have effects similar to heroin, lending credibility to painkillers being a door to the harder drug with higher potency [Comer et al., 2008]. Research finds that prescription opioid use is a risk factor for heroin use and a subset of painkiller abusers may progress to heroin use. However, a national survey finds less than 4 percent of prescription opioids abusers started using heroin within 5 years, and the proportion of painkillers overdose deaths in combination with other substances including heroin increased by 1.3 times [Muhuri et al., 2013, Compton et al., 2016, Kandel et al., 2017]. Several theories seek to explain the transition from prescription opioids to heroin with the "gateway drug" hypothesis being the most common in the literature. The gateway hypothesis states drug abuse is a progressive and hierarchical sequence between lower level classes of drugs to illicit and more potent ones such as cocaine, methamphetamine, and heroin [Kandel, 2002]. Therefore, the likelihood of heroin use may significantly increase with an individual's previous history of prescription painkillers abuse.

The OxyContin reformulation of 2010, an effort to create a tamper resistant prescription painkiller, resulted in an significant rise of transition to heroin with addicts switching to the easier to use, much more affordable, and readily available drug [Grau et al., 2007, Cicero et al., 2012]. In particular, the relative affordability of heroin is a driving factor in its popularity, compounded with the US market being flooded with low cost and high purity drugs from Latin America between the 1990s and early 2000s [Ciccarone, 2009, Mars et al., 2014, Compton et al., 2016]. Meanwhile, a cultural shift is afoot among heroin addicts becoming younger adults, male, white, hailing from both rural and metropolitan areas, and most importantly were previously or concurrently painkiller abusers. The perception of opioids to be less stigmatizing, less dangerous, and less subject to legal consequences contributed to its adoption by a previously reluctant majority who eventually turned to heroin [Inciardi et al., 2009, Peavy et al., 2012, Mars et al., 2014, Dasgupta et al., 2014, Cicero et al., 2014].

In light of the opioid crisis, forty-nine states have adopted Prescription Drug Monitoring Programs (PDMPs), electronic database systems that store controlled substance dispensing information which is made accessible to prescribers, dispensers, and law enforcement officials. PDMPs can be powerful tools in the fight against opioids abuse conditional on prescribers and dispensers cooperation. As an example, Florida saw a significant decline in the number of its “pill-mills” with approximately 250 pain management clinics closing by 2013. These closures came from the state’s adoption of PDMPs concurrently with “pill-mill” laws that established regulatory oversight of pain management clinics such as the creating of penalties for those non-compliant with state registration, ownership requirements, and restrictions on dispensing of controlled substances [Johnson et al., 2014, Chang et al., 2018, Popovici et al., 2018]. Overdose deaths declined by 18% in Florida while Staten Island, New York, experienced two consecutive years of overdose fatalities decline for the first time after eleven years [Johnson et al., 2014, Delcher et al., 2015, Paone et al., 2015]. Not only were PDMPs effective in reducing painkillers diversion, they also led to a decrease in the amount of opioids prescribed by clinicians and an increased cooperation between the latter and pharmacies [Griggs et al., 2015, Bao et al., 2016, Carlson et al., 2018]. A potential weakness of PDMPs is the lack of standardization in their implementation across states. There is currently no agreed upon threshold to define questionable behaviors by clinicians, only 22 states in 2015 require identification before dispensing a controlled substances, while only 19 states require mandatory query by both prescribers and dispensers into PDMPs databases when dispensing a controlled substance [Griggs et al., 2015, Brandeis University, 2019]. Additionally, the median registration rate into PDMPs among licensed prescribers who issue at least one controlled substance is only 35% due to fears of burdensome incursions into their clinical practices and the lack of integration of the PDMPs into a coherent clinical workflow [Haffajee et al., 2015]. Even if prescribers were to opt into PDMPs mandatory query requirements, prescribers seldom conducts queries for every patient, every single time. Most only do queries for every new patient, new prescription of opioids, or for patients with suspected abuse [Hildebran et al., 2014]. The stringency of PDMPs combined with their haphazard implementation might have turned some opioid addicts to a less regulated, illicit alternative such as heroin in order to maintain their habit. While the vast majority of prescription opioids abusers have not progressed to heroin use, only about 3.6% do, heroin incidence rate was 19 times higher among those who reported prior non-medical pain reliever use [Muhuri et al., 2013].

Research also reports an association between PDMPs and an increase in the number of days of heroin use among opioids addicts who might have been unable to "doctor-shop" or unwilling to rely on illegal or social sources [Ali et al., 2017]. This study contributes to the literature by providing a national level insight into the relationship between PDMPs mandatory query requirements and their effects on the transition to heroin from prescription painkillers abuse. It exploits the state variation in mandatory query levied on both prescribers and dispensers, prescribers only, dispensers only, or no requirement at all. Fixed and random effects models using dichotomous and first differences outcome variables will be conducted to analyze the impact of PDMPs mandatory queries into heroin consumption.

3 Data

The addiction path from prescription opioids to heroin is analyzed using multiple state level longitudinal data sets ranging from 2000 to 2017. Opioid overdose deaths per capita are obtained from the Multiple Cause of Death portion of the National Vital Statistics System which uses the International Classification of Diseases 10 (ICD-10) to categorize fatalities with external causes of injury. Following the ICD-10 classification for opioid related deaths, the outcomes of interest are classified with an accidental, intentional, or undetermined underlying cause of death coded as X40-X44, X60-X64, X85, and Y10-Y14. The contributing causes of these opioid fatalities are further divided into poisoning by opium (T40.0), heroin (T40.1), other opioids (T40.2), methadone (T40.3), other synthetic narcotics (T40.4), and other and unspecified narcotics (T40.6). Demographic data is derived from the Current Population Survey's Annual Social and Economic Supplement (ASEC) with information on characteristics such as race, income level, and education and others. ASEC observations from 2014 are excluded from the analysis due to the Census Bureau's experimental redesign of health insurance questions that affected approximately 3/8ths of the total sample. The exclusion has an irrelevant impact on the analysis. Finally, the Federal Bureau of Investigation's Uniform Crime Reporting data set supplies information on violent and property crimes at the state level from 2000 to 2014.

3.1 Summary Statistics

All states except but five and the District of Columbia have adopted a type of mandatory query requirement by 2014 as shown in table 1. The current PDMPs mandatory query requirements shows almost all states have allowed authorized users to access electronic health records. Authorized users primarily include prescribers and dispensers of prescription opioids as well as law enforcement agencies, medical licensing and regulatory boards, and state Medicaid programs. This paper uses both the *effective date* when primary authorized users were first allowed to access the data online and the *type of authorized users* to categorize states. States with authorized users but without effective dates are therefore considered to have no query requirements for either prescribers or dispensers in the study. The states without effective dates are Connecticut, Pennsylvania, Illinois, New York, Missouri, and the District of Columbia. There are 17 states granting online data access to both prescribers and dispensers, 22 states authorizing access to prescribers only, one state to dispensers only, and 5 states allowing access to neither primary users.

The data in table 2 shows the overdose deaths by substances abused per 100,000 population nationally. The average share of heroin overdose deaths is about 2.30, compared to 4.05 for other opioids, 1.56 for methadone, 2.50 for other synthetic narcotics, and 1.26 for other and unspecified narcotics. Several dichotomous variables comparing the average rate of heroin overdose deaths to various categories of opioids are created to ascertain the drug substitution. Potential transition to heroin from prescription opioids is determined by whether heroin deaths surpass the fatalities for each category of opioids. These dichotomous variables are coded as 1 if heroin deaths are greater than the fatalities for the opioid of interest. Heroin deaths surpass other opioids fatalities in only 20% of all cases observed throughout 2000 and 2017. Methadone and heroin overdoses are almost evenly split with heroin accounting for slightly more deaths. Additionally, heroin deaths are more common than other synthetic narcotics and other and unspecified narcotics in 61% and 70% of all opiates fatalities, respectively.

The data set shows non-Hispanic whites to be the majority accounting for 79% of all ASEC survey respondents compared to 12% non-Hispanic blacks, while Hispanics make up for 16% of the population. There are more females than males at 51% and 48% of the population of which 40% report a married status. Around 3.1% of the non-institutionalized population is unemployed, 8% earn of households earn a yearly income of less than $10,000 and more than half supplements their earnings with social security benefits amounting to less than $5,000. Most respondents report obtaining at least a high school degree while about 15% have not graduated high school. Bachelor's degrees recipients constitute only 12% of the population, an amount close to those with some college experience. On whether the use prescription painkillers is legitimate, the data show less than a combined 6% of all respondents report some sort of physical, mobility, or care difficulty while about 10% report poor or fair health status. Finally, the relationship between dug abuse and crime is evaluated by including data on property and violent crimes, which amount to 3% and 0.4% of the general population.

In table 3 , the data is further summarized by types of mandatory query requirements. Overall, states mandating prescribers and dispensers to query into patient records tend to face a more dire opioid overdose deaths issue. States requiring both prescribers and dispensers, or prescribers only to query health records have a per capita mean other opioids deaths of 4.27 and 4.67 respectively, compared to 2.17 for no access policy states and 2.78 for dispensers only ones. This pattern is also found in other synthetic narcotics and other and unspecified narcotics deaths with a slightly higher number found among more restrictive states. However, these states tend to have a significantly lower rate of per capita heroin and methadone deaths averaging 2.49 for prescribers and dispensers states and 2 overdose fatalities for prescribers only ones. The demographic characteristics of the population seem to be similar across all query groups. It should be noted that the small sample size on query types such as dispensers only and neither are exacerbated by missing data.

4 Methodology

4.1 Conditional Fixed Effects Logit

A conditional fixed-effect logit model is used to analyze the likelihood of heroin transition. Per capita heroin overdose fatalities are compared to every category of opioid deaths and are transformed into several dichotomous variables such that

$$y_s = \begin{cases} 1 & \text{if heroin deaths}>\text{opioid deaths} \\ 0 & \text{otherwise} \end{cases}$$

given that s represents represents each state, the unit observation. The logistic regression approach can be used to describe the relationship of the covariate X, particularly the mandatory query policies, to the dichotomous heroin and opioid inequality. Further, the logistic regression is extended into a conditional fixed-effects model in order to accommodate the longitudinal construct of the data, where each state can be used as its own controls. The outcomes of interest are unknown parameters α and β, which become the odds ratios once exponentiated.

The methodological framework is as follows:

$$\begin{aligned}\operatorname{logit}(\Pi_s) &= \log\left(\frac{\Pi_s}{1-\Pi_s}\right)\\ &= \alpha + \beta_1 Prescriber\&Dispenser_s + \beta_2 Prescriber_s + \beta_3 Year + \sum_{k=4}^{n} \beta_k x_{sk}\end{aligned} \tag{1}$$

where the conditional probability of heroin deaths exceeding opioid deaths is:

$$\Pi_s = \Pr(y_s = 1 | X_s = x_s) = \frac{\exp(\alpha + \sum_{k=1}^{n} \beta_k x_{sk})}{1 + \exp(\alpha + \sum_{k=1}^{n} \beta_k x_{sk})} \tag{2}$$

The main coefficients of interest are β_1 and β_2. After exponentiation, they provide the odds ratio for the effects prescribers only, both dispensers and prescribers mandatory query requirements on the rate of heroin deaths exceeding opioid fatalities. Note that only Oregon requires dispensers only to query health records. The dispensers only query type is consequently ignored in the study due to insufficient observations.

5 Results

The data in table 5 measure the likelihood of per capita heroin overdose deaths being greater than fatalities from various categories of opioids. Heroin death count per capita is coded as one if it exceeds methadone, other synthetic narcotics, or other and unspecified narcotics, respectively; and zero otherwise. Both the fixed effects logit regression and the subsequent fixed-effects regression models include yearly dummies, age, race, education, health insurance coverage, federal poverty status, and crime rates per capita.

5.1 Conditional Fixed Effects: Main Outcomes

A preliminary analysis on the effects of the queries on all the outcomes of interest is conducted in table 4 prior to analyzing a potential substitution to heroin. Prescribers and dispensers policies significantly contribute to an increase in per capita heroin overdose deaths by almost 0.7 and methadone fatalities by 1.7. The implementation of prescribers only query laws successfully reduce heroin overdose mortality by 0.8 per 100,000 individuals but has no impact on any other types of opioids. Obtaining a high school degree significantly reduces the likelihood of opioid overdose deaths while being in one's twenties increases leads to the opposite. An annual family income of only $10,000 to $20,000 is a risk factor in increasing heroin, methadone, and other synthetic narcotics overdose deaths. Difficulty of care leads to an increase in heroin overdose deaths while a decrease in per capita methadone fatalities is observed.

5.2 Conditional Fixed Effects Logit Results: Substitution to Heroin

As seen in table 5, states requiring both prescribers and dispensers to query into health records are 39 times more likely than states who require neither to have higher rates of heroin deaths compared to other opioids. Likewise, states requiring only prescriber queries are close to 30 times more likely to see heroin deaths surpass other opioids fatalities. These significantly higher odds ratio for the queries on heroin deaths may be a result of the laws being perfect predictors and are addressed in the subsequent robustness check section. Results for other types of opioid deaths suggest states without prescribers only policies (i.e. neither) are 12.5 times (odds ratio: 0.0835) more likely to experience higher rates of overdoses from heroin rather than methadone. No type of query requirements have any significant impact on whether heroin deaths are greater than other synthetic narcotics and other and unspecified narcotics. Furthermore, the conditional probabilities in table 8 found in the appendix show states with prescribers and dispensers policies to be close to 92% more likely to experience higher rates of heroin deaths than other opioids, and states with prescribers only measures have a 90% probability for the same event. The results also show prescribers only states to have a similar likelihood of observing more heroin deaths than methadone compared to states with no requirements.

These findings are conditional on other state characteristics including race, education, health status, and income. Whites and non-whites are equally as likely in any state are as likely to see higher rates of greater heroin deaths than prescription opioids. A higher concentration of males increases the odds of more heroin deaths compared to other opioids. A greater number of households collecting social security benefits ranging from \$10,000 to \$15,000 yearly sees a state having close to 24 times more heroin than other states. Variables accounting for health status and crime rates were insignificant in predicting heroin vs. opioids deaths.

5.3 Robustness Checks

5.3.1 Conditional Fixed Effects Regression Results

As a robustness check, a fixed-effects regression model is conducted to analyze the substitution to heroin from prescription opioids. The fixed-effects regression framework has the advantage of retaining time-invariant outcomes which were previously dropped in the logit model. The results in table 6 are consistent with the logit model with regards to other opioids, where prescribers and dispensers policies lead to 1.197 per 100,000 population increase in the rate of heroin deaths being greater than other opioids. Prescribers only states see a 1.138 increase in the number of heroin deaths when compared to other and unspecified narcotics overdoses. Graduating from high school and significantly increases the likelihood of more heroin than other opioids deaths as well as being aged 20 to 24. Earning an annual family income of \$30,000 to \$40,000 increases the probability of the more heroin deaths. Other variables related to health status, physical difficulty, and crime rates have no effects on the overdose deaths, no matter the category of opioid fatalities to which heroin is compared to.

5.3.2 First Difference Conditional Fixed Effects

As an additional check, the first differences between heroin and all categories of opioids are taken to analyze the substitution to heroin. It is a measure of proximity between heroin and opioid deaths, and a negative first difference indicates a higher number of heroin fatalities. Furthermore, an increase in the magnitude of first difference is indicative of heroin deaths increase or opioid fatalities decrease with its differentiation being beyond the scope of this study. The findings in table 7 show the strictest states to increase the gap between heroin and other opioids by 0.7 more deaths per capita and methadone by an additional 0.6 whereas other synthetic narcotics are decreased by 1.1. Prescribers only states see a decreases in the gap between heroin and methadone deaths by almost 0.7 and other and unspecified narcotics by a little over 1 more fatalities per capita.

6 Discussion

This study attempts to measure the substitution to heroin from prescription opioids by comparing the overdose death rates of heroin and prescription opioids. It further argues that mandatory query requirements, policies intended to mitigate the opioid crisis, unintentionally lead to substitution to heroin. The analysis shows such a transition is seemingly unlikely or at least very small in magnitude. Only states with the most stringent requirements, that is with both prescribers and dispensers, saw some unintended effects in the other opioids category. Consistently with the literature, the gateway hypothesis linking heroin to opioid misuse seems implausible. It is however noteworthy to mention that prior opioid abuse is a significant risk factor in the consumption of heroin, and addicts tend to abuse multiple drugs rather than substitute to a single drug such as heroin. Therefore, it can be argued that heroin consumption is increasing concurrently with prescription opioids abuse. Nevertheless, little information is obtained on the actual impact of the mandatory query requirements on the current opioid epidemic itself from the analysis. Controlling for certain demographic characteristics shows being white, male, and having a high school education increases the risk of heroin consumption, a finding consistent with the literature.

The scope of this study is limited by the unavailability of mortality data on heroin and other opioids from several states. Some states reported incomplete mortality information missing a significant number of years. Another limitation of is its focus on only overdose deaths as an outcome of interest. It may be improved by the inclusion of other outcomes such as treatment rehabilitation admissions or the supply of heroin. The inclusion of other authorized users such as law enforcement agencies or legal entities added to prescribers and dispensers should also benefit the study. Finally, the actual enforcement of the mandatory query should be accounted for. No information is available on the repercussions of a query which finds a patient to suspect of doctor-shopping or any other type of opioid abuse. Not only that, the implementation or lack thereof of the law seems to significantly vary across states with several states lacking even an effective date. Florida appears to have had the most success in implementing its mandatory query system, one which other states might wish to emulate.

References

Ali, Mir M, Dowd, William N, Classen, Timothy, Mutter, Ryan, & Novak, Scott P. 2017. Prescription drug monitoring programs, nonmedical use of prescription drugs, and heroin use: evidence from the National Survey Of Drug Use And Health. *Addictive Behaviors*, **69**, 65–77.

Bao, Yuhua, Pan, Yijun, Taylor, Aryn, Radakrishnan, Sharmini, Luo, Feijun, Pincus, Harold Alan, & Schackman, Bruce R. 2016. Prescription drug monitoring programs are associated with sustained reductions in opioid prescribing by physicians. *Health Affairs*, **35**(6), 1045–1051.

Becker, William C, Sullivan, Lynn E, Tetrault, Jeanette M, Desai, Rani A, & Fiellin, David A. 2008. Non-medical use, abuse and dependence on prescription opioids among us adults: psychiatric, medical and substance use correlates. *Drug and Alcohol Dependence*, **94**(1), 38–47.

Bohnert, Amy SB, Valenstein, Marcia, Bair, Matthew J, Ganoczy, Dara, McCarthy, John F, Ilgen, Mark A, & Blow, Frederic C. 2011. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*, **305**(13), 1315–1321.

Brandeis University, The Heller School. 2019 (Jan.). *Mandatory Query by prescribers and dispensers.*

Calcaterra, Susan, Glanz, Jason, & Binswanger, Ingrid A. 2013. National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999–2009. *Drug and Alcohol Dependence*, **131**(3), 263–270.

Carlson, KathleenF, Gilbert, Tess A, Morasco, BenjaminJ, Wright, Dagan, Otterloo, Joshua Van, Herrndorf, Aldona, & Cook, Lawrence J. 2018. Linkage of VA and state prescription drug monitoring program data to examine concurrent opioid and sedative-hypnotic prescriptions among veterans. *Health Services Research*, **53**, 5285–5308.

Chang, Hsien-Yen, Murimi, Irene, Faul, Mark, Rutkow, Lainie, & Alexander, G Caleb. 2018. Impact of Floridaâs prescription drug monitoring program and pill mill law on high-risk patients: a comparative interrupted time series analysis. *Pharmacoepidemiology and Drug Safety*, **27**(4), 422–429.

Ciccarone, Daniel. 2009. Heroin in brown, black and white: structural factors and medical consequences in the us heroin market. *International Journal of Drug Policy*, **20**(3), 277–282.

Cicero, Theodore J, Ellis, Matthew S, & Surratt, Hilary L. 2012. Effect of abuse-deterrent formulation of Oxycontin. *New England Journal of Medicine*, **367**(2), 187–189.

Cicero, Theodore J, Ellis, Matthew S, Surratt, Hilary L, & Kurtz, Steven P. 2014. The changing face of heroin use in the united states: a retrospective analysis of the past 50 years. *JAMA Psychiatry*, **71**(7), 821–826.

Comer, Sandra D, Sullivan, Maria A, Whittington, Robert A, Vosburg, Suzanne K, & Kowalczyk, William J. 2008. Abuse liability of prescription opioids compared to heroin in morphine-maintained heroin abusers. *Neuropsychopharmacology*, **33**(5), 1179.

Compton, Wilson M, Jones, Christopher M, & Baldwin, Grant T. 2016. Relationship between nonmedical prescription-opioid use and heroin use. *New England Journal of Medicine*, **374**(2), 154–163.

Dasgupta, Nabarun, Creppage, Kathleen, Austin, Anna, Ringwalt, Christopher, Sanford, Catherine, & Proescholdbell, Scott K. 2014. Observed transition from opioid analgesic deaths toward heroin. *Drug and Alcohol Dependence*, **145**, 238–241.

Delcher, Chris, Wagenaar, Alexander C, Goldberger, Bruce A, Cook, Robert L, & Maldonado-Molina, Mildred M. 2015. Abrupt decline in oxycodone-caused mortality after implementation of Florida's Prescription Drug Monitoring Program. *Drug and Alcohol Dependence*, **150**, 63–68.

Goodwin, Renee D, & Hasin, Deborah S. 2002. Sedative use and misuse in The United States. *Addiction*, **97**(5), 555–562.

Grau, Lauretta E, Dasgupta, Nabarun, Grau, Lauretta E, Dasgupta, Nabarun, Harvey, Alison Phinney, Grau, Lauretta E, Dasgupta, Nabarun, Harvey, Alison Phinney, Irwin, Kevin, Givens, Anthony, *et al.* 2007. Illicit use of opioids: is Oxycontin a gateway drug? *American Journal on Addictions*, **16**(3), 166–173.

Griggs, Christopher A, Weiner, Scott G, & Feldman, James A. 2015. Prescription drug monitoring programs: examining limitations and future approaches. *Western Journal of Emergency Medicine*, **16**(1), 67.

Haffajee, Rebecca L, Jena, Anupam B, & Weiner, Scott G. 2015. Mandatory use of prescription drug monitoring programs. *JAMA*, **313**(9), 891–892.

Han, Beth, Compton, Wilson M, Jones, Christopher M, & Cai, Rong. 2015. Non-medical prescription opioid use and use disorders among adults aged 18 through 64 years in the United States, 2003-2013. *JAMA*, **314**(14), 1468–1478.

Hildebran, Christi, Cohen, Deborah J, Irvine, Jessica M, Foley, Carol, O'kane, Nicole, Beran, Todd, & Deyo, Richard A. 2014. How clinicians use prescription drug monitoring programs: a qualitative inquiry. *Pain Medicine*, **15**(7), 1179–1186.

Inciardi, James A, Surratt, Hilary L, Cicero, Theodore J, & Beard, Ronald A. 2009. Prescription opioid abuse and diversion in an urban community: the results of an ultrarapid assessment. *Pain Medicine*, **10**(3), 537–548.

Johnson, Hal, Paulozzi, Leonard, Porucznik, Christina, Mack, Karin, & Herter, Blake. 2014. Decline in drug overdose deaths after state policy changes-Florida, 2010-2012. *MMWR. Morbidity and Mortality Weekly Report*, **63**(26), 569–574.

Kandel, Denise B. 2002. Examining the gateway hypothesis: stages and pathways of drug involvement.

Kandel, Denise B, Hu, Mei-Chen, Griesler, Pamela, & Wall, Melanie. 2017. Increases from 2002 to 2015 in prescription opioid overdose deaths in combination with other substances. *Drug and Alcohol Dependence*, **178**, 501–511.

Kolodny, Andrew, Courtwright, David T, Hwang, Catherine S, Kreiner, Peter, Eadie, John L, Clark, Thomas W, & Alexander, G Caleb. 2015. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annual Review of Public Health*, **36**, 559–574.

Le Lait, Marie-Claire, Martinez, Erin M, Severtson, Stevan G, Lavery, Sarah A, Bucher-Bartelson, Becki, & Dart, Richard C. 2014. Assessment of prescription opioid intentional exposures across the rural-urban continuum in the united states using both population and drug availability rates. *Pharmacoepidemiology and Drug Safety*, **23**(12), 1334–1337.

Mars, Sarah G, Bourgois, Philippe, Karandinos, George, Montero, Fernando, & Ciccarone, Daniel. 2014. Every never I ever said came true: transitions from opioid pills to heroin injecting. *International Journal of Drug Policy*, **25**(2), 257–266.

Muhuri, Pradip K, Gfroerer, Joseph C, & Davies, M Christine. 2013. CBHSQ Data Review. *Center for Behavioral Health Statistics and Quality, SAMHSA*, 1–17.

NIDA. 2018 (June). *Heroin.*

Paone, Denise, Tuazon, Ellenie, Kattan, Jessica, Nolan, Michelle L, OâBrien, Daniella Bradley, Dowell, Deborah, Farley, Thomas A, & Kunins, Hillary V. 2015. Decrease in rate of opioid analgesic overdose deathsâStaten Island, New York City, 2011–2013. *MMWR. Morbidity and Mortality Weekly Report*, **64**(18), 491.

Peavy, K Michelle, Banta-Green, Caleb J, Kingston, Susan, Hanrahan, Michael, Merrill, Joseph O, & Coffin, Phillip O. 2012. hooked on prescription-type opiates prior to using heroin: results from a survey of syringe exchange clients. *Journal of Psychoactive Drugs*, **44**(3), 259–265.

Phillips, Donald M. 2000. JCAHO pain management standards are unveiled. *JAMA*, **284**(4), 428–429.

Popovici, Ioana, Maclean, Johanna Catherine, Hijazi, Bushra, & Radakrishnan, Sharmini. 2018. The effect of state laws designed to prevent nonmedical prescription opioid use on overdose deaths and treatment. *Health Economics*, **27**(2), 294–305.

Rigg, Khary K., Kurtz, Steven P., & Surratt, Hilary L. 2012. Patterns of prescription medication diversion among drug dealers. *Drugs: Education, Prevention and Policy*, **19**(2), 145–155.

Simoni-Wastila, Linda, & Strickler, Gail. 2004. Risk factors associated with problem use of prescription drugs. *American Journal of Public Health*, **94**(2), 266–268.

Wonder, CDC. 2017. *Overdose Death Rates.* `https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates`. Accessed: 2018-02-05.

APPENDIX C: CHAPTER II TABLES

Table 1: Mandatory Query Types by State and Adoption Date

	Mandatory Query Requirement Type					
Adoption Year	**Prescribers & Dispensers**	**Prescribers**	**Dispensers**	**Neither**	**No Access Policy Adopted**	***Total***
1997	1	2				***3***
1999		1		1		***2***
2003		1				***1***
2004	1	1		1		***3***
2005	3					***3***
2006	1	2				***3***
2007	3	1				***4***
2008	1	2				***3***
2009	1	3				***4***
2010		1				***1***
2011	2		1	2		***5***
2012	3	4		1		***8***
2013	1	3				***4***
2014		1				***1***
-					6	***6***
Total	***17***	***22***	***1***	***5***	***6***	***51***

Table 2: Summary Statistics of Selected Variables

Variables*	**N**	**Mean**	**Std. Dev.**	**Minimum**	**Maximum**
Overdose Deaths by Substance **(per 100,000 population)**					
Heroin	552	2.30	2.37	0.10	13.49
Other Opioids	551	4.05	3.17	0.18	25.87
Methadone	544	1.56	1.03	0.12	6.11
Other Synthetic Narcotics	535	2.50	4.59	0.09	34.97
Other and Unspecified Narcotics	498	1.26	1.29	0.11	8.68
Overdose Deaths: Heroin vs. Opioids					
Other Opioids	551	0.20	0.40	0.00	1.00
Methadone	544	0.54	0.50	0.00	1.00
Other Synthetic Narcotics	535	0.61	0.49	0.00	1.00
Other and Unspecified Narcotics	498	0.70	0.46	0.00	1.00
Demographic Characteristics (%)					
White	552	78.89	10.39	18.73	95.80
Black	552	11.50	9.00	0.34	42.97
Hispanic	552	15.61	13.08	0.56	53.73
Male	552	47.69	1.20	43.87	51.73
Female	552	50.62	0.95	46.67	52.80
Unemployed	552	3.08	1.09	0.79	7.48
Education Level (%)					
Less than High School	552	14.62	2.63	8.70	22.28
High School	552	21.59	3.05	15.38	32.33
Bachelor's	552	12.36	2.35	5.92	18.56
Age (%)					
20 to 24	552	5.62	0.67	3.71	8.29
25 to 29	552	5.92	0.77	2.88	8.76
30 to 34	552	6.63	0.70	4.86	9.04
40 to 44	552	7.42	0.95	4.90	10.06
Over 65	552	10.82	2.16	5.05	18.14
Income (%)					
Family Income < $10,000	552	7.71	1.95	3.57	13.90
Social Security Income < $5,000	552	63.53	2.04	57.75	68.54
Social Security Income $10,000 to $15,000	552	3.69	1.09	1.72	8.28
Health Status (%)					
Physical Difficulty	552	2.94	2.62	0.00	8.92
Mobility Difficulty	552	1.73	1.53	0.00	5.21
Care Difficulty	552	0.85	0.77	0.00	2.69
Poor Health	552	3.01	1.01	1.32	7.32
Crime Rate (%)					
Property Crime	417	3.24	0.78	1.82	5.85
Violent Crime	417	0.43	0.15	0.12	0.83

**Expressed in percentages unless otherwise specified*

Table 3: Summary Statistics of Selected Variables by Mandatory Query Types

	Both		Prescribers		Dispensers		Neither		No Policy	
Variables*	***N***	**Mean**	***N***	**Mean**	***N***	**Mean**	***N***	**Mean**	***N***	**Mean**
Overdose Deaths by Substance **(per 100,000 population)**										
Heroin	*213*	2.49	*228*	2.00	17	2.69	*9*	0.87	*85*	2.73
Other Opioids	*213*	4.27	*228*	4.67	*17*	2.76	*9*	3.18	*84*	2.17
Methadone	*208*	1.61	*225*	1.69	*17*	2.45	*9*	0.93	*85*	0.99
Other Synthetic Narcotics	*207*	2.71	*222*	2.59	*16*	0.74	*9*	1.27	*81*	2.22
Other and Unspecified Narcotics	*191*	1.46	*202*	1.11	*17*	0.79	*3*	0.45	*85*	1.27
Demographic Characteristics (%)										
White	*213*	79.58	*228*	77.14	*17*	87.30	*9*	86.57	*85*	79.38
Black	*213*	12.02	*228*	11.41	*17*	1.92	*9*	4.45	*85*	13.08
Hispanic	*213*	19.66	*228*	13.05	*17*	14.01	*9*	14.57	*85*	12.72
Male	*213*	47.63	*228*	47.78	*17*	48.65	*9*	47.89	*85*	47.41
Female	*213*	50.72	*228*	50.39	*17*	50.44	*9*	49.86	*85*	51.10
Married	*213*	40.35	*228*	40.51	*17*	41.57	*9*	40.82	*85*	39.79
Unemployed	*213*	2.91	*228*	3.20	*17*	3.80	*9*	2.44	*85*	3.11
Education Level (%)										
Less than High School	*213*	15.11	*228*	14.41	*17*	13.69	*9*	12.83	*85*	14.32
High School	*213*	21.47	*228*	21.62	*17*	19.79	*9*	17.96	*85*	22.58
Bachelor's	*213*	13.21	*228*	12.39	*17*	12.62	*9*	13.21	*85*	12.78
Age (%)										
20 to 24	*213*	5.71	*228*	5.56	*17*	5.48	*9*	5.82	*85*	5.55
25 to 29	*213*	5.96	*228*	5.95	*17*	6.23	*9*	6.17	*85*	5.68
30 to 34	*213*	6.60	*228*	6.68	*17*	6.94	*9*	6.79	*85*	6.49
40 to 44	*213*	7.35	*228*	7.40	*17*	7.43	*9*	6.31	*85*	7.76
50 to 54	*213*	6.46	*228*	6.53	*17*	6.47	*9*	5.87	*85*	6.61
55 to 59	*213*	5.38	*228*	5.57	*17*	5.67	*9*	5.37	*85*	5.32
Over 65	*213*	10.94	*228*	10.63	*17*	10.61	*9*	10.54	*85*	11.07
Income (%)										
Family Income < $10,000	*213*	7.94	*228*	7.61	*17*	7.76	*9*	6.60	*85*	7.48
Family Income $10,000 to $20,000	*213*	9.70	*228*	9.10	*17*	10.50	*9*	8.03	*85*	8.94
Social Security Income < $5,000	*213*	63.42	*228*	63.60	*17*	63.88	*9*	61.38	*85*	63.78
Social Security Income $10,000 to $15,000	*213*	3.80	*228*	3.53	*17*	3.91	*9*	2.65	*85*	3.91
Health Status (%)										
Physical Difficulty	*213*	2.70	*228*	3.38	*17*	2.52	*9*	4.53	*85*	2.25
Mobility Difficulty	*213*	1.59	*228*	1.98	*17*	1.47	*9*	2.45	*85*	1.37
Care Difficulty	*213*	0.80	*228*	0.97	*17*	0.77	*9*	1.25	*85*	0.66
Fair Health	*213*	7.22	*228*	7.39	*17*	6.98	*9*	1.16	*85*	7.31
Poor Health	*213*	3.00	*228*	3.15	*17*	3.13	*9*	0.37	*85*	2.71
Crime Rate (%)										
Property Crime	*164*	3.52	*166*	3.13	*14*	3.84	*3*	3.11	*70*	2.73
Violent Crime	*164*	0.46	*166*	0.40	*14*	0.28	*3*	0.37	*70*	0.43

**Expressed in percentages unless otherwise specified*

Table 4: Conditional Fixed Effects Results

	Conditional Fixed Effects Regression Model				
Variables	**Heroin**	**Other Opioids**	**Methadone**	**Other Synthetic Narcotics**	**Other & Unspecified Narcotics**
Mandatory Query Requirements Types					
Prescribers & Dispensers	0.661**	-0.0500	0.0738	1.734**	0.248
	(0.255)	(0.272)	(0.0990)	(0.588)	(0.131)
Prescribers Only	-0.830***	-0.406	-0.114	-0.243	0.198
	(0.243)	(0.260)	(0.0953)	(0.576)	(0.126)
Other Variables					
Whites	-0.0206	-0.0258	-0.0744***	-0.0418	0.0226
	(0.0450)	(0.0482)	(0.0178)	(0.108)	(0.0252)
Blacks	-0.0234	0.0333	-0.0531*	0.105	-0.00285
	(0.0626)	(0.0673)	(0.0246)	(0.149)	(0.0332)
Male	0.0323	0.0146	-0.0316	-0.396*	-0.0380
	(0.0746)	(0.0808)	(0.0294)	(0.177)	(0.0405)
High School Graduate	-0.197**	-0.145*	-0.0411	-0.303*	0.00803
	(0.0630)	(0.0674)	(0.0246)	(0.148)	(0.0325)
Some College Education	-0.141	0.0919	0.0290	-0.296	-0.0565
	(0.0904)	(0.0966)	(0.0352)	(0.210)	(0.0481)
Age 20 to 24	0.288*	-0.0941	0.110*	0.616	0.0437
	(0.136)	(0.146)	(0.0531)	(0.317)	(0.0723)
Age 25 to 29	0.196	0.192	0.174***	0.766**	0.0553
	(0.117)	(0.125)	(0.0457)	(0.272)	(0.0610)
Age 60 to 64	0.0786	-0.167	0.0538	0.586	0.120
	0.138)	(0.148)	(0.0541)	(0.322)	(0.0755)
Family Income <	0.00629	-0.00846	-0.0352	0.0281	0.0231
$10,000	(0.0690)	(0.0738)	(0.0271)	(0.164)	(0.0349)
Family Income $10,000	0.263***	0.112	0.0509*	0.464**	0.0307
to $20,000	(0.0657)	(0.0705)	(0.0256)	(0.154)	(0.0341)
Family Income $30,000	0.170*	-0.106	-0.0452	0.403*	-0.0417
to $40,000	(0.0690)	(0.0737)	(0.0270)	(0.163)	(0.0368)
Social Security Income	0.0416	0.0839	-0.0303	0.225	0.00580
$10,000 to $15,000	(0.152)	(0.163)	(0.0593)	(0.356)	(0.0787)
Care Difficulty	0.617*	0.00970	-0.286**	0.740	-
	(0.272)	(0.291)	(0.106)	(0.636)	
Year Fixed-Effects	Yes		Yes	Yes	Yes
No. of Observations	552	551	544	535	498
R^2	0.320	0.0462	0.105	0.228	0.00279

*Standard Errors in parentheses; * p<0.05, ** p<0.01, *** p<0.001*

Table 5: Conditional Fixed Effects Logit Results

	Conditional Fixed Effects Logit Model (Odds Ratio)			
Variables	**Other Opioids**	**Methadone**	**Other Synthetic Narcotics**	**Other & Unspecified Narcotics**
Mandatory Query Requirements Types				
Prescribers & Dispensers	38.86*	0.579	0.500	13.71
	(65.11)	(0.621)	(0.374)	(100.1)
Prescribers Only	29.74*	0.0835*	1.348	9.091
	(49.13)	(0.0832)	(0.958)	(37.16)
Other Variables				
Whites	0.425*	1.100	0.843	12.36
	(0.172)	(0.213)	(0.136)	(17.95)
Blacks	0.289**	1.173	0.596*	6.022
	(0.137)	(0.307)	(0.126)	(6.030)
Male	7.351**	1.626	1.571	1.900
	(5.256)	(0.559)	(0.418)	(1.789)
High School Graduate	0.790	0.545*	1.532*	1.379
	(0.318)	(0.167)	(0.326)	(1.303)
Some College Education	0.241*	1.582	1.442	4.797
	(0.163)	(0.641)	(0.412)	(5.432)
Age 20 to 24	0.886	0.810	0.448*	0.000710
	(0.750)	(0.440)	(0.179)	(0.00300)
Age 25 to 29	0.113*	0.509	0.274***	0.00552
	(0.0964)	(0.257)	(0.104)	(0.0166)
Age 60 to 64	0.0494**	0.845	0.891	2.767
	(0.0509)	(0.465)	(0.354)	(6.938)
Family Income <	3.614*	0.849	1.114	0.0756*
$10,000	(1.860)	(0.233)	(0.233)	(0.0992)
Family Income $10,000	2.566*	1.535	1.136	7.639
to $20,000	(1.217)	(0.434)	(0.229)	(10.19)
Family Income $30,000	8.118***	0.688	0.797	0.298
to $40,000	(4.925)	(0.218)	(0.170)	(0.335)
Social Security Income	23.54**	2.481	0.479	1.314
$10,000 to $15,000	(25.33)	(1.704)	(0.241)	(3.514)
Care Difficulty	0.00994*	0.701	2.099	-
	(0.159)	(0.115)	(0.0838)	
Year Fixed-Effects	Yes	Yes	Yes	Yes
No. of Observations	335	506	430	279

*Standard Errors in parentheses; * p<0.05, ** p<0.01, *** p<0.001*

Table 6: Fixed-Effects Regression Results

	Fixed-Effects Regression Model Results			
Variables	**Other Opioids**	**Methadone**	**Other Synthetic Narcotics**	**Other & Unspecified Narcotics**
Mandatory Query Requirements Types				
Prescribers & Dispensers	1.197**	1.004	0.985	1.020
	(0.0726)	(0.0703)	(0.0728)	(0.0650)
Prescribers Only	1.021	1.012	1.025	1.138*
	(0.0592)	(0.0682)	(0.0742)	(0.0700)
Other Variables				
Whites	1.002	1.003	0.989	0.992
	(0.0108)	(0.0126)	(0.0134)	(0.0122)
Blacks	0.981	1.015	0.970	1.016
	(0.0147)	(0.0176)	(0.0182)	(0.0164)
Male	1.002	1.032	1.046*	1.026
	(0.0180)	(0.0215)	(0.0233)	(0.0202)
High School Graduate	0.951***	0.971	1.005	1.010
	(0.0143)	(0.0169)	(0.0186)	(0.0160)
Some College Education	0.957*	1.019	1.008	0.997
	(0.0206)	(0.0254)	(0.0266)	(0.0235)
Age 20 to 24	1.103**	0.946	0.962	0.930*
	(0.0358)	(0.0355)	(0.0384)	(0.0328)
Age 25 to 29	0.987	0.959	0.888***	0.944
	(0.0275)	(0.0310)	(0.0303)	(0.0280)
Age 60 to 64	0.988	0.966	0.954	1.038
	(0.0325)	(0.0370)	(0.0386)	(0.0386)
Family Income <	1.005	0.992	1.006	0.981
$10,000	(0.0165)	(0.0190)	(0.0208)	(0.0168)
Family Income $10,000	1.028	1.018	1.011	1.009
to $20,000	(0.0162)	(0.0184)	(0.0195)	(0.0169)
Family Income $30,000	1.048**	0.987	0.995	0.992
to $40,000	(0.0172)	(0.0189)	(0.0203)	(0.0177)
Care Difficulty	0.983	1.044	1.116	0.913
	(0.0637)	(0.0782)	(0.0892)	(0.0652)
Year Fixed-Effects	Yes	Yes	Yes	Yes
No. of Observations	551	544	535	498
R^2	0.0117	0.295	0.0850	0.0885

*Standard Errors in parentheses; * p<0.05, ** p<0.01, *** p<0.001*

Table 7: First Differences Fixed-Effects Regression Results

	Fixed-Effects Regression Model Results			
Variables	**Other Opioids**	**Methadone**	**Other Synthetic Narcotics**	**Other & Unspecified Narcotics**
Mandatory Query Requirements Types				
Prescribers & Dispensers	0.709*	0.585*	-1.106*	0.434
	0.311)	(0.260)	(0.522)	(0.298)
Prescribers Only	-0.430	-0.697**	-0.626	-1.010***
	(0.298)	(0.250)	(0.512)	(0.288)
Other Variables				
Whites	0.00350	0.0483	0.0241	0.00551
	(0.0551)	(0.0466)	(0.0961)	(0.0575)
Blacks	-0.0606	0.0200	-0.129	-0.0110
	(0.0770)	(0.0645)	(0.133)	(0.0758)
Male	0.0249	0.0648	0.423**	0.00973
	(0.0924)	(0.0773)	(0.158)	(0.0923)
High School Graduate	-0.0539	-0.159*	0.101	-0.174*
	(0.0771)	(0.0646)	(0.131)	(0.0742)
Some College Education	-0.235*	-0.187*	0.141	-0.100
	(0.111)	(0.0924)	(0.187)	(0.110)
Age 20 to 24	0.388*	0.162	-0.365	0.205
	(0.167)	(0.139)	(0.282)	(0.165)
Age 25 to 29	0.00383	0.0207	-0.551*	0.205
	(0.143)	(0.120)	(0.242)	(0.139)
Age 60 to 64	0.241	0.0182	-0.537	0.0733
	(0.169)	(0.142)	(0.286)	(0.172)
Family Income <	0.0138	0.0450	-0.0383	-0.00427
$10,000	(0.0844)	(0.0710)	(0.146)	(0.0795)
Family Income $10,000	0.155	0.219**	-0.178	0.236**
to $20,000	(0.0806)	(0.0671)	(0.137)	(0.0777)
Family Income $30,000	0.276**	0.225**	-0.216	0.257**
to $40,000	(0.0843)	(0.0710)	(0.145)	(0.0839)
Care Difficulty	0.605	0.892**	-0.0502	-
	(0.333)	(0.278)	(0.565)	
Year Fixed-Effects				
No. of Observations	551	544	535	498
R^2	0.0363	0.424	0.133	0.332

*Standard Errors in parentheses; * p<0.05, ** p<0.01, *** p<0.001*

Table 8: Conditional Logit Predicted Probabilities

Variable	Conditional Probabilities	Delta-Method Std. Error	z	p>|z|	[95% Conf.	Interval]
Heroin vs. Other Opioids						
Both Presc. & Dspr.						
0	.2240634	58.9896	0.00	0.997	-115.3934	115.8416
1	.9181845	25.48772	0.04	0.971	-49.03683	50.8732
Prescribers Only						
0	.2365744	61.2795	0.00	0.997	-119.869	120.3422
1	.9021073	29.96147	0.03	0.976	-57.82129	59.6255
Heroin vs. Methadone						
Both Presc. & Dspr.						
0	.9999316	.0012261	815.51	0.000	.9975284	1.002335
1	.9998818	.0021067	474.62	0.000	.9957527	1.004011
Prescribers Only						
0	.9999608	.0007024	1423.60	0.000	.998584	1.001337
1	.9995301	.0084195	118.72	0.000	.9830282	1.016032
Heroin vs. Other Synthetic Narcotics						
Both Presc. & Dspr.						
0	6.56e-06	.0000896	0.07	0.942	-.000169	.0001821
1	3.28e-06	.0000449	0.07	0.942	-.0000847	.0000912
Prescribers Only						
0	5.24e-06	.0000716	0.07	0.942	-.000135	.0001455
1	7.06e-06	.0000959	0.07	0.941	-.0001809	.000195
Heroin vs. Other and Unspecified Narcotics						
Both Presc. & Dspr.						
0	.9999991	.0000308	3.3e+04	0.000	.9999388	1.000059
1	.9999979	.0000745	1.3e+04	0.000	.999852	1.000144
Prescribers Only						
0	.9999996	.0000155	6.4e+04	0.000	.9999691	1.00003
1	.9999888	.0003975	2515.92	0.000	.9992098	1.000768

CHAPTER III:

OPIOID OVERDOSE DEATHS IN APPALACHIA: A RURAL-URBAN EMPIRICAL ANALYSIS

1 Introduction

This study looks at the impact of Appalachian (APL) status on opioid overdose deaths. The APL region which includes parts of Tennessee, North Carolina, Georgia, Kentucky, Virginia, and the entirety of West Virginia are disproportionately affected by the opioid epidemic with overdose deaths comparably higher than in other parts of the country. Several factors account for the higher opioid death rates in the APL including an elderly demographic, high rates of unemployment, and strong rural communities facilitating the diffusion and diversion of opioids. Furthermore, OxyContin was aggressively marketed in rural areas where an older population with chronic pain, injury prone mine workers, and a manual labor intensive workforce were routinely prescribed narcotics by primary care physicians. Rural areas in the Appalachia, West Virginia, eastern Kentucky, southwestern Virginia, Maine, and Alabama were among the first to be systematically targeted by Purdue Pharma for the promotion and marketing of OxyContin in the 1990s and are currently among those most affected by the opioid epidemic [Paulozzi, 2006, Blanco et al., 2007, McDonald et al., 2012, Keyes et al., 2014, Luu et al., 2019].

Non-medical prescription opioid use is a persistent and escalating public health concern in the United States. Unintentional drug overdose deaths have quadrupled between 1999 and 2007 with more than 70,200 deaths estimated in 2017. The sharpest increase occurred among deaths related to fentanyl and fentanyl analogs with more than 28,400 overdose deaths, while total opioid abuse fatalities rose from 8,048 in

1999 to 47,600 in 2017 [Keyes et al., 2014, Wonder, 2017]. The increased availability of opioids has fueled a rise in the addiction nationally, especially in rural areas where sales of OxyContin, a sustained-release preparation of oxycodone, soared from $48 million to $1.1 billion between 1996 and 2000 and continues to increase today [Cicero et al., 2005, Van Zee, 2009, Unick et al., 2013, Modarai et al., 2013]. This paper extends the literature by providing an empirical perspective on the effects of being part of the APL region on opioid overdose death rates at the state and national levels. It uses a combination of fixed-effects and random-effects modeling techniques to model the impact of APL status and the OxyContin Reformulation of 2010.

2 Literature Review

Rural areas are disproportionately vulnerable to non-medical use of prescription opioids with the literature reporting significant increases in overdose death rates. A study set in rural Utah finds overdose fatality rates to have increased by 317% between 1991 to 1998 and 1999 to 2003 while the national rate rose by 96.6% between 1997 to 2002 [Paulozzi, 2006]. Unintentional drug poisoning mortality rose 62% overall with metropolitan counties increasing by 51% and rural counties by as much as 159%; narcotic deaths increased by 16% in urban areas versus 248% in rural ones [Paulozzi and Xi, 2008]. The rural counties in the Central Plains report overdose fatalities exceeding 30 deaths per 10,000 residents in rural Oklahoma for 2015 [Dombrowski et al., 2016]. Lastly, a rural versus urban knowledge study design finds the prevalence of overdoses to be significantly higher among rural than urban participants at 45.9% and 31.6% respectively, although fewer rural participants reported past 30-day abuse risk behaviors [Dunn et al., 2016]. Nevertheless, the question of whether rural non-medical prescription opioid use surpasses urban is a matter of discussion in the literature. The early 2000s showed rural opioid abuse to at least equal or exceed urban misuse, although the difference is oftentimes insignificant [Wang et al., 2013, Lenardson et al., 2016, Luu et al., 2019]. A study of probationers finds rural participants to be almost five times more likely than their urban counterparts to have misused prescription opioids within three months prior to the arrest [Havens et al., 2007]. Rural adolescents are found to be 26% more likely to have misused prescription opioids after adjusting for race, health, and other drug and alcohol use [Havens et al., 2011]. They also have 35% greater odds of past year opioid abuse than large urban adolescents and present no significant differences with their small urban counterparts whereas another study finds rural female teens to be two times more likely to have severe opioid abuse disorders [Ghandour et al., 2008, Monnat and Rigg, 2016]. Likewise, pregnant women in rural areas have high rates of smoking, using marijuana, and indulged in polysubstance abuse including opioids [Jumah, 2016]. Rural drug users are significantly more likely to have earlier age of onset for use of oxycodone, hydrocodone, benzodiazepines, cocaine, and crack [Young et al., 2012]. Overall, the disproportionate abuse of opioid in rural areas are due to socioeconomic vulnerabilities including limited education, poor health status, high unemployment, and mental health issues. The most common cause for addiction in rural areas however is the perception that prescription opioids are safer to misuse than other illicit drugs [Lenardson et al., 2016, Moody et al., 2017, Rigg et al., 2018].

On the other hand, several studies show urban areas to have a slightly higher prevalence of non-medical prescription use compared to rural although the magnitude of the difference is very small. The Substance Abuse and Mental Health Services Administration reported past year non-medical use of prescription drugs was in general lower among rural areas residents than among metropolitan residents and urbanized metropolitan counties at rates of 5.4% versus 6.4% and 6.6%. These findings are consistent with non-medical use of opioids with lower prevalence in rural counties than metropolitan and urbanized metropolitan counties at rates of 4.2% versus 6.4% and 6.6% in 2013 [SAMHSA, 2013]. Another also finds urban adults more likely to engage in opioid abuse compared to rural while having a higher use of other substances and an earlier initiation into drug abuse [Rigg and Monnat, 2015]. Others report higher rates of abuse in urban than rural areas while pointing to inconsistencies in the literature with national trends potentially obscuring important regional and between state differences [Rigg et al., 2018]. Several factors including density of pharmacy and population may explain the discrepancy. Postal codes in urban, suburban and exurban, and rural areas with a higher pharmacy density tend to see higher non-medical prescription opioid abuse discharges [Cerdá et al., 2017]. A few found no association between population density and opioid abuse thus presenting no evidence of more abuse in more urban areas [Spiller et al., 2009]. Finally, some in the literature find no significant differences in the prevalence of prescription opioid abuse in rural and urban areas and relies on the determinants of drug use to support such claim. A study finds the prevalence of abuse among residents in rural and urban counties to be 4.7% and 4.3% with both types of addicts likely to suffer from severe psychological distress [Wang et al., 2013]. Others see a similar rate of abuse whether urban or rural when adjusting for age, race, and income. A study of rural middle school children present no rural-urban difference of opioid abuse in most of the grade levels [Warren et al., 2017]. However, the study shows significant rural-urban discrepancies in the types of drugs favored by rural and urban schoolchildren.

The rural-urban divide in the prevalence of non-medical prescription opioid use is due to several socioeconomic and cultural factors. Similarly with other rural areas, the Central Appalachia has a population with limited access to health care and health care providers with specialized training. A Drug Enforcement Agency program allowed physicians to receive a waiver exempting them from requirements in the Controlled Substances Act in order to treat individuals with opioid abuse disorders.[Dick et al., 2015, Rosenblatt et al., 2015] However, only 3% of primary care physicians, the largest groups of physicians in rural America, had received the waivers while serving more than 30 million Americans [Stein et al., 2015, Andrilla et al., 2017]. In fact, the shortage of pain practices in rural areas is so severe that only 5% of patients with chronic pain ever seek treatment and there are only 6 pain specialists per 100,000 population [Breuer et al., 2007]. Moreover, there are social and economic factors amplifying rural drug abuse with challenges in fostering trust and encouraging treatment. The strong social and family ties create a solid network for prescription opioid diffusion and diversion [Galea et al., 2003, Moody et al., 2017]. Further, the evidence shows current policies to be ineffective with ever increasing rates of abuse and overdose deaths in areas where strong anti-regulatory sentiments prevail [Spiller et al., 2009, Martins et al., 2009, Modarai et al., 2013]. Another aspect is the route of drug admission wherein rural and urban opioid abusers significantly differ with urban participants more commonly swallowing but rural ones snorting or injecting. Such alternative routes of admission are common with rural drug users, a fact that is likely related to drug problem severity [Young et al., 2010].

This paper contributes to the literature by providing a state and national level analysis on the rural-urban differences in the prevalence of non-medical opioid overdose deaths in the Appalachian states compared non-Appalachian regions. It brings an empirical perspective on the differential impact of the opioid epidemic APL within a somewhat mixed literature by looking at the corresponding overdose deaths. The paper is divided into the following parts: data identification, methodological framework, results interpretation, and discussion.

3 Data

Overdose deaths data per 100,000 population from the National Vital Statistics System's Multiple Cause of Death is used to analyze the divide between the Appalachia region and other states from 2000 to 2017. The Multiple Cause of Death file uses the International Classification of Diseases 10 (ICD-10) to categorize fatalities with external causes of injury such as drug poisoning. All fatalities including opioid related ones are designated as accidental, intentional, or of undetermined intent in referring to the manner of death (X40-X44, X60-X64, X85, and Y10-Y14). The contributing factors of opioid deaths are further subdivided into heroin (T40.1), other opioids (T40.2), methadone (T40.3), other synthetic narcotics (T40.4), and other and unspecified narcotics (T40.6). Furthermore, the Annual Social and Economic Supplement (ASEC) of the Current Population Survey (CPS) is used to derive demographic data with regards to population characteristics, income, educational attainment, health status, and health insurance coverage. The CPS ASEC is a nationally representative survey providing annual estimates based on a survey of more than 75,000 households. It is noted that the estimates from 2014 are excluded from the analysis as a result of the Census Bureau's experimental redesign where new health insurance questions were asked to about 3/8ths of the total sample whereas the remaining respondents were given the existing income questions. The exclusion has no material impact on the analysis.

3.1 Summary Statistics

A summary of per capita overdose deaths by opioid types and Appalachia status is found in table 1. The data shows no statistically significant differences between the means of heroin overdose deaths in APL and non-APL states with per capita averages of 2.34 to 2.39. Other synthetic narcotics deaths are much greater in non-

APL states at 4.12 compared to 2.96. Non-APL regions significantly exhibit a higher rate of other and unspecified narcotics deaths compared to APL states at 1.47 per 100,000 population compared to only 0.71 for APL during the time period analyzed. APL states however have significantly higher rates of overdose deaths in both the methadone and other opioids categories with almost twice as many deaths as non-APL regions. Other opioids overdose deaths in APL are close to double that of non-APL at 5.42 deaths per capita compared to non-APL with 3.28 deaths while the ratio for methadone fatalities are 2.04 to 1.57. Note that methadone is an opioid which can be used in medication-assisted treatment (MAT) to help people reduce or quit their use of heroin or other opiates.

Furthermore, the data in table 1 shows various demographic characteristics such as the share of observations in APL regions which is only about a tenth of the entire data set. These APL states are Tennessee, North Carolina, Georgia, Kentucky, Virginia, and West Virginia. A binary control for the OxyContin reformulation of 2010 is included in the analysis to account for its documented disproportionate impact on opioid addiction in rural areas, especially the APL. Overall, the data has a large proportion of non-Hispanic whites, slightly more females, and age is somewhat evenly distributed an average of 5 per cent to 8 per cent in each five year bin. About 15% of the survey respondents lack a high school degree whereas 22% to 23% obtained a secondary diploma. Measures of income levels include annual family income with a quarter of the population earning an amount greater than \$90,000 per year, and 8 to 9 per cent surviving on less than \$10,000 annually. Welfare income such as Social Security benefits data show about 63% receive some form of government assistance amounting to less than \$5000 each year. Moreover, the data includes an average of 7% veterans with some a small figure receiving disability benefits. Additional information relating to chronic pain, thus relating to potential legitimate opiate needs, is collected including responding with physical, mobility, or care difficulty. About 3 per cent of survey respondents report some sort of physical difficulty while a significant majority reports being in excellent, very good, or good health. Finally, data on health insurance coverage indicate a disproportionate amount of Medicaid recipients, followed by Medicare, and private insurance.

4 Methodology

4.1 Fixed-Effects Regression

The effects of the APL status on per capita opioid overdose death is analyzed using a panel regression model such that

$$Overdose_{it} = \beta_0 + \beta_1 X_{it} + \beta_2 Z_i + \beta_3 T_t + u_{it}$$

where β_1 measures the effect of a covariate X_i on state overdose death for the time period, $t = 2000, ..., 2017$, analyzed holding all else constant. T_t is a time fixed-effects to account for each year's impact on overdose deaths. Z_i is a time-invariant state fixed-effects across $i = 1, ..., 50$. The Appalachian status of interest is included in both the intercept β_0 and β_2,and letting $\alpha_i = \beta_0 + \beta_2 Z_i$, the model becomes

$$Overdose_{it} = \alpha_i + \beta_1 X_{it} + \beta_3 T_t + u_{it} \tag{1}$$

with α_i being the individual state fixed-effects where the variation comes from Z_i, and the outcome variable is allowed to be correlated with covariate X which changes over time. u_{it} is an independent error term.

4.2 Random-Effects Regression

The fixed-effects model is expanded into a random-effects model where variation across state opioid overdose rates are assumed to be random and uncorrelated with predictor variables X_i. The model is as follows

$$Overdose_{it} = \alpha_i + \delta Appalachia_i + \beta_1 X_{it} + \beta_3 T_t + \epsilon_{it} + u_{it} \tag{2}$$

where ϵ_{it} is the between-entity error term and u_{it} is the within-entity error. δ is the estimates of the effects on opioid overdose deaths given that a state is located in the Appalachia region.

5 Results

5.1 Fixed-Effects Regression

The fixed-effects regression results in table 2 shows the OxyContin reformulation of 2010 and any subsequent years to be a significant predictor in opioid overdose deaths. Across all states, the reformulation caused a highly significant overdose deaths increase of 4.61 and 1.26 more heroin and methadone deaths, respectively. The reformulation had no effect on other and unspecified narcotics, other opioids, and other synthetic narcotics. The combination of APL status and post-OxyContin reformulation however leads to a slight decrease in methadone overdoses per 100,000 people whereas other opioids and other synthetic narcotics deaths are significantly increased by 3.12 to 2.43 each. Post reformulation Appalachia seem to see no significant effect on heroin and other and unspecified narcotics. The prevalence of other opioids and other synthetic narcotics fatalities after the OxyContin reformulation in most rural areas is consistent with the literature. This points to the aggressive marketing of the opioids in non-urban areas where an older and labor intensive population prone to chronic pain became disproportionately addicted to opioids. These effects are even more pronounced in rural areas in the APL which is confirmed by the analysis results.

There is some evidence showing non-Hispanic whites to be somewhat less vulnerable to overdosing on methadone and other opioids, both categories with higher proportion of overdoses in the APL, although at a smaller rate. Obtaining a high school education reduces the potential for heroin overdoses but seem to have no effect in other opioids categories. Veteran status significantly increases the likelihood of overdosing on other and unspecified narcotics. Individuals receiving Social Security income between \$10,000 and \$15,000 have a decreased likelihood of overdosing on both other opioids and other synthetic narcotics whereas earning an annual family income of a similar amount increases the potential for heroin overdose per capita. Across all opioid categories but methadone, reporting a physical difficulty such as injury or chronic pain leads to a significant increase in overdose fatalities. Only per capita methadone overdose deaths are negatively affected by physical difficulty, perhaps due its use in medication-assisted treatment for pain. Overall, the findings show residents in APL states, with lower income, and suffering from physical difficulties post-OxyContin Reformulation are more likely to experience higher rates of opioid overdose deaths.

5.2 Random-Effects Regression

As a robustness check, the effects of APL status are assumed to be uncorrelated with the other predictor variables in the random-effects model found in table 3. The results are consistent with the previous fixed-effects model with APL status itself being significant in increasing methadone per capita overdose deaths by 0.806. OxyContin reformulation remains statistically significant and positively related with methadone overdoses by an additional 1.54 whereas 2 less deaths per capita are observed for other and unspecified narcotics. Post reformulation Appalachian regions see a 3.12 and 2.29 increase in per capita other opioids and other synthetic narcotics fatal overdoses each.

Unlike the fixed-effects model, being of non-Hispanic white descent significantly increases the likelihood for more heroin and other synthetic and narcotics deaths, while marriage significantly reduces such effects in all categories but other opioids. As found in some of the literature, veteran status positively increases the likelihood for opioid overdose fatalities. All age categories are indiscriminately at higher risk of overdosing on opioid, although younger adults tend to overdose more on heroin and methadone. All age groups are equally likely to overdose on other opioids and other synthetic narcotics. Earning an annual family income of less than \$20,000 leads to a decrease in overdose deaths for most opioid categories, which is also the case the for those receiving Social Security Income between \$10,000 and \$15,0000. However, a one per cent increase in respondents receiving work disability compensation leads to 0.25 and 0.51 more per capita methadone and other synthetic narcotics overdoses. Having a physical difficulty or being in fair health had a reducing impact on methadone deaths while being a positive risk factors for other opioids overdoses. Finally, Medicare recipients were at a decreased risks of overdosing on other and unspecified narcotics while privately insured individuals saw an increase in methadone fatalities per capita. Overall, the random-effects model provided additional insight into the impact of APL status and OxyContin reformulation, especially with Methadone overdoses which seem to be caused by several factors more prevalent in rural areas including pain treatment, fair health status, physical difficulty, a higher rate of elderly and veterans, and a higher rate of unemployment.

5.3 Robustness Checks: Purdue Pharma Targeted States

As a robustness test, states targeted by Purdue Pharma in the marketing of reformulated OxyContin are used as an instrument for rural areas. This treatment is posited as a an exogenous shock uncorrelated with inherent characteristics found in the Appalachian regions. These regions are located in West Virginia, eastern Kentucky, southwestern Virginia, Maine, Alabama, and states across the Appalachia. In the random effects framework found in table 4, the results are highly consistent with the previous results. Methadone overdose deaths soared in those targeted states. OxyContin Reformulation in those states also increased by 2.19 to 1.76 more other opioids and other synthetic narcotics deaths.

6 Discussion

States in APL experienced significantly higher rates of per capita opioid deaths as a result of their geographic location. These effects were highly significant for methadone and other opioids fatalities, and heroin and other synthetic opioids to a lesser extent. The fact that rural areas in APL have similar and even greater rates of overdose fatalities for every type of opioids but other and unspecified narcotics is a dire reminder of their significantly higher vulnerability to the opioid epidemic. Not only are they at a greater risk of opioid overdose deaths, the OxyContin reformulation was aggressively and systematically marketed in those very rural APL areas, exacerbating the likelihood of overdose. Although limited by the unavailability of mortality data at the rural and urban county level, this study nonetheless produces an insight in the APL opioid issue at the national and state level with results consistent with the literature.

The findings show a deadly epidemic that disproportionately affects a generally homogeneous population tending to be older and less educated. With an elderly population most likely suffering from chronic pain and experiencing physical difficulty, or a labor intensive industry, the use of pain relievers is oftentimes a necessity. Additionally, the poor level of educational attainment in rural places has been shown to skew the perception of non-medical opioid abuse, perceiving it as safer than other illicit alternatives. Furthermore, the strong family ties and social network within rural communities lend to a greater diffusion and diversion of opioids, thus intensifying the epidemic. Nevertheless, several national and state level policies are ongoing to curb the crisis. For instance, the Drug Enforcement Agency created a program exempting primary care physicians from certain requirements of the Controlled Substances Act and treat patient with opioid disorders in medication-assisted treatments. Other initiatives are aimed at reducing the shortage of pain specialists in rural areas by training primary care physicians, who make up the vast majority of care providers in non-urban areas, in the adequate treatment of pain. Finally, there is a need to educate rural and non-rural residents alike on the true risk of opioid abuse, especially on the risk of addiction as non-medical use of opioids is mistakenly perceived as a "safer" alternative.

References

Andrilla, C Holly A, Coulthard, Cynthia, & Larson, Eric H. 2017. Barriers rural physicians face prescribing Buprenorphine for opioid use disorder. *The Annals of Family Medicine*, **15**(4), 359–362.

Blanco, Carlos, Alderson, Donald, Ogburn, Elizabeth, Grant, Bridget F, Nunes, Edward V, Hatzenbuehler, Mark L, & Hasin, Deborah S. 2007. Changes in the prevalence of non-medical prescription drug use and drug use disorders in the United States: 1991–1992 And 2001–2002. *Drug and Alcohol Dependence*, **90**(2-3), 252–260.

Breuer, Brenda, Pappagallo, Marco, Tai, Julia Y, & Portenoy, Russell K. 2007. US board-certified pain physician practices: uniformity and census data of their locations. *The Journal of Pain*, **8**(3), 244–250.

Cerdá, Magdalena, Gaidus, Andrew, Keyes, Katherine M, Ponicki, William, Martins, Silvia, Galea, Sandro, & Gruenewald, Paul. 2017. Prescription opioid poisoning across urban and rural areas: identifying vulnerable groups and geographic areas. *Addiction*, **112**(1), 103–112.

Cicero, Theodore J, Inciardi, James A, & Muñoz, Alvaro. 2005. Trends in abuse of Oxycontin® and other opioid analgesics in the United States: 2002-2004. *The Journal of Pain*, **6**(10), 662–672.

Dick, Andrew W, Pacula, Rosalie L, Gordon, Adam J, Sorbero, Mark, Burns, Rachel M, Leslie, Douglas, & Stein, Bradley D. 2015. Growth in buprenorphine waivers for physicians increased potential access to opioid agonist treatment, 2002–11. *Health Affairs*, **34**(6), 1028–1034.

Dombrowski, Kirk, Crawford, Devan, Khan, Bilal, & Tyler, Kimberly. 2016. Current rural drug use in the US midwest. *Journal of Drug Abuse*, **2**(3).

Dunn, Kelly E, Barrett, Frederick S, Yepez-Laubach, Claudia, Meyer, Andrew C, Hruska, Bryce J, Petrush, Kathy, Berman, Suzan, Sigmon, Stacey C, Fingerhood, Michael, & Bigelow, George E. 2016. Opioid overdose experience, risk behaviors, and knowledge in drug users from a rural versus an urban setting. *Journal of Substance Abuse Treatment*, **71**, 1–7.

Galea, Sandro, Ahern, Jennifer, & Vlahov, David. 2003. Contextual determinants of drug use risk behavior: a theoretic framework. *Journal of Urban Health*, **80**(3), iii50–iii58.

Ghandour, Lilian A, Martins, SS, & Chilcoat, HD. 2008. Understanding the patterns and distribution of opioid analgesic dependence symptoms using a latent empirical approach. *International Journal of Methods in Psychiatric Research*, **17**(2), 89–103.

Havens, Jennifer R, Oser, Carrie B, Leukefeld, Carl G, Webster, J Matthew, Martin, Steven S, O'Connell, Daniel J, Surratt, Hilary L, & Inciardi, James A. 2007. Differences in prevalence of prescription opiate misuse among rural and urban probationers. *The American Journal of Drug and Alcohol Abuse*, **33**(2), 309–317.

Havens, Jennifer R, Young, April M, & Havens, Christopher E. 2011. Nonmedical prescription drug use in a nationally representative sample of adolescents: evidence of greater use among rural adolescents. *Archives of Pediatrics & Adolescent Medicine*, **165**(3), 250–255.

Jumah, Naana Afua. 2016. Rural, pregnant, and opioid dependent: a systematic review. *Substance Abuse: Research and Treatment*, **10**, SART–S34547.

Keyes, Katherine M, Cerdá, Magdalena, Brady, Joanne E, Havens, Jennifer R, & Galea, Sandro. 2014. Understanding the rural–urban differences in nonmedical prescription opioid use and abuse in the United States. *American Journal of Public Health*, **104**(2), e52–e59.

Lenardson, MHS, Jennifer, D, Gale, MS, John, A, & Ziller PhD, Erika. 2016. Rural opioid abuse: prevalence and user characteristics.

Luu, Huong, Slavova, Svetla, Freeman, Patricia R, Lofwall, Michelle, Browning, Steven, & Bush, Heather. 2019. Trends and patterns of opioid analgesic prescribing: regional and rural-urban variations in Kentucky from 2012 to 2015. *The Journal of Rural Health*, **35**(1), 97–107.

Martins, Silvia S, Storr, Carla L, Zhu, Hong, & Chilcoat, Howard D. 2009. Correlates of extramedical use of Oxycontin® versus other analgesic opioids among the US general population. *Drug and Alcohol Dependence*, **99**(1-3), 58–67.

McDonald, Douglas C, Carlson, Kenneth, & Izrael, David. 2012. Geographic variation in opioid prescribing in the US. *The Journal of Pain*, **13**(10), 988–996.

Modarai, F, Mack, K, Hicks, P, Benoit, S, Park, S, Jones, C, Proescholdbell, S, Ising, A, & Paulozzi, L. 2013. Relationship of opioid prescription sales and overdoses, North Carolina. *Drug and Alcohol Dependence*, **132**(1-2), 81–86.

Monnat, Shannon M, & Rigg, Khary K. 2016. Examining rural/urban differences in prescription opioid misuse amongUS adolescents. *The Journal of Rural Health*, **32**(2), 204–218.

Moody, Lara N, Satterwhite, Emily, & Bickel, Warren K. 2017. Substance use in rural Central Appalachia: current status and treatment considerations. *Journal of Rural Mental Health*, **41**(2), 123.

Paulozzi, Leonard J. 2006. Opioid analgesic involvement in drug abuse deaths in American metropolitan areas. *American Journal of Public Health*, **96**(10), 1755–1757.

Paulozzi, Leonard J, & Xi, Yongli. 2008. Recent changes in drug poisoning mortality in the United States by urban–rural status and by drug type. *Pharmacoepidemiology and Drug Safety*, **17**(10), 997–1005.

Rigg, Khary K, & Monnat, Shannon M. 2015. Urban vs. Rural differences in prescription opioid misuse among adults in the united states: informing region specific drug policies and interventions. *International Journal of Drug Policy*, **26**(5), 484–491.

Rigg, Khary K, Monnat, Shannon M, & Chavez, Melody N. 2018. Opioid-related mortality in rural America: geographic heterogeneity and intervention strategies. *International Journal of Drug Policy*, **57**, 119–129.

Rosenblatt, Roger A, Andrilla, C Holly A, Catlin, Mary, & Larson, Eric H. 2015. Geographic and specialty distribution of US physicians trained to treat opioid use disorder. *The Annals of Family Medicine*, **13**(1), 23–26.

SAMHSA. 2013. The NSDUH Report: nonmedical use of prescription-type drugs by county type.

Spiller, Henry, Lorenz, Douglas J, Bailey, Elise J, & Dart, Richard C. 2009. Epidemiological trends in abuse and misuse of prescription opioids. *Journal of Addictive Diseases*, **28**(2), 130–136.

Stein, Bradley D, Pacula, Rosalie Liccardo, Gordon, Adam J, Burns, Rachel M, Leslie, Douglas L, Sorbero, Mark J, Bauhoff, Sebastian, Mandell, Todd W, & Dick, Andrew W. 2015. Where is buprenorphine dispensed to treat opioid use disorders? The role of private offices, opioid treatment programs, and substance abuse treatment facilities in urban and rural counties. *The Milbank Quarterly*, **93**(3), 561–583.

Unick, George Jay, Rosenblum, Daniel, Mars, Sarah, & Ciccarone, Daniel. 2013. Intertwined epidemics: national demographic trends in hospitalizations for heroin- and opioid-related overdoses, 1993–2009. *PloS One*, **8**(2), e54496.

Van Zee, Art. 2009. The promotion and marketing of Oxycontin: commercial triumph, public health tragedy. *American Journal of Public Health*, **99**(2), 221–227.

Wang, Karen H, Becker, William C, & Fiellin, David A. 2013. Prevalence and correlates for nonmedical use of prescription opioids among urban and rural residents. *Drug and Alcohol Dependence*, **127**(1-3), 156–162.

Warren, Jacob C, Smalley, K Bryant, & Barefoot, K Nikki. 2017. Recent alcohol, tobacco, and substance use variations between rural and urban middle and high school students. *Journal of Child & Adolescent Substance Abuse*, **26**(1), 60–65.

Wonder, CDC. 2017. *Overdose Death Rates*. `https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates`. Accessed: 2019-05-08.

Young, April M, Havens, Jennifer R, & Leukefeld, Carl G. 2010. Route of administration for illicit prescription opioids: a comparison of rural and urban drug users. *Harm Reduction Journal*, **7**(1), 24.

Young, April M, Havens, Jennifer R, & Leukefeld, Carl G. 2012. A comparison of rural and urban nonmedical prescription opioid usersâ lifetime and recent drug use. *The American Journal of Drug and Alcohol Abuse*, **38**(3), 220–227.

APPENDIX D: CHAPTER III TABLES

Table 1: Summary Statistics of Selected Variables

	Appalachian Regions					Non-Appalachian Regions				
Variables*	**N**	**Mean**	**Std. Dev.**	**Min**	**Max**	**N**	**Mean**	**Std. Dev.**	**Min**	**Max**
Opioid Overdose Deaths (per 100,000 population)										
Heroin	*73*	2.34	2.86	0.10	13.49	*486*	2.39	2.53	0.15	18.44
Methadone	*101*	2.04	1.20	0.23	6.11	*649*	1.57	1.03	0.12	5.45
Other Opioids	*102*	5.42	4.93	0.84	25.87	*718*	3.28	2.31	0.18	12.65
Other Synthetic Narcotics	*100*	2.96	4.93	0.17	34.97	*590*	2.12	4.12	0.09	30.64
Other & Unspecified Narcotics	*95*	0.71	0.46	0.11	2.35	*516*	1.47	1.52	0.16	8.68
Demographic Characteristics (%)										
White	*102*	76.24	11.27	55.35	94.66	*733*	78.27	14.82	15.52	98.78
Black	*102*	17.00	9.77	2.32	36.86	*733*	11.14	12.02	0.08	70.22
Hispanic	*102*	6.52	3.51	0.55	14.71	*733*	13.34	12.21	0.62	53.73
Male	*102*	47.08	1.07	44.84	49.72	*733*	47.68	1.36	42.29	51.73
Female	*102*	50.74	0.75	48.35	52.57	*733*	50.52	1.14	45.98	54.56
Unemployed	*102*	2.94	0.96	1.51	5.60	*733*	2.97	1.04	0.79	7.48
Veteran Status	*102*	7.14	1.11	4.91	10.77	*733*	6.69	1.47	2.96	11.86
Education Level (%)										
Less than 12th Grade	*102*	16.11	2.04	12.23	21.29	*733*	14.47	2.77	8.45	22.48
High School	*102*	23.71	3.65	16.70	32.94	*733*	21.62	2.85	14.05	29.41
Bachelor	*102*	10.94	2.40	5.92	16.14	*733*	6.26	1.53	2.17	11.25
Annual Family Income Level (%)										
Less than $10,000	*102*	9.05	1.67	4.94	12.87	733	*7.70*	2.18	3.43	15.32
$10,000 to $19,999	*102*	10.94	2.22	5.47	16.66	733	*9.53*	2.32	4.40	19.20
Greater than $90,000	*102*	22.22	6.83	7.88	40.24	733	25.93	8.05	8.44	48.13
Annual Social Security Income (%)										
Less than $5,000	*102*	62.86	1.92	57.75	66.93	*733*	63.47	2.34	58.01	73.79
$5,000 to $9,999	*102*	4.49	1.33	2.40	9.32	*733*	3.97	1.24	1.72	8.28
Health Status (%)										
Excellent	*102*	31.56	4.28	20.47	40.28	*733*	34.60	4.12	22.19	47.13
Good	*102*	23.85	2.45	19.71	30.04	*733*	22.37	2.81	13.27	32.60
Fair	*102*	8.57	1.65	5.85	12.19	*733*	7.18	1.56	3.96	13.99
Poor	*102*	4.44	1.49	2.29	8.66	*733*	2.92	1.01	1.21	6.80
Physical Difficulty	*102*	2.73	3.07	0.00	8.92	*733*	2.34	2.54	0.00	8.71
Mobility Difficulty	*102*	1.50	1.68	0.00	5.14	*733*	1.37	1.48	0.00	5.21
Care Difficulty	*102*	0.75	0.86	0.00	2.69	*733*	0.68	0.75	0.00	2.57
Health Insurance Coverage (%)										
Medicaid	*102*	82.76	4.35	68.25	91.92	*733*	83.26	4.85	66.56	94.16
Medicare	*102*	62.09	1.80	57.60	65.89	*733*	62.54	2.09	57.15	69.58
Private	*102*	33.10	4.19	24.24	40.89	*733*	30.13	6.86	13.72	47.79

**Expressed in percentages unless otherwise specified*

Source: Current Population Survey - Annual Social and Economic Supplement Survey, 2000-2017, excluding 2014

Table 2: Fixed Effects Regression Results

	Overdose Deaths Per Capita				
Variables	**Heroin**	**Methadone**	**Other & Unspecified Narcotics**	**Other Opioids**	**Other Synthetic Narcotics**
Appalachian Region Indicators					
Post-OxyContin Reformulation	4.605***	1.257**	0.0351	1.042	2.134
	(1.347)	(0.443)	(0.598)	(0.991)	(2.390)
Post-OxyContin Ref. Appalachia	0.329	-0.319*	0.187	3.123***	2.430***
	(0.404)	(0.129)	(0.167)	(0.301)	(0.658)
Demographic Indicators					
White	0.0355	-0.0718***	0.00736	-0.0861*	-0.0759
	(0.0521)	(0.0166)	(0.0241)	(0.0350)	(0.0896)
High School Education	-0.183*	-0.0472	0.0453	-0.0326	-0.0738
	(0.0835)	(0.0269)	(0.0364)	(0.0589)	(0.144)
Veteran Status	0.0762	-0.00285	0.187**	0.105	-0.425
	(0.159)	(0.0503)	(0.0711)	(0.112)	(0.272)
Age 20 to 24	0.360	0.0999	-0.0708	0.144	0.673*
	(0.193)	(0.0615)	(0.0822)	(0.136)	(0.326)
Age 25 to 29	0.473**	0.131*	-0.124	0.392**	0.940**
	(0.170)	(0.0545)	(0.0762)	(0.123)	(0.299)
Age over 65	0.0610	0.0742	-0.255**	0.170	0.905**
	(0.189)	(0.0627)	(0.0825)	(0.142)	(0.329)
Family Income $10,000 to $19,999	0.255***	0.0378	0.0240	0.0783	0.169
	(0.0762)	(0.0242)	(0.0329)	(0.0542)	(0.133)
Social Security Income $10,000 to $15,000	0.312	-0.0177	0.325**	-0.360*	-0.358
	(0.250)	(0.0788)	(0.107)	(0.179)	(0.425)
Work Disability Compensation	0.108	0.0581	0.0582	0.0228	0.222
	(0.141)	(0.0449)	(0.0602)	(0.101)	(0.245)
Physical Difficulty	0.447***	-0.123**	0.142*	0.463***	0.351
	(0.126)	(0.0380)	(0.0566)	(0.0870)	(0.204)
Poor Health Status	-0.153	-0.0130	-0.127	0.126	-0.165
	(0.175)	(0.0537)	(0.0757)	(0.121)	(0.288)
Medicaid Recipients	-0.0474	0.0176	0.0117	0.0135	-0.0700
	(0.0394)	(0.0130)	(0.0175)	(0.0290)	(0.0693)
Medicare Recipients	0.0417	0.0477	-0.0474	0.116	0.179
	(0.215)	(0.0688)	(0.0975)	(0.155)	(0.371)
Year Fixed-Effects	Yes	Yes	Yes	Yes	Yes
No. of observations	559	750	611	820	690
R^2	0.357	0.0915	0.0212	0.192	0.362

*Standard Errors in parentheses; * p<0.05, ** p<0.01, *** p<0.001*

Table 3: Random Effects Regression Results

	Overdose Deaths Per Capita				
Variables	**Heroin**	**Methadone**	**Other & Unspecified Narcotics**	**Other Opioids**	**Other Synthetic Narcotics**
Appalachian Region Indicators					
Appalachian Status	0.797	0.806***	-0.189	0.589	0.657
	(0.421)	(0.139)	(0.242)	(0.596)	(0.522)
Post-OxyContin Reformulation	-0.681	1.540**	-2.009*	1.270	2.159
	(1.294)	(0.495)	(0.824)	(0.927)	(1.862)
Post-OxyContin Ref. Appalachia	0.358	-0.173	0.359	3.121***	2.289***
	(0.479)	(0.185)	(0.293)	(0.313)	(0.681)
Demographic Indicators					
White	0.0666***	0.00544	0.00524	-0.0138	0.0982***
	(0.0140)	(0.00441)	(0.0107)	(0.0162)	(0.0253)
High School Education	0.0266	-0.0123	-0.155***	-0.00429	0.0308
	(0.0547)	(0.0214)	(0.0356)	(0.0540)	(0.0817)
Veteran Status	0.0606	0.169***	0.265***	0.117	0.0628
	(0.0993)	(0.0397)	(0.0642)	(0.103)	(0.150)
Age 20 to 24	0.188	0.0601	0.0657	0.0913	0.602
	(0.221)	(0.0833)	(0.141)	(0.140)	(0.316)
Age 25 to 29	0.592**	0.178*	0.0300	0.392**	0.998***
	(0.189)	(0.0701)	(0.125)	(0.124)	(0.267)
Age over 65	0.737***	0.164*	-0.183	0.242	0.880**
	(0.190)	(0.0744)	(0.120)	(0.139)	(0.281)
Family Income \$10,000 to \$19,999	-0.0608	-0.0731*	-0.152**	0.0596	-0.140
	(0.0839)	(0.0310)	(0.0527)	(0.0551)	(0.122)
Social Security Income \$10,000 to \$15,000	-0.914***	-0.0183	0.233	-0.607***	-1.245**
	(0.274)	(0.103)	(0.169)	(0.183)	(0.396)
Work Disability Compensation	0.0353	0.253***	-0.0135	0.00813	0.506*
	(0.149)	(0.0550)	(0.0914)	(0.102)	(0.213)
Physical Difficulty	0.293*	-0.209***	0.135	0.423***	0.180
	(0.145)	(0.0517)	(0.0905)	(0.0895)	(0.197)
Poor Health Status	0.00958	0.0476	0.166	0.264*	-0.0983
	(0.0839)	(0.0310)	(0.0527)	(0.0551)	(0.122)
Medicare Recipients	-0.0225	-0.123	-0.485**	0.0420	-0.489
	(0.238)	(0.0909)	(0.156)	(0.160)	(0.347)
Year Fixed-Effects	Yes	Yes	Yes	Yes	Yes
No. of observations	559	750	611	820	690
R^2	0.591	0.486	0.401	0.457	0.569

*Standard Errors in parentheses; * p<0.05, ** p<0.01, *** p<0.001*

Table 4: Random Effects Regression Results - Purdue Pharma

	Overdose Deaths Per Capita				
Variables	**Heroin**	**Methadone**	**Other & Unspecified Narcotics**	**Other Opioids**	**Other Synthetic Narcotics**
Appalachian Region Indicators					
Purdue Pharma Target States	0.591	0.793***	-0.355	0.399	0.270
	(0.425)	(0.131)	(0.230)	(0.695)	(0.511)
Post-OxyContin Reformulation	-0.494	1.293**	-1.830*	1.699	2.419
	(1.306)	(0.501)	(0.829)	(0.958)	(1.896)
Post-OxyContin Ref. in Target States	-0.0479	-0.302	0.461	2.191***	1.761**
	(0.464)	(0.169)	(0.283)	(0.285)	(0.638)
Demographic Indicators					
White	0.0653***	0.00625	0.00458	-0.0260	0.0945***
	(0.0142)	(0.00444)	(0.0107)	(0.0197)	(0.0255)
High School Education	0.0322	-0.0105	-0.150***	0.00127	0.0461
	(0.0552)	(0.0214)	(0.0358)	(0.0564)	(0.0825)
Veteran Status	0.0750	0.157***	0.279***	0.0915	0.0620
	(0.100)	(0.0400)	(0.0646)	(0.109)	(0.152)
Age 20 to 24	0.212	0.0640	0.0772	0.0428	0.625
	(0.223)	(0.0831)	(0.140)	(0.140)	(0.320)
Age 25 to 29	0.630***	0.204**	0.0424	0.340**	1.077***
	(0.191)	(0.0694)	(0.123)	(0.125)	(0.268)
Age over 65	0.720***	0.167*	-0.192	0.198	0.863**
	(0.192)	(0.0746)	(0.120)	(0.142)	(0.284)
Family Income $10,000 to $19,999	-0.0561	-0.0782*	-0.151**	0.0809	-0.128
	(0.0846)	(0.0311)	(0.0527)	(0.0557)	(0.123)
Social Security Income $10,000 to $15,000	-0.930***	-0.00411	0.222	-0.590**	-1.242**
	(0.276)	(0.104)	(0.169)	(0.185)	(0.401)
Work Disability Compensation	0.00544	0.208***	-0.00299	-0.0290	0.412
	(0.151)	(0.0557)	(0.0919)	(0.104)	(0.217)
Physical Difficulty	0.269	-0.204***	0.116	0.417***	0.117
	(0.147)	(0.0527)	(0.0911)	(0.0915)	(0.202)
Poor Health Status	0.112	0.0851	0.176	0.266*	0.0773
	(0.192)	(0.0650)	(0.112)	(0.123)	(0.251)
Medicare Recipients	0.0183	-0.108	-0.493**	0.151	-0.398
	(0.240)	(0.0909)	(0.156)	(0.160)	(0.350)
Year Fixed-Effects	Yes	Yes	Yes	Yes	Yes
No. of observations	559	750	611	820	690
R^2	0.584	0.485	0.403	0.382	0.561

*Standard Errors in parentheses; * $p<0.05$, ** $p<0.01$, *** $p<0.001$*