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A Study of Addiction: The Opioid Epidemic, An Analysis at the State and County Level

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Abstract

Addictive diseases such as those stemming from the use of alcohol, cocaine and opioids lead to serious negative consequences at both the individual and societal level. Over the last two decades, there has been a significant increase in opioid prescriptions and addiction. The potential for addiction is related to factors that include genetics, prescriber behavior, user behavior and characteristics, in addition to environmental and systemic determinants. One measure of the seriousness of the opioid epidemic is the number of overdose deaths. In 2017, drug overdoses killed over seventy thousand Americans, and overdose deaths are projected to increase in the future. Despite the risk of addiction and overdose, opioids are commonly prescribed to combat pain. This paper uses cross-sectional county and state level data to examine the socioeconomic, demographic, and community level factors that are important in explaining opioid overdose deaths

I. Introduction: Addiction, Opioids, and the Opioid Epidemic

Understanding the opioid epidemic and developing effective policy solutions in addition to treatment options for opioid addiction requires an interdisciplinary approach. The range of relevant literature incorporates the biological/chemical and non-biological causes of addiction, pain prevalence and its management, the historical events leading to the role of opioids in treating pain, and knowledge about the epidemic from empirical studies.

A. Addiction and Opioids

1. Addictive Diseases Are Costly

Addictive diseases such as those stemming from the use of alcohol, cocaine and opioids lead to serious negative consequences at both the individual and societal level. Addiction adversely affects an individual's mental and physical health. In addition, the societal and economic costs are substantial. These diseases have been associated with an increase in other diseases such as hepatitis, domestic and child abuse, crime, and lost wages and employment.

2. Addiction is a Chronic Brain Disease

Addiction is a chronic disease of the brain that is characterized by compulsive substance use, impaired control, craving, and social problems. Like other chronic diseases, addiction often involves cycles of relapse and remission. (Dennis et al 2007, Sussman and Sussman 2011). The human brain consists of billions of complex cells called neurons which are organized into networks. When a neuron receives enough signals from other neurons, it sends its own signal to the other neurons in its network. Some drugs interfere with this process of communication by mimicking the signals of natural neurons (NIDA 2018). This inference can lead to changes in the structure of the brain and addiction.

The purpose of prescription opioids is to effectively manage pain; however, patients using opioids risk becoming addicted to the medication. Just under a third of opioid prescriptions are estimated to be misused (Doyle 2016). Opioid addiction is characterized by dependence on opioid substances. The brain is naturally inclined to repeat actions that stimulate the reward system or provoke feelings of pleasure. Once a person has taken opiates, their brain wants to repeat the pleasurable feeling and effectively trains itself to be addicted to drugs. On a neurological level, opioids attach to a neuron's opioid receptor in the brain and block pain (Labonville 2017, Van Zee 2009). Even though opioid addiction is treatable like many other chronic diseases, in practice, it is often untreated and stigmatized (Chandler et al 2009, Dennis et al 2007). Because drug abuse changes the structure of the brain, opioid addiction is progressive if left untreated, resulting in a significant impact on mental and physical health (Weber 2019).

3. Factors Affecting Addiction

In 2011, The American Society of Addictions Medicine (ASAM) released a new definition of addiction which focuses on addiction as a chronic brain disorder rather than a behavioral problem. Their definition states:

> Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences. (ASAM 2011)

It has been suggested that genetics account for about 50% of the likelihood that someone will develop an addiction. There are many other factors that determine an individual's likelihood of addiction, however, having a family history of addiction significantly increases the risk of addiction. Environmental factors such as family interactions and culture interact with an individual's biological factors and affect the extent to which genetic factors exert their influence (Smith 2012). In addition, the potential for addiction is related to factors that include individual and psychological characteristics, socioeconomic status, and geographical area. Public policy also plays an important role. For example, government regulation determines both the viability of opioid prescriptions and accessibility of opioid addiction treatment.

4. Types of Opioids

The term "opioid" typically includes opiates, semi-synthetic opioids and synthetic opioids. Opiates are natural substances that originate from opium that is extracted from the opium poppy. Opium poppies contain more than twenty different opiates (Labonville 2017). Of those opiates, only four are used by the medical industry: morphine, codeine, thebaine and papaverine. Morphine and codeine are two of the oldest pain medications still prescribed by doctors today (Elkins 2018).

Although semi-synthetic and synthetic opioids bind to the same receptors in the brain as opiates, they do not occur naturally. While synthetic opioids are entirely manufactured, semi-synthetic opioids are a hybrid resulting from chemical modifications to opiates (Labonville 2017). For example, thebaine is converted into other chemicals, such as oxycodone or hydrocodone. Therefore, oxycodone and hydrocodone are classified as semi-synthetic opioids. They are popular pain medications. Well-known synthetic opioids include methadone, fentanyl, and meperidine (Elkins 2018).

Opioids are also categorized as a narcotic. According to the Drug Enforcement Administration, the term "narcotic" was once used to describe any drug that relieved pain and caused relaxation, but is now commonly used to refer to opioids, (Elkins 2018). However, the term is no longer used in medical settings due to its association with illegal drugs (Labonville 2017).

5. Opioid Overdose and Tolerance

While opioids can be used to relieve pain, opioids also affect the part of the brain that regulates breathing. When someone takes high doses of opioids, it can lead to an overdose with the slowing or stopping of breathing and sometimes death (Elkins 2018). Symptoms of opioid overdose include confusion, delirium, frequent vomiting, pinpoint pupils, the inability to wake up, intermittent loss of consciousness, breathing problems, respiratory arrest, and cold or bluish skin around the lips or under the fingernails (AAC 2019). In 2011, the Centers for Disease Control and Prevention (CDC) classified overdoses from prescription painkillers as an epidemic. The leading cause of accidental death in the United States is due to drug overdoses. Opioids are the most common drugs involved in those deaths (Schiller et al 2019).

Tolerance occurs when a higher dose of a drug is required to achieve the same pleasurable effect delivered by an initial smaller dose. Drug tolerance develops in response to repeated use over time (NIH 2017). A person's tolerance to a drug changes their perspective on the amount of the drug that they can safely handle. If drug tolerance declines unknowingly, drug users are more likely to overdose. For example, former opioid users who have been recently released from prison or have recently detoxed are more likely to overdose than new opioid users (Kumar 2016).

B. The Opioid Epidemic

1. Chronic Pain and the Role of Opioids in Pain Treatment

Records of opium growth date back to 3400 B.C. when the Sumerians cultivated the opium poppy in lower Mesopotamia. The Sumerians referred to it as Hul Gil, the "joy plant." The use of opium spread slowly eastward from Mesopotamia and Greece. Initially, the use of opium was primarily linked to religion and mysticism. However, later accounts in medical texts such as the ancient Egyptian Ebers Papyrus, describe medical uses for opium (Niewijk 2017).

In the seventeenth century, recreational use of opium became popular soon after smoking tobacco became illegal in China. Opium dens, in which consumers bought and smoked opium, spread across China and in other countries. England was the primary supplier of China's opium when China outlawed its use. Due to the profitability of opium, England attempted to prevent the criminalization of opium. After opium became illegal in China, England continued to sell opium, which led to the First and Second Opium Wars (Niewijk 2017).

In the nineteenth century, the first widespread problem with opioids developed in the United States. Opioids were used in the early 1860s to treat wounded soldiers' pain during the American Civil War. The Union alone issued 2.8 million ounces of opium powder and tincture and 10 million opium pills to their soldiers. Consequently, many soldiers developed opioid addiction and dependency, especially to morphine. In 1856, the hypodermic syringe was introduced, and by the 1870s, it was widely used to inject morphine. While medical journals were filled with warnings about morphine addiction, many doctors were slow to heed the warning due to inadequate education and/or a lack of other pain treatments (Trickey 2018).

In 1898, the Bayer Company was first to introduce commercialized heroin with the claim it was less addictive than morphine. Heroin was ultimately found to be more addictive than morphine, and the ensuing opioid epidemic led the U.S. government to place restrictions on opioids in the 1910s and 1920s. These restrictions included making heroin illegal and requiring that formal prescriptions be written in order to receive certain opioids and other narcotics (Trickey 2018).

Heroin use surged once again in the 1960s and 1970s in the United States, fueled in part by Vietnam War soldiers who were exposed to heroin while fighting overseas (STAT 2017). President Nixon responded by declaring a "War on Drugs" in 1971. In 1973, the Drug Enforcement Agency was created by merging the Office for Drug Abuse Law Enforcement, the Bureau of Narcotics and Dangerous Drugs, and the Office of Narcotics Intelligence in an attempt to centralize federal efforts to control drug abuse. In the early 1980s, the heroin crisis evolved into the "Crack Epidemic." The War on Drugs policies were expanded in 1986 when Congress passed the Anti-Drug Abuse Act of 1986, which allocated $1.7 billion to reduce drug activity (Augustyn and Lotha 2018, HarvardX). Although the War on Drugs policies continue today, the peak of this effort was in the 1980s.

2. How Opioids Rose to Prominence in Pain Treatment

i. The Prevalence of Pain in the United States

Chronic pain is a prevalent medical condition in the United States. More than 30% of Americans have some type of acute or chronic pain (Volkow 2016). In a recent report, the CDC estimated that chronic pain affects 20.4% of adults and high-impact chronic pain affects 8.0% of adults in the population. The prevalence of pain is higher among women and older adults in addition to people who were previously but not currently employed, living in poverty, on public insurance and living in rural areas. While the impact of chronic pain is often associated with restrictions in daily activities, high impact chronic pain is debilitating, leading to "limitations in major life domains, including work, social, recreational, and self-care activities" (CDC 2018).

ii. Early Opioid Studies Show Low Addiction Risk

The high incidence of pain in the United States created an increased demand to manage pain. Drugs, especially opioids, appeared to be a good solution. In 1980, Porter and Jick wrote a five-sentence letter to the editor of the *New England Journal of Medicine*. Published in the correspondence section, the letter suggested that addiction was rare among their patients. Their patients did not have a history of addiction and were being treated for acute pain in a hospital setting (Collins 2018, Zhang 2017).[1] Portenoy and Foley (1986) also suggested that the risk of opioid addiction was low after observing 38 patients with chronic pain. Neither of these cases focused on patients with non-malignant pain, and neither study was scientifically rigorous. Dr. Jick's letter was based on information collected by his graduate student, Porter. She had been asked to note the number of addictions that occurred among their patients. Both the Jick and Porter (1980) and the Portenoy and Foley (1986) observations were used as evidence that the risk of addiction with opioid use was low. They also contributed to the perception that health care providers were allowing patients to suffer when their pain could be safely treated. Widespread dissemination of information from these observations lead to the rise of opioid prescriptions for acute non-chronic pain.. (Jones et al 2018).

Clearly the published statements from Jick and Porter (1980) and Portenoy and Foley (1986) overstated the safety of opioid prescription drugs. The impact of the addictive nature of opioids is significant. The National Institute on Drug Abuse suggests that approximately 21% to 29% of individuals with opioid prescriptions to treat chronic pain misuse them and between 8% and 12 % of these individuals develop an opioid use disorder (NIH 2019).

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[1] "Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients, Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction."

iii. Pain as a Vital Sign

Pain management policy in the United States during the late twentieth century reflected both the current attitudes towards patients that suffered with pain and a rise in disabled war veterans. Both factors led to a perception that pain was undertreated and to an increased focus on treating pain. In an effort to reduce the perceived inadequate treatment of pain, the American Pain Society (APS) campaigned for pain to be recognized as the 5th vital sign in 1996. Prior to 1996, the vital signs that were measured included body temperature, pulse rate, respiration rate, and blood pressure. These vital signs were assessed with medical instruments. The goal of the APS campaign was to ensure that pain assessment was recognized as an equally important measure of patient wellbeing as the other four vital signs. In 1999, the VA Hospital System also recognized pain as a vital sign (Koepke et al 2018). Initially, the campaign was widely supported by regulatory organizations, medical societies, and pharmaceutical companies (Bernard 2018).

The APS guidelines suggested that pain should be measured and recorded in a way that is visible using unidimensional pain scales and carefully monitored by members of the health care team (Bernard 2018). However, the interpretation of these guidelines became problematic because a patient's self-assessed pain level is subjective and may differ substantially among patients.

This APS campaign to make pain the 5th vital sign had implications that were important in contributing to the development of the opioid crisis. One of the most significant consequences was the impact on the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), the hospital credentialing agency. The JCAHO agency taught healthcare professionals to assess and treat pain.[2] They also required that pain scores be documented (Koepke et al 2018, Alam and Juurlink 2016).

The APS campaign also affected the United States Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey. The HCAHPS survey is a patient satisfaction survey that facilitates reimbursement to US healthcare providers. It is used by the Centers for Medicare and Medicaid Services (CMS) (Bernard 2018). Following the recognition of pain as the 5th vital sign, a question was added to the survey that asked how well the hospital staff was treating a patient's pain. This question led to the unintended consequence of encouraging more aggressive pain treatment in response to a patient's self-reported numerical pain scores. The aggressive pain treatment often came in the form of opioid prescriptions which otherwise may not have been prescribed if physicians were not being assessed based on responses to the survey's pain treatment question. The responses to the survey were also used in evaluating the amount of funding a facility received, thus creating an additional incentive to adjust treatment to get high scores on pain management questions in the survey.

It has been suggested that the APS 'pain as the 5th vital sign' campaign has directly contributed to the ongoing opioid epidemic in the United States. The American Medical Association, the American College of Surgeons, JCAHO, The American Academy of Family Physicians, and the Centers for Medicare and Medicaid services no longer support or advocate the recognition of 'pain as the fifth vital sign' campaign. This pain management policy is seen has one of the greatest mistakes in medical history (Levy 2018).

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[2] Pharmaceutical companies funded and wrote educational material for JCAHO regarding pain assessment and management.

iv. Marketing for Opioids in the Pharmaceutical Industry

Pharmaceutical companies also played a role in causing the opioid epidemic by aggressively marketing opioid pain medications. The most well know company was Purdue Pharma. Following the widespread recognition of pain as the 5th vital sign by the medical community and the increased acceptance of opioids to manage pain, the demand for opioid medications increased. In 1996, Purdue Pharma introduced OxyContin to relieve pain as part of an extensive marketing plan. As OxyContin sales increased from $48 million in 1996 to around $1.1 billion in 2000, the high availability of OxyContin was associated with increased opioid abuse. From 1996 to 2001, Purdue Pharma's marketing plan included conducting forty national pain-management and speaker-training conferences at resorts where more than 5,000 physicians, pharmacists, and nurses attended. Purdue Pharma promoted OxyContin among primary care providers for more liberal use, and by 2003, primary care providers made up almost half of all physicians prescribing OxyContin. Purdue Pharma also promoted the idea that the risk of addiction from OxyContin was extremely low (less than one percent) and cited Porter and Jick's (1980) note in the *New England Journal of Medicine* to support their claims (Van Zee 2009).[3]

v. A Summary of the Causes of the Opioid Crisis

Although the causes of the opioid crisis were multifaceted, primary factors were an increased demand for pain treatment, two widely cited notes based on observations of patients with acute and chronic pain underestimating opioid addiction risk, a recognition as pain as a vital sign, and aggressive pharmaceutical marketing for opioid prescriptions.

[3] After performing a bibliometric analysis of the Jick and Porter (1980) correspondence from its publication until March 30, 2017, Leung et al (2017) conclude that it was "heavily and uncritically cited as evidence that addiction was rare with long-term opioid therapy." In particular, the authors found 608 citations of the correspondence and noticed a sizable increase after OxyContin was introduced.

As the opioid crisis has evolved, many of the participants responsible for increased opioid use have admitted their role in the crisis. Dr. Jick was mortified that his note was used by pharmaceutical companies to provide evidence that opioid use was safe and to promote their opioid drugs. He later regretted publishing his 1980 letter to the editor. In 2017, the editor of the *New England Journal of Medicine* added a cautionary statement to the Porter and Jick letter. The statement warned readers of its misleading citation (Zhang 2017).[4]

As mentioned earlier, the acceptance of pain as a fifth vital sign has been seen as one of the biggest mistakes in medical history. The APS campaign for 'pain as the 5th vital sign' lost its support from regulatory organizations, medical societies, and pharmaceutical companies. Both the American Medical Association (AMA) and American Academy of Family Physicians (AAFP) removed pain as a vital sign in 2016. The AMA also publicly apologized for the physicians' role in the crisis due to their pressure to treat pain (Gart 2017).

In 2017, Purdue Pharma pleaded guilty to a felony charge of misbranding OxyContin while marketing it as a safe and low addiction risk pain medication (Meier 2018). Three executives pleaded guilty to a misdemeanor misbranding charge. The company and the executives paid a combined $634.5 million in fines. However, Purdue Pharma's legal problems are not over. There are more than 2000 lawsuits against the company for its part in the Opioid Crisis. On September 15, 2019, Purdue Pharma announced an agreement in principal to settle the opioid litigation. Key requirements of the settlement are detailed on their website. All of Purdue's assets will be contributed for the benefit of the American public due to this settlement. The settlement is estimated to provide more than $10 billion to address the opioid crisis,

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[4] On NEJM's website, the Porter and Jick letter now has an editor's note that reads, "For reasons of public health, readers should be aware that this letter has been 'heavily and uncritically' cited as evidence that addiction is rare with opioid therapy."

including the potential to provide millions of doses of life-saving opioid overdose reversal medications. Finally, Purdue will use Chapter 11 reorganization to finalize and implement the settlement agreement (Purdue Pharma 2019).

Although Purdue Pharma was the most well-known of the companies involved in the opioid crisis, other pharmaceutical companies also face lawsuits. Recently, the drug manufacturer, Teva Pharmaceuticals, and three drug distributors reached a settlement with two Ohio counties for $260 million (Hoffman 2019). John Kapoor, the founder of a pharmaceutical company, Insys Therapeutics, has recently been sentenced to 5 years and 5 months in prison for leading a racketeering conspiracy. Kapoor oversaw a scheme to bribe medical professionals to use his opioid-based pain reliever, Subsys (Chandna 2020). He is the first pharmaceutical executive in the United States to be sentenced for his involvement in the opioid crisis.

3. Evolution of Opioid Substances Abused

While opioid prescription drugs paved the course for millions of Americans to develop opioid addiction, opioid prescription drugs were not the only type of opioids abused. In 2010, the FDA approved the reformulation of OxyContin, allowing Purdue Pharma to begin distributing the reformulated product with the hope that it would be more difficult for abusers to break the pill down for injection, snorting, chewing, and smoking (Burke 2011). However, the demand for opioids did not decrease. Instead, the reformulated OxyContin was responsible for many addicted individuals substituting illicit opioids, heroin or fentanyl (Cicero 2012). Heroin is a cheaper and more easily manufactured semi-synthetic opioid alternative to expensive prescription opioids. In 2017, an estimated 494,000 people in the United States (12-years or older) reported heroin use in the past year (CDC 2019). The overdose deaths from heroin increased fivefold from 2010 to 2017 (CDC 2019). While heroin is still a relatively uncommon drug in the United States, its use is growing in all demographic areas.

Drug overdoses from fentanyl have also increased rapidly during recent years. Beginning in 2013, overdose deaths increased every quarter. During the years 2013 - 2014, the death rate more than doubled, almost doubled during the years 2014 - 2015, and more than doubled between the years 2015 - 2016 (Spencer et al 2019). Fentanyl is a synthetic opioid that is cheaply manufactured and is easily available. Its potency is 50 to 100 times greater than morphine. Fentanyl is available in a variety of forms such as tablets, powder, liquid, and patches; therefore, it is frequently mislabeled or mixed with other drugs in the black market. As obtaining prescription opioids becomes harder and opioid addicts substitute heroin, the exposure to fentanyl increases. (Carney 2019)

Illegal drug networks have pushed heroin, fentanyl, and counterfeit pharmaceuticals into suburban and rural areas in recent years. In the past, rural areas were less affected than urban areas by drug trafficking. Recent trends suggest that there has been an increase in drug trafficking in rural areas. On average, rural populations are older than urban populations, so residents tend to have a greater demand for chronic pain management. Furthermore, chronic pain and injury are more common in rural than in urban areas which has led to higher rates of drug overdose deaths in rural counties, including deaths related to opioids. Opioid overdoses in rural counties have increased at a rate more than three times the increase in urban counties (Keyes et al 2014).

4. The Current State of the Opioid Epidemic

i. Trends in the Opioid Crisis

Chronic pain is a prevalent medical condition in the United States. As mentioned earlier, the CDC estimated that chronic pain affects 20.4% of adults and high-impact chronic pain affects 8.0% of adults in the population. In spite of its prevalence and severity, chronic pain is complex and difficult to manage. After increasing dramatically, opioid prescriptions reached their peak in 2012 at a rate of 81.3 prescriptions per 100 persons. Although the national prescribing rates had fallen to 58.7 prescriptions per 100 persons by 2017, the variation in prescribing rates was substantial among states and counties. For example, 16% of counties in the U.S. had prescribing rates sufficient for every person in the county to have a prescription, and some counties had prescribing rates that were seven times the national level (CDC 2018).

The rise in opioid abuse has been accompanied by deaths due to opioid overdoses. The statistics highlight the seriousness of the opioid problem. Data from the CDC indicate an approximate six-fold increase in opioid overdose deaths since 1999. More than 47,000 people died of an opioid overdose in 2017, and 36% of those deaths involved prescription opioids (CDC 2018). Opioid related deaths have contributed to a decline in the U.S. life expectancy for the third year in a row (Haskins 2019, Bernstein 2019).

The opioid crisis has also led to other problems. For example, many addicts share needles when using drugs. It is estimated that a fourth of the new HIV infections each year in the United States are due to sharing needles while injecting drugs. The increase of new HIV infections affects public health negatively and costs millions of dollars for treatment (Sullivan 2005). In addition, because drug abuse is recognized as a major problem for society, tougher penalties for drug offenses in the U.S. have led to a significant increase in individuals incarcerated (Chandler et al 2009). The rise in imprisonment has additional negative effects on the economy as the labor force declines and public funds are reallocated to the prison system. The economic burden of prescription abuse of opioids alone has been estimated to be $78.5 billion annually for the United States. This estimate includes healthcare costs, the cost of addiction treatment, lost productivity, and criminal justice costs (NIH 2019, Florence 2016). The burden for communities due to opioid use varies substantially throughout the United States and is related to factors based on socioeconomic, demographic, and community level differences.

The latest report from the IQVIA Institute for Human Data Science showed that prescription opioid dosage volume declined 17 percent in 2018, marking the single-largest annual drop ever recorded within the United States. Although overdose deaths involving prescription opioids have declined, overdoses from other types of opioids continue to show an increase (Ingraham 2019).

ii. Policies to Prevent Opioid Misuse

Efforts to prevent opioid misuse are ongoing and evolve with new information about the epidemic. Strategies include decreasing both the supply of and the demand for opioids in addition to reducing harm to drug users. For example, the majority of hospitals have adopted policies limiting patient opioid prescriptions to seven days. Prescription drug monitoring programs (PDMP) have also become widespread. These programs restrict patients from “doctor shopping,” the process of going to multiple medical doctors until the desired prescription is received. Pharmacies are also part of the solution through compliance programs, appropriate drug disposal, patient education, security initiatives, and increasing naloxone access (NACDS 2019). Medical cannabis laws have also been shown to reduce opioid misuse. State medical cannabis laws legalizing the use of medical marijuana are associated with both lower prescribing rates and significantly lower state level opioid overdose death rates (Bachhuber et al 2014, Wen and Hockenberry 2018).

iii. Treatments for Opioid Addiction

Even though opioid addiction is treatable, in practice, it is often untreated and stigmatized (Chandler et al. 2009). Strictly cutting off the supply of an individual's opioids is not an adequate approach to help addicted individuals. In order for treatment to be effective, it must be tailored to the individual patient as addiction often comes with other illnesses such as depression or anxiety disorder. The most effective treatment for opioid addiction usually includes a combination of therapy and medication (Dennis et al 2007). However, only 17.5% of people with a prescription use disorder received individual treatment in 2016. Methadone, buprenorphine, and naloxone are the three commonly used medications. Methadone, a long-acting synthetic opioid agonist medication, can prevent withdrawal symptoms and reduce craving in opioid-addicted individuals. Buprenorphine, a synthetic opioid medication, acts as a partial agonist at opium receptors and is able to reduce or eliminate withdrawal symptoms. Naloxone is an opioid antagonist. It binds to opioid receptors and can reverse and block the effects of other opioids; therefore, it is used to temporarily reverse the effects of an opioid overdose such as slowed or stopped breathing. Although highly effective, these medications are underutilized. Less than 50% of treatment programs in the private sector offer these medications and only a third of eligible patients actually receive them (NIDA 2018). In 2015, the Secretary of Health and Human Services announced five initiatives to address the opioid crisis: 1) improve access to treatment and recovery services; 2) promote the use of overdose-reversing drugs; 3) strengthen our understanding of the epidemic through better public health surveillance; 4) provide support for cutting-edge research on pain and addiction; and 5) advance better practices for pain management (NIDA 2018).

C. Summary

The introduction to this thesis has provided background information in which to contextualize the opioid epidemic. The scope of studies needed to fully understand the opioid epidemic includes research on addiction, opioids, pain management, policy, and treatment for opioid abuse. An implication of this literature is that a successful solution to the opioid epidemic must be multifaceted involving research efforts in many disciplines.

As mentioned previously, a significant measure of the seriousness of opioid addiction is the number of overdose deaths. Despite the risk of addiction and overdose, opioids are commonly prescribed to combat pain. This paper uses cross-sectional county and state level panel data to examine the socioeconomic, demographic, and community level factors that are important in explaining opioid overdoses.

Section II includes a review of the literature. Empirical studies that examine the factors related to opioid overdose deaths are discussed. A theoretical model of rational addiction is presented in Section III. Section IV develops two empirical models for an analysis of opioid deaths based on state and county level data. The empirical results are also discussed. Section V offers conclusions.

II. A Review of the Literature: Risk Factors Associated with Opioid Abuse

In a systematic review of factors related to opioid overdoses in the United States and Canada, King et al (2014) organize opioid mortality risk factors into three broad categories that include prescriber behavior, user behavior and characteristics, and environmental and systemic determinants.

A. Prescriber Behavior

The behavior of prescribers has been shown to play a key role in opioid-related overdose deaths. Prescriber behaviors related to an increase in overdoses include prescribing opioids to more patients, prescribing opioids to patients frequently, prescribing opioids in higher dosages and prescribing more potent opioids such as methadone and oxycodone (King et al 2014). Opioid prescribing varies greatly among physicians. Some studies suggest that prescriber behavior is linked to prescriber characteristics. For example, a physician's prescribing behavior varies with the type of medical training received, resident specialty, or physician bias (Leventhal et al 2019, Todd et al 1994).

1. Opioid Prescription Sales and High-Volume Prescribing

Empirical research suggests that opioid related mortality is associated with both the number of patients receiving opioid prescriptions and how frequently (volume) a physician prescribes opioids.

Opioid sales, substance abuse treatment admissions related to opioid pain relievers, and opioid overdose deaths increased significantly from 1999 to 2009 (Paulozzi et al 2011b). Paulozzi and Ryan (2006) examine opioid overdoses at the state level and find that the variation in the availability of opioid painkillers is related to the spatial distribution of drug overdose deaths. States with lower opioid death rates have lower rates of both opioid pain reliever sales and nonmedical use of opioid pain relievers (Paulozzi et al 2011b).

Dhalla et al (2011) examine volume prescribing behavior and find that opioid deaths are concentrated among patients treated by physicians who prescribe opioids frequently. In addition, a study by Kim et al (2016) suggests that patients receiving opioids from high-volume prescribers have a higher probability of prescription overlap with other opioids and benzodiazepines.

2. Opioid Dosage

As opioid prescriptions and sales increased, the prescribed dosages also increased (King et al 2014). Research suggests that opioid prescriptions in high doses are associated with an increased risk of opioid overdose deaths among patients receiving opioid prescriptions for pain. Bohnert et al (2011) examined the records of patients with cancer, chronic pain, acute pain, and substance use disorders. They analyzed the relationship between the maximum prescribed daily opioid dose, dosing schedules, and the risk of opioid overdose death. Their results suggest that the risk of opioid overdose is positively related to the maximum prescribed daily dose of opioid medication. Gomes et al (2011) also compared the number of opioid overdose deaths among patients treated with varying daily doses of opioids. Their results support those reported by Bohnert et al (2011) and also suggest a strong association between the number of high dose opioid prescriptions dispensed and opioid-related mortality.

3. Prescription of Methadone and Oxycodone

Prior to 1990, opioid prescriptions for weaker opioids such as codeine were commonly used to treat pain. However, prescriptions using more potent opioids such as methadone and long-acting formulations of oxycodone increased rapidly (Manchikanti et al 2008, Paulozzi

2009). Paulozzi and Ryan (2006) examine state data and find that opioid mortality rates are significantly correlated with the use of methadone and oxycodone.

Methadone is a long-acting synthetic opioid agonist medication that is used both to relieve pain and to reduce or prevent substance abuse. It can prevent withdrawal symptoms and reduce craving in opioid-addicted individuals. Although methadone dosing is challenging because the difference between therapeutic and toxic levels is minimal, it is a cheaper generic drug; therefore, physicians may prefer it for patients who use private or government sponsored insurance (King et al 2014). Paulozzi et al (2012) examine the relationship between methadone prescriptions and opioid overdoses. They find that the overdose death rate from methadone is significantly greater than the overdose death rates from other types of opioid prescriptions. Results from Webster et al (2011) support their conclusions. They find that although methadone makes up less than 5% of opioid prescriptions, it is involved in one third of opioid overdose deaths and 30% of all drug overdoses treated in emergency departments.

Oxycodone is a powerful opioid and a popular prescription drug among providers due to its long-acting pain relief. It is the primary ingredient in OxyContin, one of the most abused prescriptions (Juergens 2019a). Oxycodone prescriptions rose rapidly between 1991 and 2007, increasing by 850%. Dhalla et al (2009) found that the increase in oxycodone prescriptions were accompanied by a fivefold increase in oxycodone-related overdose deaths. As mentioned previously, due to the widespread abuse of these prescriptions, the FDA approved the reformulation of OxyContin in 2010 in order to make it more difficult for abusers to break the pill down for misuse (Burke 2011). Havens et al (2014) find that abuse of the original extended release formulation of oxycodone fell significantly after the reformulation of OxyContin.

Additionally, they find no evidence that the reformulated extended release formulation was substituted for the original extended release formulation.

4. Prescriber Characteristics

Empirical studies have examined the relationship between prescriber characteristics and prescriber behavior. For example, the type of training and resident specialty of prescribers might affect the dosage and the quantity of opioid prescriptions that they write. Leventhal et al (2019) examine opioid prescribing practices of emergency physicians based on their level of training or resident specialty. They compare milligram equivalents (MME) of morphine prescribed to patients.[5] Their results suggest that non-emergency department residents placed in emergency departments prescribe larger amounts of opioids.

Other studies have analyzed how physician bias may influence perceptions of the severity of a patient's pain. Todd et al (1994) examine the difference between patient and physician estimates of pain severity for Hispanics and non-Hispanic whites. They find no difference in the severity of pain in Hispanic and non-Hispanic white patients or in the disparity between patient and physician pain assessments. Their results imply that Hispanic and non-Hispanic white patients are given the same prescriptions; therefore, there should be no difference in the likelihood of opioid addiction due to a difference in opioid prescriptions. Tamayo-Sarver et al (2003) find similar results when they examine pain prescriptions in a national sample of emergency departments. Their analysis of data on pain prescriptions for black, Latino, and white patients indicate no significant correlation between race and prescriptions. However, physicians were less likely to prescribe opioids to blacks relative to whites and Latinos.

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[5] Morphine milligram equivalents (MME) or morphine equivalent doses (MED) are standard values based on morphine and its potency when compared to another opioid drug (Labonville 2016).

B. User Behavior and Characteristics

The behavior and the characteristics of an opioid user may increase the risk of an opioid related death. User behavior which may contribute to opioid overdoses includes diversion, doctor or pharmacy shopping, and using multiple drugs. User characteristics linked to an increase in opioid related mortality include mental health status and sociodemographic characteristics (King et al 2014, Davis et al 2017).

1. Prescription Drug Diversion and Doctor or Pharmacy Shopping

Prescription drug diversion is "the unlawful channeling of regulated pharmaceuticals from legal sources to the illicit marketplace" … it "includes transferring drugs to people they were not prescribed for" (Wood 2015). Doctor or pharmacy shopping are two ways in which prescriptions may be diverted. Doctor or pharmacy shopping occurs when patients visit more than one doctor or pharmacy to obtain prescriptions. Although data restrictions make it difficult to quantify the exact number of opioid overdoses in which diversion has played role, empirical studies suggest that doctor or pharmacy shopping is associated with an increase in opioid deaths.

Hall et al (2008) examine the records of all West Virginia residents who died of unintentional pharmaceutical overdoses in 2006. They find that pharmaceutical diversion was linked to 63.1% of those deaths while doctor shopping was associated with 21.4% of them. They conclude that a majority of overdose deaths in West Virginia were associated with the diversion of prescription opioids and nonmedical opioid use. Peirce et al (2012) also examine drug diversion in West Virginia. They compared living subjects receiving opioid prescriptions with individuals who died from an opioid drug overdose for evidence of doctor and pharmacy shopping. They find that the deceased subjects had a significantly higher number of doctor shoppers (25.21% versus 3.5%) and pharmacy shoppers (17.84% versus 1.3%). They also find that approximately 20.23% of doctor shoppers were also pharmacy shoppers and 55.60% of pharmacy shoppers were also doctor shoppers. Their conclusions suggest the need for prescription monitoring programs to provide more prescriber oversight.

McDonald and Carlson (2013) provide national estimates for doctor shopping. Their study is unique in two ways. First, they point out that prior estimates of doctor shopping were based on insurance claims or state drug monitoring programs. Using those types of data, doctor shopping activity was estimated to occur with 0.2% - 13% of all opioid patients. Because doctor shoppers often pay with cash to avoid being detected, McDonald and Carlson use a dataset that includes all opioid prescriptions dispensed to individuals across all retail pharmacies. Second, prior estimates of doctor shopping activity were based on the professional judgement of physicians to define doctor shopping so the estimates had a lot of variability. To overcome this problem, McDonald and Carlson developed a mathematical model that grouped patients by how many different prescribers they had visited within the past year. This approach led to an "extreme" group of 135,000 likely doctor shoppers. These individuals visited 10 different doctors on average and obtained approximately 32 opioid prescriptions in the prior 10 months. They find that although doctor shoppers make up 0.7% of all patients receiving opioid prescriptions, they purchase approximately 2% of all opioid prescriptions.

Simeone (2017) examines doctor shopping activity with state data and finds that the number of diverted prescriptions declined from 1.75% of all prescriptions in 2008 to 1.27% of all prescriptions in 2012. In addition, the number of morphine equivalent milligrams declined from 2.95% of total metric tons in 2008 to 2.19% of total metric tons in 2012. They note that their empirical analysis provides evidence that efforts to control diversion such as prescription monitoring programs have been effective.

2. Polydrug Toxicity

Polydrug use refers to using more than one drug at a time to intensify the effects of a single drug. King et al (2014) point out that many opioid related deaths also involve other drugs such as prescription medications for sedatives, additional opioid prescriptions, alcohol, and illicit drugs. They suggest that opioid overdose may be "part of an epidemic of multidrug mortality" (p. 37).

Numerous studies have linked polydrug toxicity and opioid abuse. Piercefield et al (2010) find that drug overdose deaths often involve multiple substances, and the most common substance is prescription opioids. Over half of all alcohol-related emergency room visits involved illicit and prescription drugs in 2011 (Juergens 2019b). Esser et al (2019) analyzed data from individuals who responded to questions about prescription opioid misuse and alcohol consumption. Their research suggests that prescription opioid misuse was more prevalent among binge drinkers than nondrinkers and that one fifth of prescription opioid overdose deaths also involve alcohol. Slavova et al (2017) find that many fatal fentanyl overdoses are associated with heroin adulterated with fentanyl and suggest that the lack of routine emergency department drug testing likely results in underreporting non-fatal overdoses involving fentanyl and other synthetic drugs.

3. Mental Health Status

Davis et al (2017) examine the relationship between mental health disorders due to mood and anxiety and prescription opioid use. They estimate that 18.7% of Americans with mental health disorders use prescription opioids and adults with mental health conditions receive 51.4% of the total opioid prescriptions in the United States each year. They also find that having a mental disorder significantly increases the likelihood of treating pain with opioids (18.7% versus

5.0%; $p < 0.001$). Because more than half of opioid prescriptions in the United States go to the 16% of Americans with mental health disorders, their results imply that improving pain management among the population with mental health disorders is critical to reducing national dependency on opioids. An association between opioid use and suicide has also been found in empirical studies. Ilgen et al (2016) examine opioid dosage as a potential factor for an increased risk of suicide among patients with chronic pain. They find that the risk of suicide rises with an increase in the dose of opioid prescriptions.

4. Sociodemographic Characteristics

Opioid related deaths are related to sociodemographic characteristics such as age, race, ethnic background, gender, and socioeconomic status. Deaths from opioid use are also related to whether opioid users reside in urban or rural areas.[6]

Many empirical studies have examined the importance of sociodemographic factors in assessing the risk of opioid deaths. Paulozzi et al (2011a) examine the relationship between age, race, ethnicity, sex, and opioid overdose rates. Although their results suggest that opioid overdose death rates are highest among individuals 35 to 54 years old, they conclude that differences in race, ethnicity, or demographics cannot fully explain state variations in opioid prescription sales or in nonmedical use of opioids.

King et al (2014) evaluate 22 studies that focused on sociodemographic differences. These studies suggest that, generally, opioid deaths are "higher among men, non-Hispanic Whites and American Indian/Alaska Natives, middle-aged individuals, those living in rural areas,

[6] Because socioeconomic factors are significantly correlated with urban or rural residential status, empirical studies often examine both characteristics. A more complete discussion of the relationship between urban and rural residential status and opioid overdose risk is found in the last section on environmental and systemic determinants.

and those of lower socioeconomic status" (p. 36). However, they note "considerable heterogeneity" with these overall patterns. Research also suggests that sociodemographic trends vary over time and with the specific drug.

Empirical research by others support King's conclusions. Green et al (2010) provide evidence that an individual's age and race may be correlated with abuse of a specific drug. They find that heroin-only deaths are higher among non-whites, are more likely to involve alcohol or cocaine, and typically occur in public locations and large cities. Alternatively, prescription opioid-only deaths are more likely to involve other medications and occur in suburban or rural locations, compared to heroin overdose deaths from methadone. Jones et al (2015) find that non-Hispanic whites experienced higher methadone overdose death rates than other racial or ethnic groups. Alexander et al (2018) find that the opioid epidemic was primarily driven by heroin from 1979 to the mid-1990s. Both white and black populations were affected. During the mid-1990s to 2010, the increase in opioid mortality was driven by natural and semi-synthetic opioids among whites; however, there was no increase in mortality among blacks. Heroin and synthetic opioids have been primarily responsible for the increase in opioid related mortality for both populations from 2010 to the present.

Gender also plays a role in the risk of opioid overdose. While more men die from drug overdoses than women, some studies indicate that the percentage increase in both opioid abuse and deaths is greater among women. Jones et al (2015) find that men experience higher overdose death rates than women. Mack et al (2013) find that opioid related overdose deaths for women increased fivefold between 1999 and 2010, while opioid overdose deaths among men increased 3.6 times. They also find that emergency department visits related to misuse or abuse of opioids among women more than doubled between 2004 and 2010. Binswanger et al (2013) used data from the prison system in the state of Washington to examine the factors responsible for mortality following release from prison between 1999 and 2009. They find that opioids were related to 14.8% of all deaths and that women experienced an increased risk of an opioid-related overdose.

C. Environmental and Systemic Determinants

Empirical studies suggest that environment and systematic factors may be related to the risk of opioid-related deaths. Environmental and systematic factors include area urbanization or socioeconomic status (SES), geography, economic opportunity, and interventions which focus on policies to reduce the supply of and the demand for opioids and to reduce harm. Other factors, such as state laws on Cannabis policy, may have an indirect impact on opioid overdoses.

1. Urbanization or Socioeconomic Status

Urban and rural residential status may be a factor in predicting the risk of opioid addiction. Guy et al (2017) suggest an association between higher opioid prescription rates and rural residence. Lister et al (2019) examine opioid prescribing and opioid-overdose death rates in Michigan to compare urban and rural counties. They find that urban counties have a high rates of opioid overdose deaths, but rural counties have higher rates of opioid prescribing. Paulozzi (2006) finds that the majority of publicity has focused on opioid abuse in rural areas such as Appalachia and that higher prescription drug overdose death rates have been reported in more rural areas within states. However, Rigg et al (2018) find that opioid overdose death rates are not disproportionately higher in rural areas. They suggest that infrastructural, socioeconomic, and social factors have contributed to the higher prevalence of opioid-related mortality in rural areas. For example, they note that limited access to addiction treatment, underdeveloped prevention workforces, lack of harm reduction programs, and health care shortages hinder rural communities from properly addressing the opioid crisis.

The association between rural residence and opioid prescriptions may also be linked to doctor and/or pharmacy shopping and pill mills within rural communities. “Pill mill” is a term that describes an illegal operation where a doctor, clinic, and/or pharmacy prescribes or sells prescriptions inappropriately (Rigg et al 2010). Hall et al (2008) suggest that many individuals have been successful in doctor shopping and that pill mills have been effectively distributing opioids to the public, especially in rural communities.

Peters et al (2019) use county level data to analyze opioid overdoses during the sub-periods, 2002-2004, 2008-2012, and 2014-2016. They find that the type of opioids abused varies regionally. They suggest that the opioid crisis involves several epidemics occurring at the same time. They identify three distinct epidemics (prescription opioids, heroin, and prescription-synthetic opioid mixtures) and a syndemic which involves a population with more than one epidemic. Syndemics are a set of linked health related issues that interact with each other and cluster in population subgroups, creating a greater burden for those subgroups (Shiel 2018). Peters et al (2019) find that each epidemic and syndemic affects different populations. The prescription opioid-related epidemic is associated with access to opioids from pharmacies and is most common in rural southern states. It affects urban and rural counties that have been “left behind” the rest of the nation. The “left behind” counties are former agricultural and manufacturing communities that have been in decline since the 1990s. These communities are less populated and more remote, older and mostly white, and have a history of drug abuse. On the other hand, the counties most affected by heroin and the opioid syndemic are more urban, connected to interstates, ethnically diverse, and more economically stable. Peters et al (2019) suggests that their research implies that multiple types of policies must be used to address the regionally diverse distinct types of epidemics.

The latest CDC report by the National Center of Health Statistics (Hedegaard et al 2019) on urban-rural differences in drug overdose rates indicates that drug overdose deaths increased in both urban and rural counties during the period 1999 to 2017. However, the urban-rural differences in overdose death rates vary over time and by the type of drug involved. The following paragraph summarizes their conclusion:

> From 1999 through 2003, rates were higher in urban than in rural counties. Rates were similar from 2004 through 2006, then higher in rural counties from 2007 through 2015. In 2016 and 2017, age-adjusted rates of drug overdose deaths were higher in urban than in rural counties. In 2017, the rates of drug overdose deaths involving heroin, synthetic opioids other than methadone, and cocaine were higher in urban counties than in rural counties. In contrast, the rates of drug overdose deaths involving natural and semisynthetic opioids and involving psychostimulants with abuse potential were higher in rural counties than in urban counties. (p. 5)

2. Geography

Geographic variation in opioid prescribing patterns and opioid overdose death rates exists within the United States. Schieber et al (2019) use state level data from 2006 to 2017 to analyze changes in opioid prescribing practices over time and how the changes are distributed across states. They focus on six key prescription measures: "annual amount of opioids prescribed in morphine milligram equivalents (MME) per person; mean duration per prescription in days; and 4 separate prescribing rates—for prescriptions 3 or fewer days, those 30 days or longer, those with a high daily dosage (≥90 MME), and those with extended-release and long-acting formulations" (p. 1). They find an increase in the mean duration and prescribing rate for long-term prescriptions of opioids but a decline in the amount of opioids prescribed per person and in the prescribing rate for high-dosage prescriptions, short-term prescriptions, and extended-release and long-acting formulations. They point out that although some decreases were significant, the results remained high. They also find significant variability (2- to 3-fold) in 5 of the 6 prescribing measures among states.

The most recent report on geographical variation in opioid related deaths by the CDC uses data from 2017. During this year, 70,237 drug overdose deaths occurred in the United States. The report indicated a significant increase of 9.6% in the age-adjusted rate of overdose deaths from 2016 (19.8 per 100,000) to 2017 (21.7 per 100,000). During 2017, 47,600 overdose deaths involved opioids (67.8% of all drug overdose deaths). Synthetic opioids (other than methadone) were the primary opioids abused. The variability in drug overdose rates as summarized in the report (online) follows:

> In 2017, the states with the highest rates of death due to drug overdose were West Virginia (57.8 per 100,000), Ohio (46.3 per 100,000), Pennsylvania (44.3 per 100,000), the District of Columbia (44.0 per 100,000), and Kentucky (37.2 per 100,000).
>
> States with statistically significant increases in drug overdose death rates from 2016 to 2017 included Alabama, Arizona, California, Connecticut, Delaware, Florida, Georgia, Illinois, Indiana, Kentucky, Louisiana, Maine, Maryland, Michigan, New Jersey, New York, North Carolina, Ohio, Pennsylvania, South Carolina, Tennessee, West Virginia, and Wisconsin.

Although they focus on county data and rural-urban residence, Peters et al (2019) suggest that regional differences in opioid overdose mortality vary with the type of opioid. As mentioned earlier, three distinct epidemics (prescription opioids, heroin, and prescription-synthetic opioid mixtures) and a syndemic are identified. They describe regional differences for each epidemic and syndemic. The prescription drug epidemic is concentrated in rural southern states where access to opioids involves local pharmacies. They point out that even though prescription drug overdose mortality from pharmaceuticals reached the highest level nationwide in 2013 and declined afterward, prescription opioids still present a problem in some areas. The heroin epidemic is most severe in western and Midwestern states with urban areas close to interstates with heavy drug trafficking, especially those used by cartels bringing in heroin from Mexico.

The synthetic opioid epidemic is most pronounced in urban areas in the Northeast. They also point out that these synthetic drugs are often mixed with heroin or cocaine. Finally, multiple opioid epidemics exist together (a syndemic) in areas of the country where the opioid crisis began, such as Kentucky, Ohio and West Virginia.

3. Economic Opportunity

Many empirical studies examine the relationship between economic opportunity, opioid prescriptions, and opioid abuse. Ghertner et al (2018) note that individual characteristics associated with opioid abuse include having low income, being uninsured, or receiving Medicaid. However, they point out that even though the individual level relationship is clear, the association between the level of opioid abuse and economic conditions in a community has not been fully examined.

Empirical research results in studies of the relationship between economic conditions and opioid abuse are mixed. Guy et al (2017) find that higher levels of unemployment are positively associated with higher levels of opioid prescriptions in county level data. They also find substantial variation in opioid prescribing patterns suggesting a lack of agreement on appropriate prescribing practices. Hollingsworth et al (2017) find that an increase in the county unemployment rate by one percentage point is associated with a 3.6% increase in the opioid death rate. Some studies explore evidence of reverse causality, that is, that opioid abuse has a negative impact on labor market conditions. Krueger (2017) finds a decline in labor force participation in areas with higher opioid prescriptions. Similar to Krueger, Harris et al (2019) suggest that per capita opioid prescriptions have a significant negative effect on the labor force participation rate, employment-to-population ratio, and unemployment rate. Aliprantis et al. (2019) also find a strong negative link between opioid prescription rates and labor force participation when using county level employment data. They estimate that prescription opioids account for 44% of the decrease in male labor force participation from 2001 to 2015 in the U.S., with less educated men most affected. Ghertner and Goves (2018) explore the relationships between three measures of economic opportunity (poverty rates, unemployment rates, and the employment-to-population ratio), two measures of the prevalence of prescription opioids (retail opioid sales and Medicare Part D opioid prescriptions) and two measures of substance use (drug overdose deaths and opioid-related hospitalizations) using county level data. Their results indicate that overall, the opioid crisis has a greater negative impact on areas with lower economic activity. However, they note that the extent of the relationship varies with the region of the U.S. They point out that "counties differ in their economic, demographic, cultural, and political contexts" and further note that these factors may explain much of the diversity in the relationship p. 8). They also note that one limitation of their study is that it does not find a causal relationship between economic opportunity, the prevalence of opioids, and substance use.

Papers by Ruhm (2018) and Currie et al (2018a) contribute to the issues raised by Ghertner and Goves (2018). Ruhm (2018) uses county level data from 1999-2015 to examine the contribution of the deterioration in medium-run economic conditions versus changes in the drug environment in explaining drug fatality rates. He finds a weak relationship between economic decline and drug mortality rates which is mostly explained by confounding factors. He finds that the risk of drug deaths varies over time and across population subgroups in a way that is consistent with the availability and cost of drugs. Currie et al (2018a) examine the direction of the casual effect in the relationship between opioid prescriptions and employment. They use quarterly county level data on all opioid prescriptions filled at U.S. pharmacies from 2006 to 2014. Their analysis includes three parts. Initial regressions examine how the employment-to-population ratio within an area changes as prescription rates vary. They do not find a significant relationship between changes in the per capita opioid prescriptions and changes in the employment-to-populations ratio. They also estimate models of the effect of per capita opioid prescription rates on employment-to-population ratios, using opioid prescriptions for the elderly as an instrument for opioid prescriptions for younger ages, and models of the effect of employment-to-population ratios on opioid prescription rates using a shift-share instrument. Their results suggest that no simple causal relationship exists between economic conditions and opioid abuse. In a separate article, Currie and Schnell (2018b) point out that poor economic conditions are not responsible for the opioid epidemic. They also conclude their article with the statements below:

> What this means is that we must look at the opioid epidemic for what it is: a self-inflicted perfect storm that arose from a combination of newly available opioids, new attitudes about the importance of pain management, loose prescribing practices, and a lack of professional accountability. The solution to the problem must lie in addressing some of these root causes. (p. 4)

4. Interventions

Policy responses to the opioid epidemic include national, state, and community level efforts to reduce both the supply and demand for opioids and to reduce harm. More education about opioids for providers, patients, and the public at the national level is one example. King et al (2014) discussed several studies that provide evidence that the guidelines, policies, and consensus statements about how to manage pain played a role in the number of opioid-related deaths. In 1997, as opioids were encouraged to treat chronic pain, opioid-related mortality increased; however, new guidelines in 2007 with warnings about appropriate opioid dosages were followed by a reduction in opioid deaths. Prescription Drug Monitoring Programs at the state level is another example. Prescription Drug Monitoring Programs restrict the availability of opioids by discouraging patients from doctor shopping and providers from high-volume prescribing. All states but Missouri have legislation authorizing the creation and operation of a PDMP. Interact for Health, an independent philanthropic foundation that serves the Greater Cincinnati area, represents a community response to the opioid epidemic. The foundation developed an education campaign to reduce the stigma associated with opioid addiction, set up a regional hotline, and provides funding for harm reduction strategies such as naloxone distribution (Chubinski and Lydenberg 2020).

The evidence on the success of various interventions is mixed. Doleac et al (2019) examine recent research on policies designed to decrease opioid abuse and opioid overdose deaths. They focus on studies that attempt to quantify the casual effects of the policies on opioid abuse and mortality. They point out that limiting the supply of opioids yet providing care for individuals who need the medication involves tradeoffs. For example, PDMPs can reduce opioid-related mortality, but they may also induce opioid users to substitute illicit opioids such as heroin. Additionally, harm reduction strategies are associated with positive outcomes for some but encourage risker opioid use among others.

Doleac et al (2019) also notes that average effects sometimes mask important differences across states. For example, state laws regarding PDMPs vary. Some state laws require that doctors access prior prescriptions given to patients before writing a prescription; on the other hand, some states require only that information on prior prescriptions be provided. If a state requires the use of information on prior prescriptions, then the law is a "must-access" PDMP. Meara et al (2016) examine the impact of a variety of state policies on the opioid prescriptions given to Medicare patients. They find that state policies such as PDMPs do not reduce opioid prescriptions. However, Buchmueller and Carey (2018) distinguish between states that require that doctors access PDMP data and those states that do not. They find that must-access PDMPs significantly reduce measures of opioid misuse while voluntary PDMPs did not have a significant effect. Ayres and Jalal (2018) use county level panel data on all opioid prescriptions in the United States to determine the effects of policies such as PDMPs. They also find that PDMPs are most effective in reducing prescription rates if their use is required.

Other policies may have an impact on opioid use or opioid prescribing practices even though they were not put into place with that specific goal. For example, many states have decriminalized cannabis while some states have passed legislation allowing the use of medical or recreational cannabis. Bachhuber et al (2014) find that state laws allowing medical cannabis are associated with significantly lower opioid overdose death rates. Livingston et al (2017) compare changes in the level of monthly opioid-related overdose deaths before and after Colorado legalized recreational cannabis. They find that legalization of recreational cannabis sales resulted in a 0.7 deaths per month decrease in opioid-related overdose deaths. Bradford et al (2018) also find that medical cannabis laws are associated with significant reductions in opioid pain reliever prescribing in the Medicare Part D population. Wen and Hockenberry (2018) analyzed the relationship between the state implementation of medical and recreational marijuana laws, opioid prescribing rates, and spending among Medicaid enrollees. Their study suggested that medical marijuana laws are associated with a 5.88% decrease in opioid prescribing and recreational marijuana laws are associated with a 6.38% decrease in opioid prescribing.

Ruhm (2018) points out that many empirical studies have been done on the effectiveness of a variety of policies on opioid abuse and opioid mortality. He mentions policies associated with medical marijuana, abuse-deterrent drug formulations, Naloxone availability, Medicare Part D, the availability of substance abuse treatment, advertising, and state policies influencing the availability of prescription opioids. However, he concludes that each of these polices explain, “at most, only a small portion of the overall change in overdose deaths” (p.5).

A review of the literature suggests that understanding the opioid epidemic is complex and that effective policies to reduce opioid abuse must have an impact on prescriber behavior, user behavior. and the environment. The policies must also be multifaceted and tailored to allow for regional differences.

III. Theoretical Model

Because addiction is a chronic disease, it is related to theories in health economics. The most well-known theories that serve as a basis for the empirical work that follows are Grossman's (1972) model of the demand for health and Becker's and Murphy's (1988) model of rational addiction.

A. The Production of Health

Grossman (1972) developed a model to explain an individual's health. Grossman begins by assuming that people derive utility from health and a composite of all other goods. The utility function is:

$U_t = U_t\ (H_t, G_t)$

where H_t equals the stock of Health

and G_t equals all other goods.

Health is modeled as a production process. The production function of health summarizes the relationship between health inputs such as medical care and lifestyle and health outcomes such as life expectancy. The model treats investment in one's stock of health as a form of investment in human capital. Similar to other types of capital goods, the stock of health must be maintained by making investments in health that exceed the amount by which health stock deteriorates over time. The change in health stock can be expressed as gross investment in health less depreciation of existing health stock which can be written as:

$\Delta H_j = H_{j,\ t+1} - H_{jt} = I_{jt} - \Delta_{jt} H_{jt}$

where ΔH_j equals net investment in health for individual j

$H_{j,\ t+1}$ equals health stock at time t+1

H_{jt} equals health stock at time t

I_{jt} equals investment in health for individual j at time t, and

$\Delta_{jt}H_{jt}$ equals the depreciation of health stock, where Δ_{jt} equals the annual rate of depreciation in individual j's health stock.

Gross health investment (I) is a function of medical services (M) and the time devoted to the production of health (T). Individuals with more human capital (C) are more efficient producers of health. Grossman also assumes that depreciation in health is related to age (A) and behavioral factors (B) such as alcohol consumption, smoking, and obesity which negatively impact health, as well as others, such as good nutrition and exercise, which have a positive effect on health. The behavioral input also includes chemical dependency and addiction which lead to a deterioration in health stock.

The gross investment in health function may be written as:

$I_{jt} = I_{jt} (M_{jt}, T_{jt}, C_{jt}, A_{jt}, B_{jt})$.

B. Rational Addiction

Behavioral factors that involve addictions to goods such as cigarettes, alcohol, and illicit drugs are inputs in the production of health that have a negative impact on health status. However, if addictive goods change the utility function of individuals, preferences may not be time-consistent. Becker and Murphy (1988) develop a model in which individuals rationally choose to consume addictive goods. Their theory is based on the assumption that individuals incorporate all available information into their calculations of utility and that they are aware of the addictive properties that may change their future preferences. Therefore, preferences are time-consistent in their model. Current consumption increases the desire for future consumption, and, as tolerance increases, the need to consume additional quantities of the addictive good in order to achieve the same effect. The rational addict considers both the benefits and the harmful consequences when choosing the level of consumption of the addictive good each period. Their model implies that addiction is more likely in individuals who discount the future heavily, that is, these individuals focus less on the future effects from current consumption choices.[7]

Becker et al (1991) extend Becker and Murphy's model by adding addictive capital stock to the utility function. In this model, consumption of the addictive good leads to addictive capital stock that reinforces the desire for consumption of the addictive good as it makes future consumption more pleasant. For example, an individual may begin smoking cigarettes knowing its addictive properties. The initial cigarette may be unpleasant, but the experience becomes more pleasant over time. The repetitive use of cigarettes reinforces the individual's demand for the addictive good. As the addictive capital stock grows, current consumption of the addictive good increases. The smoker will want to smoke more and more. Addiction develops when individuals experience withdrawal symptoms as they stop consuming cigarettes.

Models of addictive behavior have implications for the development of optimal public policy solutions. The models above imply that since individuals take all information into account before deciding to consume an addictive good, any expected increase in price will decrease current consumption. Therefore, government policy can be used to reduce tobacco consumption by increasing cigarette taxes. However, if the decision to consume addictive goods is rational, an implication of these models is that government regulatory policy towards addictive goods should depend only on interpersonal externalities. Gruber and Köszegi (2001) extend Becker and Murphy's model by assuming inconsistent preferences as individuals make decisions about smoking. In this case, current levels of consumption of the addictive good may be too

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[7] Although the assumption of rational choice may seem restrictive, some empirical studies offer support for Becker and Murphy's model (Bentzen et al 1999)

high because individuals underestimate the ability to stop smoking in the future. In this case, optimal government policy solutions should consider both the externalities on others and the internalities on the addict. This model is especially relevant for highly addictive substances such as illicit drugs (Henderson 2018).

IV. Empirical Model

Theoretical models and empirical studies suggest that prescriber behavior, user behavior and characteristics, and environmental and systemic factors play a key role in determining opioid addiction. The opioid overdose mortality rate is the most commonly used measure of opioid addiction in the empirical literature. This paper develops empirical models based on state and county data to investigate the relationship between variables used to measure prescriber behavior, user behavior and characteristics, and environmental and systemic factors and opioid overdose deaths. For each level of analysis, the variables used in the empirical model and data are described in the first section followed by a discussion of the empirical results in the second section.

A. State Level Analysis

1. Data

The first empirical model uses state level panel data for the years 2014-2015 to examine factors related to opioid overdose deaths in the United States. Only the states that had values for all of the variables used in the empirical model are included in the analysis. The states include Arizona, Arkansas, Colorado, Florida, Georgia, Hawaii, Iowa, Kentucky, Maine, Maryland, Massachusetts, Michigan, Minnesota, Nebraska, Nevada, New Jersey, New Mexico, New York, North Carolina, Oregon, Rhode Island, South Carolina, Texas, Vermont, Virginia, Washington, West Virginia, and Wisconsin. There are 56 observations used in this study. All of the data excluding the cannabis law data was obtained from the State Health Access Data Assistance Center (SHADAC). Data for cannabis laws was gathered from a historical timeline on ProCon.org.

2. Model Specification and Regression Results

As discussed earlier, previous research suggests that prescriber behavior, user behavior and characteristics, and environmental and systemic factors are related to opioid overdose mortality. Proxies for each of these factors are used to develop the empirical model.

Prescription sales of oxycodone (PSO) and hydrocodone (PSH) per 100,000 persons are included as variables to measure prescriber behavior within a state. Sales of both drugs increase access to opioids and make opioid addiction more likely. Both variables are expected to be positively associated with opioid overdose deaths. (Paulozzi et al 2011).

Four variables are used as measures of user behavior and characteristics. The variables include the percentage of individuals in the civilian non-institutionalized population with at least one visit to the emergency department during the past twelve months (ED), binge drinking behavior measured as the percent of adults consuming four (women) or five (men) or more drinks on one occasion during the past 30 days (BD), firearm suicides per 100,00 persons (SUI), and preventable hospitalizations per 100,000 persons (PH). Potentially preventable hospitalizations are admissions to a hospital for certain acute illnesses or worsening chronic conditions that might not have required hospitalization if the condition been managed successfully by a primary care provider (Moy et al 2013). This measure may also be interpreted as the tendency for individuals to overuse emergency rooms and urgent care in place of primary care (Brumley et al 2007).

The rate of emergency department visits is expected to be positively associated with opioid overdose deaths. Prior studies have identified frequent visits to the emergency department as a marker for opioid abuse. The frequency of emergency department visits has been linked to nonmedical opioid use, drug diversion and poorly managed pain. Brady et al (2015) find a strong association between the rate of emergency department visits and an increased risk for overdoses from prescription drugs.

Theory suggests that the net effect of binge drinking on opioid overdose deaths is ambiguous because alcohol may be a complement to or a substitute for opioid use. Esser et al (2019) find evidence of a complementary relationship as binge drinkers were almost twice as likely as nondrinkers to misuse prescription opioids.

States with a greater number of firearm suicides and preventable hospitalizations are expected to have more opioid overdose deaths. Both variables are associated with mental disorders, chronic pain, and substance abuse. (Meiman et al 2015; Ilgen et al 2016; Martin 2018).

Four variables are used to measure environmental and systemic factors. The variables include the unemployment rate (UR), the amount of state public health funding per person (F), the state excise tax on cigarettes (CT) and the existence of laws allowing medical or recreational cannabis (C).

The net effect of the unemployment rate on opioid overdose deaths is ambiguous. Theoretically, as the unemployment rate increases and economic conditions decline, an increase in opioid abuse and overdoses would be expected. However, as discussed earlier in the review of the empirical literature, evidence on the relationship between the unemployment rate and the opioid overdose rate is mixed (Currie and Schnell 2018). Some studies find a positive relationship between the unemployment rate and opioid overdose deaths while other studies find that the relationship between economic conditions and opioid deaths is weak once the availability and cost of drugs are considered. Additional studies also find evidence of reverse causality between these two variables, that is, opioid abuse has a negative impact on the unemployment rate (Harris 2019).

The net effect of state public health funding per person on opioid overdose deaths is ambiguous. While state public health public funding can be used to increase measures to combat the opioid epidemic, public health funding also increases access to health care and pain prescriptions such as opioids.

In theory, the impact of the state excise tax on cigarettes on the opioid overdose death rate is ambiguous, depending on whether cigarettes serve as a substitute or a complement to opioid use. If cigarettes are a substitute for opioids, an increase in the excise tax on cigarettes would reduce cigarette consumption and increase opioid abuse and overdoses. If cigarettes and opioids are complements, an increase in the excise tax on cigarettes would have the opposite effect on opioid overdoses. There is some empirical research to suggest that cigarettes and opioids are complements. Michna et al (2004) find that cigarette smoking is associated with a higher risk of opioid abuse. Chun et al (2009) studied the smoking behavior of patients being treated for opioid addiction and find that heavier smoking activity is associated with a stronger drug addiction.

A dummy variable is used for state laws which allow the use of medical or recreational cannabis (1 = the use of medical marijuana or recreational cannabis is legal). Opioid overdose deaths have been driven by prescriptions to treat chronic pain. Because medical cannabis is used to treat pain, states in which medical cannabis is legal may have lower rates of opioid abuse and overdose deaths. Bachhuber et al (2014) find that medical cannabis laws are associated with significantly lower state level opioid overdose mortality rates. Additional studies have examined opioid overdose death rates in states that have legalized marijuana for recreational use such as

Colorado, which experienced a 7% drop in opioid related mortality. However, one meta-analysis suggests that while legalizing marijuana is associated with a small reduction in opioid prescriptions, the impact on opioid overdose deaths is inconsistent (Chihun and Li et al 2019).

Because panel data is used, a dummy variable for the year (0 = 2014; 1 = 2015) is included to capture time fixed effects, that is, the possibility that factors not captured in the model affect all variables and vary from one year to year.

An explanation of the variables and descriptive statistics is in Table 1. Descriptive statistics are computed from data in 28 states over two years, 2014-2015. The sample includes 56 observations.

Table 1

Label	Variable	Mean	Std. Dev.	Expected Sign
Y	Natural and semi-synthetic opioid overdose deaths excluding heroin per 100,000 persons	5.05	3.59	
PSO	Prescription sales of oxycodone per 100,000 persons	20.530	6.58	+
PSH	Prescription sales of hydrocodone per 100,000 persons	10.44	6.05	+
UR	Unemployment rate	0.06	0.01	Ambiguous
SUI	Firearm suicides per 100,000 persons	7.04	2.92	+
PH	Preventable hospitalizations per 100,000 persons	1359.7	283.19	+
ED	Percent of civilians who visited the emergency department during the past year	0.0187	0.04	+
BD	Percent of adults binge drinking during the past 30 days	0.164	0.03	Ambiguous
C	Presences of legal medical or recreational cannabis legislation	0.57	0.5	-
F	State public health funding per person	40.5	39.09	Ambiguous
T	State cigarette excise tax rate	1.78	1.12	Ambiguous
YR	Year of observation (2014 = 0, 2015 = 1)	.5	.5	Ambiguous

The initial specification of the empirical model is:

(S1) $Y = \beta_0 + \beta_1 PSO + \beta_2 PSH + \beta_3 UR + \beta_4 SUI + \beta_5 PH + \beta_6 ED + \beta_7 BD + \beta_8 C + \beta_9 F + \beta_{10} T + \beta_{11} YR + \varepsilon$

where Y equals the natural and semi-synthetic opioid overdose deaths excluding heroin per 100,000 persons.

Regression analysis was used to evaluate three model specifications of the model in Microsoft Excel. The empirical results for all specifications are reported in Table 2. The R-squared value measures the proportion of the variation in the dependent variable (Y) explained by the independent variables for a linear regression model. The adjusted R-squared adjusts the statistic based on the number of independent variables in the model. The adjusted R^2 for the initial model (S1) is 0.6427 which means that 64.27% of the Y is explained by the independent variables in the specification. One variable, PSH, has a different sign than expected in the initial regression (S1) results. The F-test for a linear regression indicates whether any of the independent variables in a multiple linear regression model are jointly significant. The F-test indicates that the variables are jointly significant at $\alpha = 0.001$. The t-tests indicate that PSO and F are significant at $\alpha = 0.01$, SUI and ED are significant at $\alpha = 0.10$, while all other variables are insignificant. Tests for superfluous variables and omitted variables tests suggest that PSH and T are superfluous, and they were removed from the model.

The second specification is:

(S2) $Y = \beta_0 + \beta_1 \text{ PSO} + \beta_2 \text{ UR} + \beta_3 \text{ SUI} + \beta_4 \text{ PH} + \beta_5 \text{ ED} + \beta_6 \text{ BD} + \beta_7 \text{ C} + \beta_8 \text{ F} + \beta_9 \text{ YR} + \varepsilon.$

The adjusted R^2 increased only slightly from 0.6427 in specification (S1) to 0.6581 in specification (S2). Multicollinearity is when one independent variable in a multiple regression model can be used to predict another independent variable. Multicollinearity generally occurs between two or more independent variables that have a high correlation. Their correlation creates redundant information in the model. Multicollinearity may produce overinflated standard errors, consequently, independent variables that should be statistically significant are found to be statistically insignificant.

A test for multicollinearity indicates no serious collinearity between the independent variables. The variance inflation factor (VIF) quantifies the severity of multicollinearity in an ordinary least squares regression analysis and provides an index that measures how much an estimated regression coefficient is increased because of collinearity. If the VIF value is above 5, multicollinearity may be problematic for that independent variable. All of the VIF values are all below 4.

Heteroskedasticity occurs when the variability of the error term varies with the independent variables. The White test is a general approach which tests for the presence of heteroskedasticity in the model. The White test indicates that heteroskedasticity is present at the 5% level. The Park test is used to test individual variables for heteroskedasticity. The Park test for Preventable Hospitalizations (PH) indicates the presence of heteroskedasticity, therefore, PH was removed from the model.

The third specification of the model is:

(S3) $Y = \beta_0 + \beta_1 \text{ PSO} + \beta_2 \text{ UR} + \beta_3 \text{ SUI} + \beta_4 \text{ ED} + \beta_5 \text{ BD} + \beta_6 \text{ C} + \beta_7 \text{ F} + \beta_8 \text{ YR} + \varepsilon$

The adjusted R^2 decreased in the third model specification but not significantly. The final specification (S3) is consistent with theory. Three variables are significant at α= .01 (prescription sales of oxycodone per 100,000 persons, percent of civilians who visited an emergency department during the past year, and state public health funding per person), one variable is significant at α= 0.05 (firearm suicides per 100,000 persons), and one variable is significant at α= 0.10 (presences of legal medical or recreational cannabis legislation), and two variables (the unemployment rate and percent of adults binge drinking during the past 30 days) are insignificant.

Serial correlation is a potential problem for time-series data. Serial correlation is the correlation of an observation with a delayed copy of itself as a function of delay. The Durbin–Watson statistic is a test statistic used to detect the presence of first order serial correlation when errors in one-time period are correlated with errors in the next time period. The Durbin-Watson test suggests that serial correlation is not present in the final specification (S3). Tests for multicollinearity indicate no collinearity between the independent variables. However, there is some heteroskedasticity with the model specification. The heteroskedasticity is likely due to the limited number of observations and omitted variables reflecting the complexity of the opioid epidemic.

In summary, the regression analysis based on state-level data is consistent with theory and prior empirical research. The adjusted R^2 is 0.6448; the final specification has an explanatory power of 64.48%. Empirical results suggest that there is a highly significant positive association between natural and semi-synthetic opioid overdose deaths and prescription sales of oxycodone (α= 0.01). These results are similar to prior empirical studies and highlight the important role that prescriber behavior plays in determining opioid overdose deaths.

The empirical results also suggest the importance of user behavior and characteristics. Emergency department visits have a highly significant positive association with natural and semi-synthetic opioid overdose deaths (α= .01). As mentioned earlier, frequent emergency department visits have been linked to nonmedical opioid use, drug diversion and poorly managed pain (Brady et al 2015). Firearm suicide rates are also significantly and positively correlated with opioid overdose deaths (α= .05), suggesting that mental health status is an important determinant in opioid overdose deaths. This is consistent with research by Davis et al (2017) who find that having a mental health disorder significantly increases the likelihood or treating pain with opioids. Although binge drinking is insignificant, it is negatively associated with opioid overdose deaths which implies opioids and alcohol may be substitute goods.

The importance of environmental and systemic factors is also supported by the results based on state level data. The presence of legal cannabis legislation has a significant negative association with opioid overdose deaths ($\alpha = .10$). These results suggest that cannabis and opioids may be substitutes, possibly because both drugs relieve pain. The unemployment rate is insignificant. This is consistent with some of the prior research that suggests that the weak relationship that exists between economic decline and drug mortality rates is mostly explained by confounding factors (Ruhm 2018).

Table 2			
State Level Results			
Dependent Variable: Y			
Independent Variables	**Coefficients (P-values)**		
	(S1)	(S2)	(S3)
PSO	0.1993*** (0.0100)	0.2041*** (0.0023)	0.2165*** (0.0015)
PSH	-0.0141 (0.8931)	—	—
UR	34.6347 (0.4606)	31.7127 (0.4239)	50.2381 (0.1978)
SUI	0.5316* (0.0850)	0.5013*** (0.0053)	0.2999** (0.0201)
PH	0.0033 (0.1757)	0.0031* (0.0991)	—
ED	19.7035* (0.0956)	20.3075* (0.0540)	29.0558*** (0.0023)
BD	9.1051 (0.6468)	8.4535 (0.6485)	-0.2936 (0.9871)
C	-0.0080 (0.9941)	-0.0298 (0.9750)	-1.1614* (0.0931)
F	0.0410*** (0.0001)	0.0405*** (0.00001)	0.0379*** (0.00003)
T	0.0027 (0.9958)	—	—
YR	0.0780 (0.9061)	0.0786 (0.9030)	0.2152 (0.7415)
Constant	-15.9469* (0.0268)	15.5188** (0.0137)	-10.6586* (0.0554)
Adjusted R^2	0.6427	0.6581	0.6448

***Significant at the 1% level
**Significant at the 5% level
*Significant at the 10% level

B. County Level Analysis

1. Data

The second empirical model uses county level cross-sectional data for the year 2017 to examine factors related to opioid overdose deaths in the United States. Observations from counties in Kentucky, Ohio, Pennsylvania, Virginia, and West Virginia are used in this analysis.

A total of 68 observations were used. All the data for the independent variables in the model was obtained from the County Health Rankings & Roadmaps database. Data for the dependent variable, opioid overdose deaths, was obtained from the CDC Wonder database.

2. Model Specification and Regression Results

As in the state level analysis, proxies for prescriber behavior, user behavior and characteristics, and environmental and systemic factors are used to explain overdose mortality in model specifications at the county level.

The opioid prescribing rate per 100 persons (OPR) is included as a measure of prescriber behavior within a county. Opioid prescriptions increase access to opioids and make opioid addiction more likely. The opioid prescribing rate is expected to be positively associated with opioid overdose deaths (Paulozzi et al 2011b).

Four variables are used as measures of user behavior and characteristics. The variables include the average number of physically unhealthy days reported by an individual per month (PUD), the percent of adults reporting frequent mental distress (FMD), binge drinking behavior measured as the percent of adults reporting excessive drinking (BD), and preventable hospital stays, calculated from discharges for ambulatory care sensitive conditions per 1,000 Medicare enrollees (PHS).

Both the average number of physically unhealthy days reported by an individual per month and the percent of adults reporting frequent mental distress are expected to be positively associated with the opioid mortality rate. As the review of the literature suggests, physical and mental health status are factors that determine the dosage and rate of opioid prescribing. Having a mental disorder significantly increases the likelihood of treating pain with opioids (Davis et al 2017).

Binge drinking behavior and preventable hospital stays are included as variables in both the state and county analysis. As discussed in the state level analysis, the overall relationship between binge drinking behavior and opioid overdose mortality is ambiguous, and preventable hospital stays are expected to be positively correlated with opioid overdose deaths.

Five variables are used to measure environmental and systemic factors. The variables include the unemployment rate (UR), the percent of children in poverty (CP), the high school graduation rate (HS), the percent of uninsured adults (UI), and the number of primary care physicians per 100,000 persons (PCP).

The unemployment rate is included as a variable in both the state and county analysis. As discussed in the state level analysis, the overall relationship between the unemployment rate and opioid overdose mortality is ambiguous. The percentage of children in poverty is predicted to be positively associated with opioid overdose deaths as lower-income individuals are more likely to abuse opioids relative to the general population (Jones 2016). The percent of uninsured adults has an ambiguous association with opioid overdose deaths. Insurance provides access to addictive opioid prescriptions but uninsured individuals are associated with poverty which suggests a greater risk for opioid abuse (Chase 2019, Orgera and Tolbert 2019, Jones 2016). High school graduation rates are expected to be negatively correlated with opioid overdose deaths (independent of income) as more educated individuals are produce health more efficiently. For example, more educated individuals have a greater ability to understand the negative consequences of unhealthy behaviors (Grossman 1972). The net effect of the number of primary care physicians per 100,000 persons on opioid overdose mortality is uncertain. Although an increase in primary care physicians may increase access to health care and the opportunity for more effective treatments for addiction, an increase in physicians may also be associated with an increase in opioid prescriptions to treat pain.

An explanation of the variables and descriptive statistics is in Table 3. Descriptive statistics are based on data from 68 counties in 2017. The sample includes 68 observations.

Table 3				
Label	**Variable**	**Mean**	**Std. Dev.**	**Expected Sign**
Y	Crude rate of accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens]	24.484	15.672	
FMD	Percent of adults reporting frequent mental distress	11.537	1.361	+
BD	Percent of adults reporting excessive drinking	17.431	2.256	Ambiguous
UR	Unemployment Rate	5.014	0.951	Ambiguous
OPR	Opioid Prescribing Rate per 100 persons	63.791	16.692	+
CP	Percent of Children in Poverty	19.506	7.866	+
HS	High School Graduation Rate	84.475	8.292	-
PCP	Primary care physicians per 100,000 persons	79.589	25.922	Ambiguous
PUD	Average number of reported physically unhealthy days per month	3.670	0.546	+
PHS	Preventable hospital stays; discharges for ambulatory care sensitive conditions/Medicare enrollees * 1,000	54.142	12.053	+
UI	Percent of adult population uninsured	10.197	2.227	Ambiguous

The initial specification of the model is:

(C1) $Y = \beta_0 + \beta_1 FMD + \beta_2 BD + \beta_3 UR + \beta_4 UR + \beta_5 OPR + \beta_6 CP + \beta_7 HS + \beta_8 PCP + \beta_9 PUD + \beta_{10} PHS + \beta_{11} UI + \varepsilon$

where Y = the crude rate of accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens].[8]

Regression analysis was used to evaluate three model specifications of the model in Microsoft Excel. The empirical results for all specifications are reported in Table 4. The signs

[8] I was unable to find strictly opioid overdose deaths for the county data. However, opioids contribute to the majority of the deaths caused by accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens].

on all variables in the initial model specification (C1) are consistent with predictions with the exception of the rate of high school graduates. The F-test indicates that the variables are jointly significant at $\alpha = 0.001$. The t-tests indicate that one variable, the unemployment rate (UR), is significant at $\alpha = 0.01$. Tests for superfluous variables and omitted variables suggest that FMD is superfluous, and it was removed from the model.

The second specification is:

(C2) $Y = \beta_0 + \beta_1 BD + \beta_2 UR + \beta_3 UR + \beta_4 OPR + \beta_5 CP + \beta_6 HS + \beta_7 PCP + \beta_8 PUD + \beta_9 PHS + \beta_{10} UI + \varepsilon$

There is almost no change in the adjusted R^2 in the second model specification (0.4515 in the first specification and 0.4586 in the second specification). Even though the high school graduation rate is insignificant, the sign remains positive. Multicollinearity tests indicate potential collinearity problems with two variables, CP and PUD as their VIF values exceeded 5. When the variable, CP was removed from the model, the VIF values for the all remaining variables were below 5. The White test indicates that impure heteroskedasticity is present in this specification of the model. The Weighted Least Squares (WLS) is a method used to remove heteroscedasticity. WLS incorporates weights associated with each data point. The size of the weight indicates the precision of the information contained in the associated observation. All of the variables are rates or percentages and WLS did not yield improved results in the third specification. The variable, PHS was removed to reduce the heteroscedasticity.

The third specification of the model is:

(C3) $Y = \beta_0 + \beta_1 BD + \beta_2 UR + \beta_3 OPR + \beta_4 HS + \beta_5 PCP + \beta_6 PUD + \beta_7 UI + \varepsilon$

Once again, the adjusted R^2 did not change significantly. The signs of all variables in the final specification (C3) is consistent with those that were hypothesized. Two variables are significant at $\alpha = 0.01$ (Unemployment Rate, UR and Physically Unhealthy Days, PUD), one variable is significant at α= 0.05 (Opioid Prescribing Rate, OPR), and the remaining four variables (Binge Drinking, BD; High School Graduation, HS; Primary Care Physicians, PCP, and Uninsured, UI) are insignificant. Serial correlation is often not present in cross-sectional data, and correlation tests indicated there were no problems with correlation. The White test indicates that impure heteroskedasticity is present in this specification of the model; however, the heteroskedasticity was less of problem for the final specification (C3) than the previous specification (C2). All of the variables are rates or percentages, so it is not surprising that WLS did not yield improved results in the third specification (C3). The impure heteroskedasticity is likely due to the limited number of observations and omitted variables reflecting the complexity of the opioid epidemic.

In summary, the regression analysis based on county level data is consistent with theory and prior empirical research. The adjusted R^2 is 0.4448; the final model has an explanatory power of 44.48%. The results suggest that opioid prescription rates have a significant and positive correlation with opioid overdose deaths (α= 0.05). This result is consistent with the analysis at the state level and with prior empirical studies. It provides additional evidence that prescriber behavior plays an important role in determining opioid overdose deaths.

The empirical results also suggest the importance of user behavior and characteristics. There is a strong significant positive association between opioid overdose deaths and physically unhealthy days (α= 0.01). Individuals who are physically unhealthy are more likely to suffer from chronic pain or high impact chronic pain and to be treated with opioids. The impact of chronic pain is associated with restrictions in daily activities while high impact chronic pain is debilitating, leading to major limitations in work, social, recreational, and self-care activities (CDC 2018). Theoretically, the relationship between binge drinking and opioid deaths is ambiguous, depending on whether alcohol and opioids are substitutes or complements. In both the state and county analysis, binge or excessive drinking is negatively correlated with opioid overdose deaths. Even though the relationship is insignificant, this may imply that alcohol and opioids are weak substitutes.

The importance of environmental and systemic factors is also supported by the results based on county level data. The empirical results at the county level suggest a highly significant negative association between opioid overdose deaths and the unemployment rate ($\alpha= 0.01$). Although this result differs from the insignificant positive association with unemployment found in the analysis based on state level data, the empirical literature on the relationship of unemployment and opioid abuse is mixed. Harris et al (2019) find a significant negative effect between opioid prescriptions and the unemployment rate. Other empirical studies imply a weak relationship between economic decline and drug mortality rates which is mostly explained by confounding factors (Ruhm 2018). Finally, Currie et al (2018a) suggest that no simple causal relationship exists between economics conditions and opioid abuse. The final variable used to measure environmental and systemic factors, high school graduation rates, has an insignificant negative association with opioid overdose morality. These results, while insignificant, imply education and an increase in economic opportunity is a deterrent to opioid overdose deaths.

Primary care physician per 100,000 persons and the uninsured population were also included in the regression model to capture environmental and systemic factors. Both variables have insignificant negative associations with opioid overdose morality. In theory, greater access to medical care either because there are more physicians available to treat patients or because there are more insured individuals who can afford care, has an ambiguous relationship to opioid mortality. Prescriber behavior varies widely among physicians and as the number of physicians and the number of insured patients increase, this may provide greater access to opioid prescriptions. On the other hand, an increase in physicians and insured individuals may provide access to better and more effective pain management leading to fewer opioid prescriptions. These results suggest that more physicians are associated with fewer prescriptions. New guidelines for prescribing practices and managing pain have been implemented in recent years leading to a decline in opioid prescribing rates. The county level results also suggest that an increase in the rate of uninsured individuals leads to a decrease in opioid overdose deaths which may suggest that greater access to medical care leads to more opioid prescriptions for pain.

Table 4			
County Level Results			
Dependent Variable: Y			
Independent Variables	**Coefficients (P-values)**		
	(C1)	**(C2)**	**(C3)**
FMD	2.3615 (0.7989)	—	—
BD	2.3615 (0.6209)	-1.7659* (.0886)	-1.0264 (0.2680)
UR	-9.4963*** (0.0011)	-9.6217*** (0.0008)	-7.3811*** (0.0027)
OPR	0.1855 (0.1551)	0.1800 (0.1631)	0.2429* (0.0523)
CP	0.6733 (0.2735)	0.8263 (0.1189)	—
HS	0.1656 (0.4900)	0.1471 (0.5318)	-0.0300 (0.8857)
PCP	-0.0140 (0.8236)	-0.0134 (0.8297)	-0.0024 (0.9698)
PUD	7.5456 (0.5011)	12.0032 (0.5014)	17.9789*** (0.0017)
PHS	0.1063 (0.6478)	0.0852 (0.7074)	—
UI	-1.1012 (0.3710)	-1.3321 (0.2400)	-0.2866 (0.7562)
Constant	13.8110 (0.7989)	29.4623 (0.5014)	1.8438 (0.9628)
Adjusted R^2	0.4515	0.4586	0.4448

***Significant at the 1% level
**Significant at the 5% level
*Significant at the 10% level

V. Conclusions

Over the last two decades, the opioid epidemic has led to serious negative consequences. Opioid addiction adversely affects an individual's mental and physical health. In addition, the societal and economic costs are substantial. Opioid addiction is associated with an increase in other diseases such as hepatitis, domestic and child abuse, crime, lost wages and employment. Although the causes of the opioid crisis were multifaceted, primary factors were an increased demand for pain treatment, two widely cited notes based on observations of patients suffering from acute and chronic pain which underestimated opioid addiction risk, the recognition of pain as a vital sign, and aggressive pharmaceutical marketing for opioid prescriptions.

This study investigates the risk factors that are associated with opioid addiction. The opioid overdose mortality rate is used as a measure of the seriousness of the opioid epidemic. Theoretical concepts from Grossman's production function of heath (1972) and Becker and Murphy's model of rational addiction (1988) are used to develop empirical models that explore the relationship between risk factors and opioid overdose deaths.

The production function of health summarizes the relationship between health inputs such as medical care and lifestyle and health outcomes such as life expectancy. Medical services and the time devoted to the production of health impact an individual's health. Depreciation in health is related to age and behavioral factors such as alcohol consumption, smoking, and obesity. Addiction to substances such as opioids also leads to a deterioration in health stock. Becker and Murphy developed a model in which individuals rationally choose to consume addictive goods. Their model implies that addiction is more likely in individuals who discount the future heavily, that is, these individuals focus less on the future effects from current consumption choices. Their model also implies that individuals respond to price increases in specific addictive substances by consuming cheaper substitute goods.

More broadly, Grossman's model of health suggests that health outcomes are affected by a variety of health factors which include clinical care, health behaviors, social and economic factors, and environmental characteristics. Clinical care includes both access to care and quality of care. Health behaviors include decisions about diet, exercise, and use of cigarettes, alcohol, and drugs. Social and economic factors include employment, income, education, family, social support, and community safety. Characteristics of the physical environmental include housing and transit. Following King et al (2014), health factors that affect the opioid mortality rate are grouped into three broad categories: prescriber behavior, user behavior and characteristics, and environmental and systemic factors.

The empirical analysis examines the relationship between risk factors that are associated with prescriber behavior, user behavior and characteristics, environmental and systemic factors and opioid overdose mortality. Two regression models are used to analyze data at the state and county level. The state level analysis is based on panel data. The county level analysis is based on cross-sectional data.

The behavior of prescribers may increase the risk associated with opioid overdose deaths in several ways and it has been shown to play a key role in opioid-related overdose deaths. Three measures of prescriber behavior are initially included in this study: prescriptions sales of oxycodone and hydrocodone at the state level and opioid prescribing rates at the county level. Prescription sales of hydrocodone was dropped from the empirical model after tests indicated that it was superfluous. Both analyses at the state and the county level indicate that there is a significant positive association between prescriber behavior and opioid overdose mortality. The empirical results at the state level indicate that an increase in the prescription sales of oxycodone are statistically associated with an increase in natural and semi-synthetic opioid overdose deaths at the 1% level. Similarly, the analysis at the county level suggests that an increase in opioid prescription rates is positively correlated with the crude rate of accidental poisoning by narcotics and psychodysleptics at the 5% level. While the latter measure of opioid overdose mortality includes substances that are not opioids, opioids make up the majority of those substances. These results highlight the important role that prescriber behavior plays in determining opioid overdose deaths and in contributing to the opioid epidemic. The results are consistent with many empirical studies described in the literature review and are also consistent with the historical events described in the introduction, where aggressive pharmaceutical marketing of opioids is linked to the opioid epidemic.

The behavior of users and user characteristics may also increase the risk associated with opioid overdose deaths. Variables used to measure user behavior and characteristics in the state level analysis include preventable hospitalizations, emergency department visits, binge drinking, and firearm suicides. Variables used to measure user behavior and characteristics in the county level analysis include preventable hospitalizations, binge drinking, frequent mental distress, and physically unhealthy days.

Both the empirical analysis at the state and county level result in a final specification in which preventable hospital stays are removed due to the presence of heteroskedasticity. However, emergency room visits are statistically associated with opioid overdose mortality at the 1% level in the state level analysis. This is consistent with prior studies which find a strong association between the rate of emergency department visits and an increased risk for overdoses from prescription drugs (Brady et al 2015).

Although binge drinking behavior is included in both empirical models, it is insignificant. Theoretically, the overall relationship between binge drinking and opioid overdose mortality is ambiguous, and depends on whether alcohol and opioids are substitutes or complements. While not significant in either model, an increase in binge drinking suggests a decline in the opioid overdose mortality rate which implies that alcohol and opioids may be substitutes. However, the empirical results are mixed and some researchers find evidence of a complementary relationship (Esser et al (2019).

As with preventable hospitalizations, firearm suicides are associated with mental disorders, chronic pain, and substance abuse (Meiman et al 2015; Ilgen et al 2016; Martin 2018). Consistent with these findings, firearm suicide rates are positively correlated with opioid overdose deaths at a 5% level of significance in the state level analysis. Both physical and mental health status are factors that determine the dosage and rate of opioid prescribing. The presence of a mental disorder significantly increases the likelihood of treating pain with opioids (Davis et al 2017). The county level analysis suggests that an increase in physically unhealthy days is associated with an increase in opioid overdose mortality at the 1% significance level. Although frequent mental distress was initially included in the county level analysis, it was removed from the final specification because tests suggested that it was a superfluous variable.

The final broad category of health factors that affect the opioid mortality are environmental and systemic factors. Variables used to measure environmental and systemic factors in the state level analysis include the unemployment rate, per capita state public health funding, the state excise tax on cigarettes, and the existence of medical or recreational cannabis legislation. Variables used to measure environmental and systemic factors in the county level analysis include the unemployment rate, the percent of children in poverty, the high school graduation rate, the percent of uninsured adults, and the number of primary care physicians per 100,000 persons.

The unemployment rate is included in both the state and county analysis. The effect of the unemployment rate on opioid overdose deaths is ambiguous. Theoretically, as the unemployment rate increases and economic conditions decline, an increase in opioid abuse and overdoses would be expected. However, evidence on the relationship between the unemployment rate and the opioid overdose rate is mixed. In addition, some studies find evidence of reverse causality between these two variables, that is, opioid abuse has a negative impact on the unemployment rate (Harris 2019). Although the unemployment rate is positively associated with opioid overdose mortality in the state analysis, it is insignificant. The empirical results at the county level suggest that the unemployment rate is negatively correlated with opioid overdose deaths and is statistically significant at the 1% level.

The net effect of state public health funding per person on opioid overdose deaths is ambiguous. While state public health public funding can be used to increase measures to combat the opioid epidemic, public health funding also increases access to health care and pain prescriptions such as opioids. Public per capita health funding is positively related to opioid overdose deaths and significant at the 1% level in the state level analysis. This suggests that an increase in public health funds may have an overall effect of increasing access to opioids.

Cigarettes and cannabis are alternative addictive goods. In theory, the impact of the state excise tax on cigarettes on the opioid overdose death rate is ambiguous, depending on whether cigarettes serve as a substitute or a complement to opioid use. Cigarette excise taxes were included in the state level analysis, however, this variable was removed from the model after test indicated that it was superfluous. Opioid overdose deaths have been driven by prescriptions to treat chronic pain. Because medical cannabis is used to treat pain, states in which medical cannabis is legal may have lower rates of opioid abuse and overdose deaths. The presence of cannabis legislation is significant at the 10% level and is negatively associated with opioid overdose deaths in the state level analysis. These results suggest that cannabis and opioids are substitutes, which is consistent with the empirical findings in Bachhuber et al (2014) and (Chihun and Li et al (2019).

The final environmental and systemic risk factors are measures at the county level. These measures include the percent of children in poverty, the high school graduation rate, the percent of uninsured adults, and the number of primary care physicians per 100,000 persons. The percentage of children in poverty was removed from the model after tests indicated significant multicollinearity. The percent of uninsured adults has an ambiguous association with opioid overdose deaths. Insurance provides access to addictive opioid prescriptions but uninsured individuals are associated with poverty which suggests a greater risk for opioid abuse (Chase 2019, Orgera and Tolbert 2019, Jones 2016). Although the uninsurance rate is insignificant, it is negatively associated with opioid overdose mortality, suggesting that more access to medical care provides more access to opioid prescriptions. High school graduation rates are expected to be negatively correlated with opioid overdose deaths (independent of income) as more educated individuals are produce health more efficiently. For example, more educated individuals have a greater ability to understand the negative consequences of unhealthy behaviors (Grossman 1972). High school graduation rates have an insignificant negative association with opioid overdose morality. Although these results, are insignificant, the negative association implies that education and an increase in economic opportunity is a deterrent to opioid overdose deaths.

The net effect of the number of primary care physicians per 100,000 persons on opioid overdose mortality is uncertain. Although an increase in primary care physicians may increase access to health care and the opportunity for more effective treatments for addiction, an increase in physicians may also be associated with an increase in opioid prescriptions to treat pain. The statistical relationship between primary care physicians and the opioid overdose mortality rate is insignificant but negative, which suggests that more physicians are associated with fewer prescriptions. This result may be due, in part, to prescribing guidelines. New guidelines for prescribing practices and managing pain have been implemented in recent years leading to a decline in opioid prescribing rates.

A major theme of this paper is that understanding the opioid epidemic is complex. The empirical results at the state and county level suggest that there are many risk factors associated with opioid overdose mortality. Additionally, the opioid crisis has not impacted the nation in a uniform way. In particular, some communities, such as counties in Kentucky, Ohio, West Virginia, and Pennsylvania have been impacted much more severely than others. Finally, the opioid drug problem has evolved in different ways over time for specific communities. Some counties and states now have severe problems with heroin and fentanyl. As many empirical researchers have suggested, more studies at the community level are needed as many factors contribute to the institutional environment faced by different regions of the country. The complexity of the opioid epidemic is consistent with Grossman's model of health in which health outcomes are affected by a variety of health factors which include clinical care, health behaviors, social and economic factors, and environmental characteristics.

An implication of this analysis and similar empirical studies is that addressing the opioid epidemic requires multifaceted and targeted solutions in order to effectively and efficiently allocate resources. Additionally, developing effective policy solutions in addition to treatment options for opioid addiction requires an interdisciplinary approach. As discussed earlier, the range of relevant knowledge includes the biological/chemical and non-biological causes of addiction, pain prevalence and its management, the historical events leading to the role of opioids in treating pain, and knowledge about the epidemic from empirical studies based on analyses at several levels including individuals, communities, and states. The results of empirical studies focused on the opioid epidemic can guide legislators as they propose policies to reduce and treat opioid addiction or addiction to other substances.

In particular, this study suggests that opioid prescriptions (prescriber behavior), mental and physical health and emergency department visits (user behavior and characteristics), and cannabis legislation (environmental and systemic factors) are all important risk factors in opioid overdose deaths. These findings have several implications. First, solutions to combat the opioid epidemic will involve balancing the need to effectively manage chronic pain while preventing opioid addiction and abuse. Second, effective solutions will involve multiple strategies which restrict the supply and reduce the demand for opioids. The strong association between opioid prescriptions and opioid overdose mortality implies that strategies to restrict the legal access of opioids, such as preventing drug diversion, prescription drug monitoring programs, provider education, and prescribing guidelines might be effective. Strategies to reduce the demand for opioids may include educating patients about the dangers of opioid use. In addition, increasing access to treatment for addiction disorders and access to medical care for individuals with mental and physical impairment may reduce opioid use. Finally, reducing the harmful consequences associated with opioid addiction by increasing the availability of naloxone to reverse overdoses or increasing buprenorphine to reduce withdrawal symptoms would be helpful. Policies that regulate substances that serve as opioid substitutes may also be useful in reducing opioid abuse. The results from the state level analysis suggest that policies that legalize cannabis may be helpful in reducing opioid overdose deaths. Overall, the results of this paper support the need for the development of public health policies which are designed on the basis of empirical information. Targeting strategies to specific local needs can more effectively improve both the health of individuals and the economic and societal well-being of communities.

In conclusion, this study suggests the need for future research. While my empirical results were consistent with much of the previous literature, there are ways in which my study could be improved and expanded. As more data becomes available, incorporating additional variables, observations, and modeling techniques could improve the ability of the model to predict opioid overdose deaths. For example, I initially planned to examine the impact of state laws passed to limit prescription opioids (PDMPs) on opioid overdose mortality. As discussed in the review of the literature, some research suggests that PDMPS are not significant in reducing opioid overdose deaths. However, state laws regarding drug monitoring programs differ. Some state laws simply make information on prior opioid prescriptions received by patients available to physicians while other states require physicians to look at prior opioid prescriptions received by their patients. Programs that require physicians to examine prior opioid prescriptions given to their patients are significantly related to a reduction in opioid overdose deaths. As I collected data on PDMPS, I realized that including this variable would require access to a more detailed dataset. Although all states except one have passed drug monitoring programs, the laws vary not only by whether the physician is required to look at the patient history of drug prescriptions, but also by the specific type of prescription monitored and by the type of physician specialist required to access the patient history. I had also planned to examine the impact of a county legislation on alcohol sales explore whether a county was dry or wet had an impact on opioid overdose mortality. However, almost all of the counties in the data set where wet. Furthermore, the ability to access and use data at the individual level would be helpful in examining the impact of demographic characteristics on the risk for opioid overdose deaths. Finally, using a more complicated time-series cross-sectional modeling approach could improve both the state and county level analysis.

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