MARIJUANA LEGALIZATION EFFECT ON OPIOID ABUSE: A SYNTHETIC CONTROL APPROACH

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ABSTRACT

The opioid epidemic constitutes one of the worst drug crises in the history of U.S. State-level policies, in general, have done little to prevent prescription opioid abuse. A noteworthy exception to other clinical efforts to curb opioid abuse is marijuana. Despite preliminary evidence, many states are hesitant to introduce legislation to expand access to medicinal marijuana or liberalize laws on recreational use of marijuana, fearing additional research is needed. Utilizing a synthetic control method and annual state-level data from 2006 to 2018, this study examines the effect of recreational marijuana legalization on opioid abuse. The findings strongly indicate marijuana legalization is not a statistically significant factor in reducing opioid abuse in Colorado State. This provides important implications for states designing policies to provide opioid addicts with marijuana substitutes and states hoping to address concerning rises in opioid abuse. Further research needs to be done to develop a robust understanding.

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DEDICATION

I dedicate this work to my family for the immerse support given to me.

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INTRODUCTION

Background

Chronic pain plays a significant detrimental role within the U.S., where approximately 30 to 40 percent of adults (18 or older) suffer from chronic pain (Johannes, Le, Zhou, Johnston, & Dworkin, 2010; Tsang et al., 2008). Further, the 2016 National Health Interview Survey estimates finds approximately 8 percent of adults in the U.S. (nearly 19.6 million people) has high-impact chronic pain. The study notes that chronic pain is prevalent among women, older adults, unemployed adults, persons living in poverty, adults with government health insurance and rural people (Dahlhamer et al., 2018). Previous literature finds a strong association between chronic pain and mobility, anxiety, depression, and numerous other difficulties which can reduce the quality of life for patients (Gureje, Von Korff, Simon, & Gater, 1998; Smith et al., 2001). The total annual health care cost of chronic pain management in the U.S. is estimated at $560 billion to $635 billion (Gaskin & Richard, 2012).

Opioids are commonly used for the treatment of acute and chronic pain conditions. Opioids are prescribed from natural substances (e.g., Morphine and Codeine), synthetic compounds (e.g., Fentanyl, Methadone and Tramadol) and semisynthetic components (e.g., Oxycodone, Oxymorphone, and Hydromorphone) depending on the chemical source and pharmacological production process (Thorn, Klein, & Altman, 2009).

Zhong et al. (2013) find that opioids are the third most frequently prescribed medication in the United States.[1] Dowell et al. (2016) indicate that the commonly prescribed opioids are Codeine, Fentanyl transdermal, Hydromorphone, Methadone, Morphine, Oxycodone,

[1] The most commonly prescribed medications are anxiolytics, antipsychotics, opioid and nonopioid analgesics, and anticholinergics (Sera, McPherson, & Holmes, 2014).

Oxymorphone and Tapentadol. Their popularity stems from their effectiveness in treating a variety of pain conditions and from previous health policy. In the 1970s and 1980s, numerous studies indicated a minimal risk of addiction to opioid use and its role in the treatment of pain (McAuliffe et al., 1985; Medina & Diamond, 1977; Portenoy & Foley, 1986; Porter & Jick, 1980). Opioids were also comparatively less expensive than nonpharmacological interventions.[2] Both considerations motivated physicians opioid prescribing patterns which resulted in an increase in opioid prescription rate (Franklin et al., 2005).

One potential pharmacological option to reduce U.S. opioid abuse is cannabis (or marijuana in herbal form). Medical marijuana in the U.S. is intertwined in the healthcare system, sometimes prescribed by physicians, and distributed by pharmacies much like other prescriptions. Marijuana is also consumed for pleasure and obtained from retail stores.

Marijuana has an extensive historical reputation of treating numerous ailments including: tetanus, cholera, pruritis, uterine dysfunction, labor and menstrual pains, gout, asthma, neuralgia, rheumatism, convulsions, and depression is well established (Grinspoon & Bakalar, 1998; Harris, Dewey, & Rasdan, 1997; Ogborne et al., 2000). Medical research also consistently finds cannabis provides effective treatment for chronic and temporary pain resulting from a wide variety of injuries and conditions (Hill, 2015; Koppel et al., 2014).

Unlike opioids and many synthetic versions, cannabis is also considerably less addictive and behaviorally less habit-forming (Grinspoon & Balkar, 1995). However, its medicinal and recreational uses, and scientific studies examining its use have been severely curtained by federal drug policy. Marijuana is categorized as a Schedule I drug under the U.S. Drug Enforcement

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[2] Opioids were also one of the few drugs used during therapeutic treatment (Schatman, 2011).

Agency; considered to have no medicinal properties with a high likelihood of abuse (Kane, 2001). Nonetheless, many states have legalized and decriminalized marijuana for medical use, recreational use, or both. As of 2019, about 34 states and the District of Columbia have passed laws legalizing marijuana in some form. Of these states, 11 have enacted legislation allowing for recreational use of marijuana. In contrast, only New Mexico, Pennsylvania, New York, and New Jersey allow opioid addicts to qualify for a medical marijuana card (Quinton, 2019).

Problem Statement

Previous reliance on opioids to treat a variety of pain-related ailments have created widespread dependence on an addictive and potentially harmful drug. Consequently, widespread opioid use has increased emergency related visits to hospitals (Coben et al., 2010) and related drug-use concerns. Between 1999 and 2017, about 400,000 people died as a result of abusing opioids in the U.S., with prescription opioids causing 218,000 deaths. In just 2017, more than 47,000 people died from opioid-related causes, a third of whom had a legal prescription for opioids (Centers for Disease Control and Prevention, 2018a; Scholl, Seth, Kariisa, Wilson, & Baldwin, 2018). As of January 2019, the National Institute on Drug Abuse estimates approximately 130 people die daily from overdosing on opioids (Miron et al., 2019).

The annual cost of opioid use and abuse to the nation is estimated to be over $80 billion due to lost productivity at the workplace, litigation fees, and preventive measures. Out of the total cost, health care and substance abuse treatment account for almost $34 billion (Florence, Luo, Xu, & Zhou, 2016). Today, this concerning and persistent trend beginning in the early 1990s is sometimes referred to as the U.S. opioid epidemic (Miron et al., 2019), where a variety of state and federal regulations motivated regular prescription of these painkilling agents and limited communication of their addictiveness (Miron et al., 2019).

Combatting the opioid crisis has spurred intense investigation from economists, policy experts, clinicians, political figures, and substance abuse/ rehabilitation personnel. In the previous decade, dozens of state-level policies have been implemented to curb opioid abuse. Many of these policies attempted to curb abuse and overdose by implementing stringent (as well as costly and professionally burdensome) restrictions on how many prescriptions are permitted, when and how often these prescriptions can be refilled, how potent the opioids may be, and what ailments they can be prescribed to treat. With few exceptions, these policies have done little to prevent prescription opioid abuse (Miron et al., 2019). Further, these policies frequently drive opioid addicts into illicit markets, often electing to use heroin and other dangerous substitute drugs (Compton, Jones, & Baldwin, 2016; Dasgupta et al., 2013; Pollini et al., 2011)

Medical professionals and researchers have also become intimately involved in mitigating opioid abuse. As an article published in the *New England Journal of Medicine* titled "Ending the Opioid Crisis: A Call To Action" notes, "The pharmaceutical industry, payers, academia, and government will have to work together to develop additional safe alternatives to opioids and to ensure that they are accessible to patients" (Murthy, 2016, p. 2415). Much of these recent efforts pertain to implementing synthetic opioids and other drugs to help addicts cope with physical withdrawal symptoms. Unfortunately, these drugs can be prohibitively expensive and demonstrate mixed results in helping patients curb addiction (Compton, Boyle, & Wargo, 2015).

Despite preliminary evidence, many states are hesitant to introduce legislation to expand access to medicinal marijuana or liberalize laws on recreational use of marijuana, fearing additional research is needed (Kondrad, 2013; Quinton, 2019; Shi, 2017; Wen & Hockenberry, 2018). To the extent that marijuana legalization can combat the opioid epidemic, state legislation

will be either its largest barrier or greatest asset to combat opioid abuse. This necessitates further studies on the subject matter for policy recommendation.

Research Questions

1. What is the relationship between marijuana liberalization, and performed through state legislation, and mitigating the opioid epidemic?

2. What are the effects of recreational marijuana on opioid prescriptions and overdoses?

3. How will a more robust understanding of this relationship affect contemporary addiction and health policy related to the opioid epidemic?

Objectives

1. To better understand the relationship between marijuana legislation and opioid abuse from a policy analysis framework.

2. To apply a synthetic control approach to examine the effects of recreational marijuana on opioid prescriptions and reported overdoses.

3. To provide better information for policymakers to use in making health policy decisions.

Justification

This research uses a modern and inciteful empirical technique to analyze whether a pressing problem (opioid abuse) can be addressed with a reliable and accessible solution (marijuana). Recent history and state policy research indicate that if addicts or patients in need of pain relief will be granted access to cannabis, it will be through state legislation. This study provides timely and important implications for policymakers, economists, medical professionals, and lawyers with interest in public health, cannabis policy, or the opioid epidemic broadly.

Contribution

This research contributes to literature by utilizing a synthetic control approach to examine the effects of introducing recreational marijuana on opioid prescriptions and reported overdoses. Synthetic control methods allow me to analyze the impact of marijuana legalization for recreational use on opioid overdoses by contrasting Colorado with a synthetic version of the same state where marijuana never became legal (a synthetic counterfactual). To create a counterfactual, a weighted average of similar states will be constructed to mimic the trends of Colorado as closely as possible leading up to legalization. This synthetically constructed Colorado will act as a counterfactual, against which I shall compare the actual state of Colorado where legalization takes place. Such quasi-experimental methods allow the researcher to more accurately trace the chain of causal elements responsible for effecting the outcome in question as compared to more traditional methods (Angrist & Pischke, 2010). The synthetic control method, in particular, is an excellent tool for assessing the impact of policies adopted by individual states (see, e.g., Abadie, Diamond, & Hainmueller, 2010) or for comparative political analysis more generally (Abadie et al., 2010). Surprisingly, this approach has never been adopted to analyze my research question.

The focus of the empirical approach is specifically on the effects of legalizing recreational marijuana on opioid overdose in Colorado. Colorado was, along with Washington, one of the first states to introduce both sets of legislation, providing a sufficiently long observational period to draw fruitful policy implications. In comparison to other states, Colorado also has comparatively fewer restrictions on physician prescription practices (Miron et al., 2019). It allows me to examine the effects of marijuana legalization in a less restrictive environment. From a state-policy perspective, Colorado is also currently investigating expanding patient

access to medical marijuana to address chronic pain issues (Wingerter, 2019). With physicians actively pursuing legislators for fewer restrictions on cannabis prescription, my research focus provides critical and timely information for a pressing problem by analyzing a promising solution.

Summary of Results

Colorado legalized recreational marijuana use in 2012 and began retail sales in 2014. In the construction of the synthetic control, the year 2014 was used as the treatment period. The donor pool comprised of U.S. states that had not legalized recreational marijuana. A combination of Arizona (37.3%), Illinois (14.9%), New Hampshire (16.3%), Texas (9.3%), Hawaii (7.7%), New York (6.5%), New Jersey (4.0%), Florida (2.4%), Nebraska (0.9%), and Delaware (0.7%) constituted the synthetic counterfactual which matched closely the actual Colorado state. The synthetic Colorado closely matched actual Colorado during the pre-treatment period with a Root Mean Squared Prediction Error (RMSPE) of 0.711. The average treatment effect was about 53.71%. The results strongly indicate marijuana legalization is not a statistically significant factor in reducing opioid abuse in Colorado State. Additional robustness checks indicate the results of the primary experiment is valid.

LITERATURE REVIEW

Investigating the impact of marijuana legalization requires a robust understanding of the policies on opioid abuse and marijuana legalization. In this section, I review the relevant medical, policy, legal and economic research on the topic.

The Extent and Cost of the Opioid Epidemic

Opioid prescriptions in the U.S. are typically used to alleviate pain. Opioid prescription rates in the U.S. increased from about 7.24 per 1000 persons in 2006 (a total of 215,917,663 prescriptions) to 8.12 per 1000 persons in 2012 (a total of 255,207,954 prescriptions). Although prescription rate decreased to 5.87 per 1000 persons in 2017 (a total of 191,218,272 prescriptions), percentage decline in the total number of prescriptions from 2006 to 2017 was approximately 11.4 percent (Centers for Disease Control and Prevention, 2018b). Further, the Centers for Disease Control and Prevention revealed that although prescription rate decreased in 2017, the rate for some counties across the nation was much higher than the total rate in that year. In particular, rural and low-income counties are hard hit by the epidemic.

These drugs are highly addictive and pose a risk for abuse by patients. Increased opioid prescription rates coincide with elevated rates of addiction, overdose, and death. From 2000 to 2015, national opioid overdose deaths in terms of age-adjusted rate increased substantially from 3.1 per 100,000 to 10.7 per 100,000. Natural and semisynthetic opioids contributed most to opioid overdose deaths over this period (i.e. 1.0 per 100,000 in 2000 to about 4.0 per 100,000 in 2015) (Centers for Disease Control and Prevention, 2016; Rudd et al., 2016,). According to Rudd et al. (2016), opioid overdose deaths in the U.S. accounted for more than half of drug overdose deaths in 2014. Morphine, oxycodone, and hydrocodone prescriptions (all derived from opiates) specifically constitute the leading cause of opioid overdose deaths. Weiss et al. (2017) also find

almost a 100 percent increase in emergency related visits to hospitals as stemming from opioid abuse between 2005 and 2014.

Even when prescribed with caution, opioid use can result in serious side effects. For example, although opioids are prescribed to treat stress and depression, side effects for such treatment include depression, fatigue, loss of memory, and hallucinations (Reissig & Rybarczyk, 2005).[3] Castelli and Frazier (2018) and Swegle and Logemann (2006) note that opioids stimulate the chemoreceptor trigger zone (an area in the medulla oblongata that receives and communicates signals from drugs, hormones, etc.) and increase nausea sensations which could lead to vomiting. Opioid addiction may also result in urinary retention and urodynamics (Marret et al., 2007; Ramsin et al., 2008), negatively impact the nervous system (Yuan & Foss, 2000), and decrease respiratory health (Lalley, 2008; Pattinson, 2008; Yaksh & Wallace, 2011). Rudd et al. (2016) note the leading cause of opioid overdose deaths is respiratory depression.

The economic cost of opioid abuse is also considerable due to the drugs commonality. The estimated economic cost of opioid prescription abuse in 2007 was approximately $55.7 billion compared to total cost of about $9.2 billion in 2001. The major contributing cost was workplace cost due to lost productivity ($25.6 billion; 46 percent), followed by health care cost ($25.0 billion; 45 percent) and criminal justice costs ($5.1 billion; 9 percent) (Birnbaum et al., 2006, 2011). Hansen et al. (2011) estimate a similar estimated total cost of opioid abuse of $53.4 billion in 2006. A recent study, estimate that fatal overdose and abuse resulting from opioid prescription, cost the nation about $80 billion a year. About 52 percent of the cost is related to health care, overdose treatment and lost productivity (Florence et al., 2016).

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[3] It is important to consider many medications used to combat depression and other mental health concerns might exacerbate the condition when dosage and extraneous factors are not considered.

Policy and Opioid Abuse

Because most opioid abuse originates from physician prescriptions, (Kolodny et al., 2015) many states and enterprises implement prescription drug monitoring programs (PDMP). PDMPs gather prescription data from pharmacies and report them to physicians. The main aim of this policy is to identify patients who obtain prescription from several physicians (a term known as doctor shopping) and to track prescription rate, illegal prescribing, dispensing and use of controlled substances (Deyo et al., 2013; Hall et al., 2008).

PDMPs have a longwinded history in the U.S., first implemented by nine states in the 1940s. These initial monitoring programs were paper based, resulting in a laborious and time-consuming effort to curb risky prescribing. Oklahoma adopted the first digital PDMP in 1990. Currently all states have digital PDMP, although their reporting processes differ (Fink et al., 2018).

These programs' success on curbing opioid abuse specifically varies considerably. Using a probit regression model, Bao et al. (2016) predicts about a 30 percent probability reduction in opioid prescription by physicians. Similarly, Patrick et al. (2016), estimate that implementation of the PDMP reduces opioid abuse deaths by approximately 1.12 per 100,000 population (age-adjusted rate). Others find similar results (Reisman, Shenoy, Atherly, & Flowers, 2009; Simeone & Holland, 2006; Simoni□Wastila & Qian, 2012). Further, states with comparatively proper record keeping, more robust monitoring, weekly update, mandatory registration of providers, prescription drug take back, and dose-limit laws had opioid abuse deaths reduced greatly (Brady et al., 2014; Haffajee et al., 2018; Moyo et al., 2017; Sun et al., 2018; Wen, Schackman, Aden, & Bao, 2017; Yarbrough, 2018).

However, degrees of monitoring and forms of assessment vary across each state. For example, state policies vary in the way they enter data into their databases. Some states require pharmacists to enter information on dispensing controlled substance immediately while other states require entry within seven days (Fink et al., 2018). For the state of Colorado, until 2014, all in-state and nonresident pharmacies were required to enter information on dispensing controlled substance twice monthly. Effective October 15, 2014, the Pharmacy Board required entry by pharmacies every day (Colorado Department of Regulatory Agencies, 2015).

Others find PDMPs offer limited abilities to combat overdose and abuse. Reifler et al. (2012) note PDMP's only managed to slow opioid abuse, not decrease it (or that opioid abuse increased at a decreasing rate). Further, other studies note that, although prescription opioid overdose can be reduced through monitoring programs, abuse and overdose often increases through illicit markets (Compton et al., 2016; Dasgupta et al., 2013; Pollini et al., 2011). Shei et al. (2015) find individuals who abuse opioids often do not have a history or record of previous opioid prescriptions prior to developing an addiction. Often, abusers obtain prescription opioids from family members who are prescribed opioid analgesics. Abusers also seek prescriptions from "pill mills" (i.e. a prescriber who prescribes controlled drugs spuriously to patients in exchange for bribe) or visit multiple pharmacies to fill the prescription (Peirce, Smith, Abate, & Halverson, 2012; Yang et al., 2015). These are illegal practices which are difficult to monitor.

Prescription drug monitoring programs also have limited ability to enforce their recommended prescribing practices. Drug monitoring program guidelines stipulate that opioids should be used in the treatment of non-cancer chronic pain only when other pain killers have not provided adequate treatment (Chou et al., 2009) however, Daubresse et al. (2013) reveal that among all pain visits, opioid analgesics prescription almost doubled whiles non-opioid analgesics

prescription remained unchanged. Patients with chronic pain often receive opioid prescriptions for a longer period, increasing the risk of developing dependence (Chou et al., 2015; Kuo, Raji, Chen, Hasan, & Goodwin, 2016). Unfortunately, chronic pain, patients face few alternatives and often become addicted (Chou et al., 2014; Dowell et al., 2016).

Even when PDMPs require of patients detailed drug history physicians before prescribing, it may not reduce opioid prescriptions (Lin, Wang, Boyd, Simoni-Wastila, & Buu, 2018). The primary goal for physicians to enroll in the PDMP query system is to be relicensed. This provides little incentive for physicians to follow prescribed rules by querying the system before prescribing opioids (Haffajee, Jena, & Weiner, 2015; Lin et al., 2018). Further, more stringent PDMP requirements detract physicians from their often busy schedules, creating a tradeoff between compliance and care quality (Haffajee et al., 2015).

Patient characteristics, including race, ethnicity, income levels, as well as their health insurance coverage also impact their likeliness to be prescribed opioids. Lin et al. (2018) find patients with government health insurance were more likely to be prescribed opioid analgesics compared with patients with private insurance. Studies also revealed that Hispanics, Blacks and African Americans are less likely to be prescribed opioids for pain treatment compared to Whites (Anderson, Green, & Payne, 2009; Drwecki et al., 2011; Pletcher et al., 2008; Tamayo-Sarver et al., 2003; Todd, Samaroo, & Hoffman, 1993).

Monitoring policies' ability to combat opioid abuse and addiction come with considerable limitations. They are also often costly, and burdensome. Consequently, many are looking to medical science, rather than public policy, to find alternative ways to avoid addiction while still providing effective and needed treatment. An emergingly popular candidate is marijuana.

Medical Benefits of Marijuana

Marijuana (also known as cannabis) has an extensive and global history of providing medical care for numerous ailments[4] (Harris, Dewey, & Rasdan, 1997). Marijuana's effectiveness in treating numerous conditions including tetanus, cholera, pruritis, uterine dysfunction, labor and menstrual pains, gout, asthma, neuralgia, rheumatism, convulsions, and depression is well established (Grinspoon & Bakalar, 1998; Ogborne et al., 2000). However, there are numerous federal laws which pose restrictions on marijuana use and access for medical research in U.S. Permissions from federal agencies are often required before clinical trials can be conducted. Even when permissions are granted, obtaining marijuana for research is difficult (Harris, 2006). Thus, the academic literature on the effectiveness of medicinal marijuana is comparatively small.

However, current research finds numerous benefits of marijuana use, including treatment of bipolar disorder, mania, depression, irrational guilt, inability to concentrate, insomnia, irresponsible sociable behaviors, loss of appetite, and as a supplement to lithium or as a relief to lithium's side effects (Dansak, 1997; Grinspoon & Bakalar, 1998; Ogborne et al., 2000). Even in recreational use, marijuana provided health benefits for its users including reduction in epilepsy seizures. A study conducted by Porter and Jacobson (2013) on cannabidiol-enriched marijuana use in pediatric treatment-resistant epilepsy reveal that marijuana with high cannabidiol content could greatly reduce seizures and/or completely stops seizures.

Tetrahydrocannabinol (THC) one of the chemical compounds found in marijuana is considered effective against vomiting and nausea to assist patients undergoing chemotherapy

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[4] Grinspoon and Bakalar (1993) date medicinal use of marijuana back to 2700 BC.

(Sallan, Zinberg, & Frei III, 1975). Similarly, Cannabidiol (another chemical compound in marijuana) is noted to have great anti-inflammatory effect and could be used for the treatment of inflammatory diseases including Chron's disease and ulcerative colitis. It also lacks psychoactive effects (Bhattacharyya et al., 2010; Esposito et al., 2013; Leweke, Leichsenring, Kruse, & Hermes, 2011).

Marijuana as a Pain Reliever

Most importantly for my research question and contemporary opioid policy, marijuana provides effective pain relief. A study conducted by the National Academies of Sciences, Engineering, and Medicine (2017) entitled *Health Effects of Marijuana for Medical Use*, confirmed its effectiveness in the treatment of chronic pain in adults. The Center for Medicinal Cannabis Research at University of California San Diego conducted a randomized control clinical trial on medical effect of inhaled marijuana and assert that marijuana should be considered first in the treatment of painful neuropathy and related symptoms (Grant, Atkinson, Mattison, & Coates, 2010).

Several other clinical trials have assessed marijuana's effect on pain including chronic pain, neuropathic pain and multiple sclerosis. Blake et al. (2006) reveal that marijuana substantially assists patients cope with pain. Critically the study also finds no adverse effects from withdrawal, indicating little risk for developing dependence. Narang et al. (2008) find a decrease in the severity of pain and subsequently, increased satisfaction compared to placebo in their study on "Efficacy of Dronabinol as an Adjuvant Treatment for Chronic Pain Patients on Opioid Therapy." Pinsger et al. (2006) estimated the efficacy and efficiency of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain. The results reveal a significant reduction in spinal pain as well as headache intensity. Skrabek et al.

(2008) in determining the effect of marijuana for treatment of pain in fibromyalgia conclude based on the findings of the study that marijuana is effective in the treatment of fibromyalgia as it significantly relief pain and improves quality of life.

Ellis et al. (2009) find smoking marijuana significantly reduces the intensity of pain and works to improve the quality of life for patients with neuropathic pain stemming from HIV. Abrams et al. (2007) similar find smoking marijuana resulted in an approximate 34 percent reduction in daily pain in experimentally induced hyperalgesia. The authors also reported no significant side-effects reported by respondents in the study. A double-blinded, placebo-controlled and crossover study conducted by Wilsey et al. (2008) to evaluate the effect of smoking marijuana on neuropathic pain, reveal improvement in neuropathic pain as well as minimal psychoactive effects. Andreae et al. (2015) studied the short-term effect of inhaled marijuana smoke on neuropathic pain and conclude that inhaled marijuana had the ability to provide short-term relief of neuropathic pain. In the treatment of multiple sclerosis, Zajicek et al. (2012) demonstrate that marijuana extract had a greater potential in the treatment of muscle stiffness.

Many of the studies cited above also note there is little evidence that marijuana, especially medical marijuana, poses significant health risks. There is no link between marijuana consumption, even at higher doses, and fatality (Welch & Martin, 2003). Marijuana also poses little threat for addiction development (Cohen, 2009). Green and Ritter (2000) examined the relationship between marijuana use and depression. Few studies have indicated negative health and related consequences including depression, anxiety, brain impairment, risk of motor accidents, addictions, risk of cancer, etc. (Buckner, Ecker, & Cohen, 2010; Caspi et al., 2005; Hartman & Huestis, 2013; Patton et al., 2002). However, causality is difficult to establish as a

result of other factors which could dispose an individual to risk of mental illness as well as limited or lack of data, selection bias and methodological gap (Strang, Witton, & Hall, 2000; Volkow et al., 2014). For example, Lyketsos et al. (1999) estimated the long-term effect of marijuana on cognitive decline in persons below 65 years and found no significant effect in cognitive decline between heavy users, light users and non-users of marijuana. The authors therefore conclude that cognitive decline could possibly be associated with aging.

Legalization of Marijuana and Related Policy Concerns

In 1970, the U.S. Congress passed the Controlled Substance Act which categorized marijuana as a Schedule I drug, considered unsafe for medical purposes with a high likelihood of abuse (Kane, 2001). Although federal drug policy remains largely the same, state policies have recently began to adopt their own exceptions (DeBonis, 2009; Marijuana Policy Project, 2012; Tiersky, 1998).

California was the first state to legalize marijuana under specific medical circumstances in 1996 (Hoffmann & Weber, 2010). In the year 2000, Colorado legalized marijuana for medical purpose and in the year 2014, legalized marijuana for recreational use (Hopfer, 2014). Several states and the District of Columbia have legalized marijuana for medical purpose, and 12 states including the District of Columbia have legalized marijuana for recreational use. The devastation and persistence of the opioid epidemic has led several states to consider utilizing liberalized marijuana laws to combat opioid abuse. For example, New Mexico, Pennsylvania, New York, and New Jersey allow opioid addicts to qualify for a medical marijuana card (Quinton, 2019).

State-Level Marijuana Legalization

States which have implemented legislation legalizing marijuana for recreational, medical, or both have commonalities in their restrictions to ensure public health and environmental

protection. Across the states, cultivators, manufactures, testing facilities and retailers are required to be licensed. Cultivation of marijuana plants by residents varies among states. In states such as New York, California, Massachusetts and the District of Columbia, residents can grow up to six plants in their homes while states like Colorado and Michigan allow up to 12 plants but away from public view. Public and open consumption of marijuana is prohibited in all states. The legal age for possessing marijuana of any form across states in general is 21 years and older. It is therefore illegal to transfer marijuana products to minors and other individuals younger than 21 years (Pacula & Smart, 2017). All states except Washington prohibit a licensee to be involved in both the production and distribution of marijuana.

States also differ across many avenues in their marijuana polices. In the District of Columbia, sales of marijuana for recreational purpose is prohibited as well as illegal for a person to transfer any amount of marijuana to another aged 21 years and above for renumeration (Marijuana Work Group, 2016). In contrast, states such as Washington, Oregon, Alaska, Illinois and Colorado have legalized sales of marijuana for recreational use and impose tax on it. Washington legalized retail sales of marijuana in July 2014, Oregon in October 2015, Alaska in September 2016 (Hall & Lynskey, 2016), Colorado in 2012,[5] (Monte, Zane, & Heard, 2015), and Illinois in June 2019,[6] (Shepherd, 2020). Washington and Alaska allow adults to purchase/possess up to 7 grams of marijuana concentrates, 1 ounce of marijuana flower, 16 ounces of infused product in solid form or 72 ounces in beverage form. Oregon and Illinois have similar restrictions, except that purchase/possession of marijuana concentrates is limited to 5 grams (Pacula & Smart, 2017; Shepherd, 2020). Adult residents in Colorado can purchase a

[5] Sales by retail stores in Colorado started in January 2014.
[6] Retail sales for Illinois began in January 2020.

maximum of 1 ounce of marijuana flower or 8 grams of marijuana concentrates (Pacula & Smart, 2017).

Marijuana Policy in Colorado

In Colorado, the law prohibits minors and other individuals below 21 years from entering marijuana retail stores as well as requires proof of age before purchase. Marijuana products need to be packaged such that it does not appeal to individuals below 21 years. Internet pop-up and any other forms of advertisement that is deemed to target minors is prohibited. Further, outdoor advertisement in any form (e.g. giving leaflet or flier to persons in public or posted on any public or private property) is illegal, except for signs and directions to certified retail stores (Colorado Department of Revenue, 2018).

For medical purposes, the law on medical marijuana allows more providers (including dentists, physician assistants, podiatrists, optometrists, and advanced nurse practitioners with prescriptive authority) to recommend medical marijuana to treat medical conditions such as post-traumatic stress disorder, autism spectrum disorder and any condition for which opioid was prescribed. Individuals could obtain a medical marijuana card for any of the medical conditions stipulated by the law on medical marijuana in Colorado (Colorado Department of Public Health and Environment, 2019b).

Three types of taxes are imposed on marijuana in Colorado (i.e. excise tax on wholesale and retail, special sales tax on retail, and regular state sales tax on medical/retail marijuana). A 15 percent excise tax is imposed on unprocessed marijuana, 15 percent special sales tax on retail marijuana and 2.9 percent state sales tax on medical and retail marijuana. As noted earlier, legalizing marijuana does not only have medical benefit but economic benefits as well. About 90

percent of the taxes collected are channeled into education by building and upgrading public schools (Colorado Department of Education, 2019).

Marijuana Legalization and Opioid Abuse

Using a logistic regression, Azagba, Shan, Manzione, Qeadan and Wolfson (2019) assessed the trends in opioid misuse among marijuana users and non-users in United States using National Survey on Drug Use and Health data from 2007 to 2017 and found a significant decrease in opioid misuse among marijuana users compared to non-users.

Bachhuber et al. (2014) studied the relationship between medical marijuana laws and opioid overdose deaths in the U.S. for all 50 states from 1999 to 2010. They conclude that states with medical marijuana laws had significant reduction in opioid overdose deaths over the years after implementation of the laws.

Using data from the CDC, Blake (2020) finds opioid prescribing rates 15 of 19 states examined experienced decreases in opioid prescribing rates one year after marijuana legalization.[7] Blake specifically notes that Ohio experienced the highest decrease (19.2 per 100 persons) while New York experienced the smallest decrease (1.6 per 100 persons). Although Blake's (2020) findings largely indicate a substitution between marijuana and opioid use, heterogeneous effects found at the state level require a more robust analysis to understand complicating factors involved when deciding to prescribe opioids or marijuana.

Boehnke, Litinas and Clauw (2016) estimated the relationship between medical cannabis use and opioid medication use in a retrospective cross-sectional survey of patients with chronic

[7] New Jersey, New Mexico, Michigan and Arizona were the four states which had an increase in opioid prescribing rate, with Michigan having the highest increase (9 per 100 persons) and New Jersey having the least number of increase (1.6 per 100 persons).

pain who visited a medical cannabis dispensary in Michigan between November 2013 and February 2015. Using Pearson's correlation, Student t-tests, paired T-tests and Analysis of Variance tests, the results of the study reveal that medical cannabis use is associated with a decrease in opioid use as well as decreased side effects of medications and an improved quality of life.

Bradford et al. (2018) used longitudinal data from 2010 to 2015 to examine the relationship between U.S. state medical cannabis law and opioid prescription under Medicare part D. The medical cannabis laws considered in this study were states with active dispensaries and states with home cultivations. Using multiple regression analysis, results of the study reveal a statistically significant reduction in daily opioid prescription, particularly in states with active dispensaries.

Lake et al. (2019) used multivariable generalized linear mixed-effects model to assess daily cannabis and illicit opioid use among individuals who experienced constant pain from June 2014 to December 2017. The findings of the study indicate that frequency of cannabis use have significantly higher odds of reducing frequency of illicit opioid use.

Powell, Pacula and Jacobson (2018) used difference-in-difference approach to compare the effect of medical marijuana legalization on opioid-related deaths for states adopting and not adopting medical marijuana laws. Data for the study was from 1999 to 2013. Their findings suggest that as states liberalize regulation of dispensaries, medical marijuana is substituted for addictive opioids which significantly reduce opioids overdose deaths.

Shi (2017) estimated the effect of medical marijuana policies on hospitalization rate for marijuana and opioid dependence using linear time-series models with two-way fixed effects. The study used state-level annual hospitalization data from 1997 to 2014 for 27 states which

participated in State Inpatient Databases (SID). A statistically significant negative association was found between medical marijuana policies and opioid related hospitalizations but no significant association with marijuana related hospitalizations.

Shi et al. (2018) studied the effect of recreational marijuana legalization on opioids prescription among Medicaid subscribers using difference-in-difference method. State-level data from 2010 to 2017 for eight states and District of Columbia that legalized recreational marijuana was accessed from Medicaid State Drug Utilization database. Based on the results, states which legalized recreational marijuana in 2015 had Schedule III opioids prescriptions and spending reduced significantly but had no significant reduction in Schedule II opioids prescriptions and spending.

Vigil et al. (2017) used logistic regression model and least squares approach to compare prescription opioid use among patients enrolled in Medical Cannabis Program and patients not enrolled. Data was drawn from the Prescription Monitoring Program between 2010 and 2015 in New Mexico. The study reveals higher odds of absence of opioid prescriptions during the last three months of observation as well as decline in average daily intravenous morphine dosages. Further, respondents enrolled in the Medical Cannabis Program for at least one year indicated reduction in pain, improvement in quality of life, social life, activity levels and concentration.

Wen and Hockenberry (2018) use a difference-in-difference method to examine the association between medical and recreational marijuana laws and opioid prescribing rates for Medicaid enrollees from 2011 to 2016. The results reveal significant decrease in opioid prescribing rate for states with medical and adult-use marijuana laws compared to states without medical and recreational marijuana.

Caputi and Humphreys (2018) assessed the association between medical marijuana use and prescription drugs use medically and nonmedically. The study used cross-sectional data from 2015 National Survey on Drug Use and Health, and results were estimated using logistic regression. The findings of the study reveal medical marijuana users are more likely to report medical and nonmedical use of prescription drugs in the past 12 months of the study.

Though several studies have been done to access the relationship between marijuana use and prescription opioid abuse, the previous literature use time series, probit, and standard regression techniques, but there are very limited quasi-experimental papers, and none that use synthetic control. The studies provide limited implications for policy impact analysis due to the use of cross-sectional data, limited sample size, statistical errors and small sampling periods for post-legalization of marijuana. Further, combining various states into an analysis distorts some of the information. State level stuff holds regulatory barriers constant and can better test singular changes. In this regard, further research is recommended to examine if there exist a causal relationship between marijuana use and prescription opioid abuse.

Studies in Colorado

Colorado is one of the few states that have recorded a surge in drug abuse as well as opioid abuse and overdose deaths. Until 2015, the age-adjusted total drug overdose death rates per 100,000 persons in Colorado was higher than the age-adjusted total drug overdose deaths in the entire U.S. per 100,000 persons. Among the [most commonly reported][8] drug overdose deaths is opioids, soaring from 2.5 deaths per 100,000 population in 1999 to 9.8 in 2017 (Colorado Department of Public Health and Environment, 2018).

[8] Prescription opioids, heroin, methamphetamine and cocaine are the most commonly reported drug overdose deaths (Colorado Department of Public Health and Environment, 2018).

Very few studies have assessed the relationship between marijuana and opioid abuse in Colorado. Livingston et al. (2017) examined recreational marijuana legalization and opioid-related deaths in Colorado from January 2000 to December 2015 using an interrupted time-series design. Results of the study reveal that sales and use of recreational marijuana significantly reduce monthly opioid related deaths.

Kropp et al. (2019) studied the effect of recreational marijuana legalization on opioid prescription rate in Colorado from 2007 to 2017 using t-test. Although the study uses simple statistical method, the findings reveal that recreational marijuana legalization significantly decrease opioid prescription. A limitation to this study was that related health policies which could serve as confounding variables were not assessed. It also does not estimate causality effect between the two.

Studies have also examined other effects of marijuana in Colorado. They find increase in emergency department visits, risk of motor vehicle crashes, poison center calls, crime rates, workplace injury, and respiratory effects as a result of marijuana legalization (Colorado Department of Public Health and Environment, 2019a; Davis et al., 2016; Monfort, 2018; Wang et al., 2018). However, these studies did not actually test for causality as well as account for confounders, which could possibly affect the relationship between marijuana use and these outcomes.

Summary

The literature largely finds that drug abuse and overdose deaths is a major issue in the U.S. and at the center is opioid overdose deaths. Although there have been some measures to curb abuse, the epidemic persists. In a quest for more efficient and effective drug as an alternative to opioid, researchers recommend marijuana. Nonetheless, some studies raise doubt

about its usefulness and medical benefits. This notwithstanding, these studies rely on self-report, do not follow participants overtime, lack robust techniques to assess causality and do not account for confounders. To assess the impact of marijuana legalization critically and empirically on opioid abuse, this study employs synthetic control approach which fills the methodological gap in the literature.

METHODOLOGY

Method of Analysis

Quasi-experimental methods, including randomized control trials, difference-in-difference method, propensity score matching, and synthetic controls are frequently used in comparative studies to assess the effect of policies. Although each method provides unique insight, the synthetic control method offers the most insight into my research question. Further, randomized control trials, difference-in-difference method and propensity score matching provide limited implications for their policy impact analysis.

A major shortcoming of randomized controlled trials, although often used in medical research, is the challenge of conducting a double-blind test as a result of deciphering allocation schedules. For this reason, majority of randomized controlled trials have failed in performing a blind test (Schulz, 1995). Randomized controlled trials also may not be possible for certain experiments, for example, assigning marijuana to patients with opioid addiction or chronic pain. In such experiment, culture and myth or people's belief would serve as a barrier for their participation, making it totally impossible to carry out the experiment.

Although structurally like the synthetic control method, the difference-in-difference method cannot have a differential trend to be implemented. Thus, outcomes between the two groups is not changed by other factors than the policy change. Ryan, Burgess, and Dimick (2015) reveal that in practice, this parallel trend assumption may not be plausible and recommend consideration for alternative methods. Propensity score matching does not account for possible unobservable factor(s) which influence both the decision to adopt the treatment and the outcome. However, combining propensity score matching with difference-in-difference method is a hybrid approach which helps to deal with time-invariant unobservable(s). The synthetic control

approach which combines propensity score matching and difference-in-difference method is an alternative to this hybrid approach.

This study uses the synthetic control method or approach developed by Abadie and Gardeazabal (2003). The synthetic control method is an excellent tool for assessing the impact of policies adopted by individual states (see, e.g., Abadie, Diamond, & Hainmueller, 2010) or for comparative political analysis more generally (Abadie et al., 2010). The synthetic control has many advantages over the traditional linear regression model and the other quasi-experimental methods. First, synthetic control approach combines several units in a donor pool as a control for comparison with the unit which has been exposed to the intervention. This gives a more robust comparison compared to any single unit. The combined units in the donor pool approximate the characteristics of the affected unit better than any single unit. For instance, Abadie and Gardeazabal (2003) combined two Spanish regions in comparison with the Basque country to estimate what the economic growth would have been in the absence of terrorism. Second, the researcher has no control over the outcome of the study because it does not require access to postintervention outcomes as well as remaining blind to how each decision affects the conclusion of the study (Abadie et al., 2010). Third, it combines the matching and difference-in-difference method as well as accounts for the effect(s) of confounders changing over time. Finally, synthetic approach gives a visual representation of the results showing the effect with and without the intervention.

Synthetic control approach has been applied in several research to study the effect of policy interventions. It has been used to study the effect of corporate political connections (Acemoglu, Johnson, Kermani, Kwak, & Mitton, 2016), immigration policy (Bohn, Lofstrom, & Raphael, 2014), legalized prostitution (Cunningham & Shah, 2018), right-to-carry laws

(Donohue, Aneja, & Weber, 2019), one child policy in China (Gietel-Basten, Han, & Cheng, 2019), taxation (Kleven, Landais, & Saez, 2013), organized crime (Pinotti, 2015) and many other non-health related policies.

Synthetic control method has been used in health related studies to study the effect of California's tobacco control program widely known as proposition 99 (Abadie et al., 2010), marijuana legalization and crime (Chu & Townsend, 2019; Furton, 2018), contraceptives and teen birth rates (Lindo & Packham, 2017), medical marijuana laws on body weight (Sabia, Swigert, & Young, 2015), universal health coverage (Rieger, Wagner, & Bedi, 2017), democratic reforms on child mortality (Pieters, Curzi, Olper, & Swinnen, 2016), school district nutrition policies on dietary intake and overweight (Bauhoff, 2014), ban on trans fats and public health (Spruk & Kovac, 2020), bariatric surgery on health care costs (Kurz et al., 2019), etc.

For this study, synthetic control method allows for the analysis of the impact of marijuana legalization for medical and recreational use on opioid abuse by contrasting Colorado with a synthetic version of the same state where marijuana never became legal (a synthetic counterfactual). To create a counterfactual, a weighted average of similar states was constructed to mimic the trends of Colorado as closely as possible leading up to legalization. This synthetically constructed Colorado acted as a counterfactual, against which the actual state of Colorado where legalization took place was compared.

Theoretical Framework

I obtain a sample of $J + 1$ states, indexed by j, where $j = 1,2, \dots, J + 1$. For simplicity, a single treated state is assumed (i.e. the state affected by the intervention or policy) and denoted as $j = 1$ and a donor pool (i.e. collection of potential comparison states not affected by the policy) of $j = 2, \dots, J + 1$. Abadie, Diamond, and Hainmueller (2015) note that the donor pool

should be limited to outcomes that are believed to be driven by the same structural process as for the treated state and that were not subject to structural shocks to the outcome variable during the sample period of the study. This is because the control states for comparison are to approximate the treated state in time without the intervention. Again, a balanced panel/ longitudinal data set is assumed, where all the states are observed at the same time periods $t = 1, 2, \dots, T$[9] and preintervention periods denoted as $1, \dots, T_0$. Further, postintervention periods T_1 are denoted as $T_0 + 1, \dots, T$. State $j = 1$ is exposed to the intervention at periods $T_0 + 1, \dots, T$, and preintervention periods $1, \dots, T_0$.

For each state j, an outcome of interest Y_{jt} can be observed as well as a set of predictors h of the outcomes, $X_{1j}, \dots, X_{hj}$, which are not affected by the intervention and may include pre-intervention values Y_{jt}. Let X_1 be an $h\ x\ 1$ vector containing the values of the preintervention characteristics of the treated state for which I intend to match closely as possible, and X_0 be an $h\ x\ J$ matrix collecting the values of the same variables for the states in the donor pool. For each state *j* and time *t*, the potential response at time of no intervention is represented as Y_{jt}^N. The potential response at time of intervention (i.e. post-intervention period) $t > T_0$ for state $j = 1$ (state affected by the intervention) is defined as Y_{1t}^I. The effect of the intervention of interest for the affected state in period $t > T_0$ is represented as:

$$\alpha_{1t} = Y_{1t}^I - Y_{1t}^N \quad (1)$$

From equation (1), effectively estimating the impact of a policy intervention is equivalent to the challenge of estimating Y_{1t}^N for $t > T_0$, which reveals how the state exposed to the

[9] T is a total of 12 periods (years) from 2006-2018 for this study.

intervention would have been in the absence of the intervention. Equation (1) allows for change in time with the effect of the intervention, since a policy implemented may not have immediate effect.

Synthetic control is defined as a weighted average of the states in the donor pool. It can be represented by a $J\ x\ 1$ vector of weights $W = (w_2, \dots, w_{J+1})'$, where $0 \leq w_j \leq 1$ for $j = 2, \dots J+1$ and $w_2 + \cdots + w_{J+1} = 1$. The value chosen for W is equivalent to a synthetic control. Abadie et al. (2015) propose choosing a value of W such that the characteristics of the synthetic control best resembles the characteristics of the state exposed to the intervention.

For a set of weights W, the synthetic control estimator of Y_{1t}^N is represented as:

$$\hat{Y}_{1t}^N = \sum_{j=2}^{J+1} w_j Y_{jt} \tag{2}$$

and the synthetic control estimator of α_{1t} is represented as:

$$\hat{\alpha}_{1t} = Y_{1t} - \hat{Y}_{1t}^N \tag{3}$$

The weights are restricted to be positive to avoid extrapolation, and no greater than one. Equation (3) can be written as

$$\hat{\alpha}_{1t} = Y_{1t} - \sum_{j=2}^{J+1} w_j Y_{jt} \tag{4}$$

If a single state say s, in the donor pool is used as a synthetic control, then $w_s = 1$, $w_j = 0 \in j \neq s$, and

$$\hat{\alpha}_{1t} = Y_{1t} - Y_{st} \tag{5}$$

For adjacent-neighbor estimators, s is the index value that minimizes $\|X_1 - X_j\|$ over j for some norm $\|.\|$.

The preintervention characteristics in X_1 and X_0 may include preintervention values of the outcome variable. The difference between the preintervention characteristics of the treated state and the synthetic control is given by the vector $X_1 - X_0W$. The value of W is selected such

that it minimizes the difference between the preintervention characteristics of the treated state and the synthetic control. According to Abadie et al. (2010), and Abadie and Gardeazabal (2003), $W^* = (\mathrm{w}_2^*, \ldots, \mathrm{w}_{J+1}^*)'$ is chosen as the value of W that minimizes:

$$||X_1 - X_0 W|| = [\sum_{m=1}^{h} v_m (X_{1m} - X_{0m} W)^2]^{1/2} \quad (6)$$

Where v_m denotes weight reflecting the relative importance assigned to the m^{th} variable when $X_1 - X_0 W$ is measured. The matching variables in X_0 and X_1 are meant to predict the postintervention outcomes. Large weights v_m should be assigned to the values of the variables for the synthetic controls to closely reproduce the values of the variables for the treated state.

To measure the effect of the treatment, let Y_{jt} be the outcome of state j at time t, Y_1 be a $T_1 \; x \; 1$ vector collecting the postintervention values of the outcome for the state affected by the intervention. The synthetic control estimator of the effect of the treatment is given by the comparison between the outcome for the treated state and the outcome for the synthetic control at that period:

$$\hat{\alpha}_{1t} = Y_{1t} - \sum_{j=2}^{J+1} w_j^* Y_{jt} \quad (7)$$

The challenge is how to choose v_m. A simple selector of v_m is the inverse of the variance of X_{1m} and X_{0m}, which rescales all rows of $[X_1 : X_0]$ to have unit variance. Alternatively, Abadie et al. (2010), and Abadie and Gardeazabal (2003) choose v_m that minimizes the mean squared prediction error (MSPE) of the synthetic control with respect to Y_{1t}^N

$$\sum_{t \in T_0} (Y_{1t} - w_2 (v_1) Y_{2t} - \cdots - w_{J+1}(v_h) Y_{J+1t})^2$$

for some set $T_0 \subseteq \{1, 2, \ldots, T_0\}$ of preintervention periods.

Inference

Abadie et al. (2010) propose a test statistic to measure the ratio of the post-intervention fit relative to the pre-intervention fit. For $0 \leq t_1 \leq t_2 \leq T$ and $j = [1, \dots, J+1]$, let

$$R_j(t_1, t_2) = \left(\frac{1}{t_2 - t_1 + 1} \sum_{t=t_1}^{t_2} (Y_{jt} - \hat{Y}_{1t}^N)^2\right)^{1/2}, \quad (8)$$

$\hat{Y}_{1t}^N$ denotes the outcome on period t produced by a synthetic control when state j is coded as treated and using all other J states to construct the donor pool. This is the root mean squared prediction error (RMSPE) of the synthetic control estimator for state j and time periods $t_1, \dots, t_2$.

The ratio between the post-intervention RMSPE and pre-intervention RMSPE for state j is

$$r_j = \frac{R_j(T_0+1, T)}{R_j(1, T_0)} \quad (9)$$

r_j denotes the quality of the fit of a synthetic control for states j in the post-treatment period, relative to the quality of the fit in the pre-treatment period. Abadie et al. (2010) use the permutation distribution of r_j for inference.

Alternatively, inference is based on the distribution $R_j(T_0 + 1, T)$ after disregarding those placebo runs with $R_j(1, T_0)$ substantially larger than $R_1(1, T_0)$ (see Abadie et al., 2010). Replacing $Y_{jt} - \hat{Y}_{1t}^N$ in $R_j(T_0 + 1, T)$ with their positive $(Y_{jt} - \hat{Y}_{1t}^N)^+$ or negative $(Y_{jt} - \hat{Y}_{1t}^N)^+$ parts leads to one-sided inference (Abadie, 2019). The inferential technique determines whether the effect of the actual intervention estimated is large relative to the distribution of the effects estimated for the control states.

Creating the Synthetic Control

In an ideal experiment, we could observe what would have happened in a world where marijuana was not legalized in Colorado State. Unfortunately, there is only a single unit under

examination and imperfect counterfactuals to compare them against. The synthetic control method allows for the construction of an artificial counterfactual. The method was developed by Abadie and Gardeazabal (2003), who set out to identify the effect of terrorism in Spain's Basque Country. To create a quasi-counterfactual for Colorado State, a donor pool of similar states must be created. The states in the donor pool must possess similar characteristics and trends to that of Colorado State and should not have received the treatment during the period of the study. A strongly balanced panel or longitudinal data set for a total of 12 years from 2006-2018 covering the pre-intervention (2006-2013) and post-intervention (2014-2018) periods is set up.

The "synthetic" Colorado State is constructed using a weighted average of variables from similar U.S. states which did not receive the treatment (legalization of recreational marijuana). This synthetic counterfactual is meant to track the opioid deaths rate prior to the legalization of recreational marijuana. The degree to which the pre-treatment period is accurately tracked will allow the synthetic to substitute for the counterfactual that the study is missing.

Constructing a counterfactual Colorado State requires choosing suitable indicator variables and assigning correct weights to each donor unit (i.e. U.S. states). A 'synthetic Colorado State' is constructed from a pool of states that reflect patterns in both the outcome variable. This synthetic counterpart uses weighted averages of similar states to imitate—as closely as possible—the trends of the actual state of Colorado leading up to the opening of the first retail recreational marijuana store in 2014 (i.e., the pre-treatment period). The selection of indicator variables is intended to minimize the difference between the outcome variable in the synthetically constructed state and the actual State of Colorado. States in the donor pool that possess similar characteristics and trends to that of Colorado are given higher weights, such that the total values equal 100%.

Data and Description of Variables

To test the effect of recreational marijuana legalization on opioid abuse, state level data for each state that did not legalize recreational marijuana over the 2006 to 2018 period was used. The data was obtained from different sources (see Table 1). Variables used for the study were grouped into outcome and indicator variables. Stata version 16 was used for the analysis.

Outcome Variable

The outcome variable is opioid related deaths. Opioid overdose deaths is measured as the age-adjusted rates of opioid overdose deaths by state annually as a result of consuming any opioid analgesic or heroin. Data on opioid related deaths was obtained from the Centers for Disease Control and Prevention, National Center for Injury Prevention and Control.
The outcome variable(s) changes as a function of the indicator variables while the indicator variables help to match the conditions of the treated state (i.e., Colorado) to the conditions of the weighted averages of the states in the donor pool during the pre-treatment period.

Indicator Variables

The indicator variables which are assigned must be justified based on the subjective assessment of their contribution to determining the outcome variable of interest (opioid related deaths). The interest is in developing a synthetic counterfactual based on the outcomes alone, but in conjunction with the processes that bring them about. Thus, I chose indicator variables that minimize the difference between the weighted average of the variables for the synthetic Colorado as well as the actual State of Colorado (see Table 3). The indicator variables used for the study included oxycodone prescriptions per 1,000, hydrocodone prescriptions per 1,000, health insurance, physician rate per 100,000 population, alcohol consumption, gender, race, marriage rate, population density, and unemployment rate.

Oxycodone and hydrocodone prescriptions are measured as the dispensing rate per 1,000 persons. Data was obtained from the Centers for Disease Control and Prevention, National Center for Injury Prevention and Control.

Physician rate is measured as active physicians per 100,000 Population. The data on physician rate was obtained from the Association of American Medical Colleges database.

Alcohol consumption is measured as the gallons of ethanol consumed each year per population aged 14 and older. The data on alcohol consumption was obtained from the National Institute on Alcohol Abuse and Alcoholism.

Health insurance is measured as percentage of the population that has some health insurance coverage. Gender used for this study is measured as the percentage of males in a state in a particular year. Marriage rate is measured as the population aged 15 years and older who are married per 100,000 persons.[10] Population density is measured as the population per square mile. Race is measured as the percent of the population that is Hispanic. Data for health insurance, gender, marriage rate, population, and race were obtained from the United States Census Bureau database.

Unemployment rate is measured as the total number of individuals of working age group unemployed to the total working age group. Data for unemployment was obtained from the Bureau of Economic Analysis.

Lag measures of the outcome variable were used as indicator variables to predict the outcome variable in the construction of the synthetic Colorado. The measurement lags are the

[10] Marital status data excludes same-sex marriage since same sex marriage was only accounted for starting in 2019. Married couples include married spouse present, married spouse absent and separated.

years 2007, 2009, 2011, and 2013. The variables, measurements, and data sources are summarized in Table 1.

Variables such as number of hospital beds per 1,000 citizens, median household income, educational attainment, median age, obesity rate, percent black or African American that could serve as indicator variables were dropped since the weighted average of these variables for the synthetic Colorado did not closely match the weighted averages of the variables for Colorado state.

Table 1. Variables, Measurements and Data Sources

Variables	Measurements	Sources
Opioid overdose deaths	Age-adjusted rates of opioid overdose deaths by state annually as a result of consuming any opioid analgesic or heroin	Centers for Disease Control and Prevention, National Center for Injury Prevention and Control
Oxycodone prescriptions	Dispensing rate per 1,000 persons	
Hydrocodone prescriptions	Dispensing rate per 1,000 persons	
Health insurance	Percent of the population that has some health insurance coverage	United States Census Bureau database
Physician rate	Active Physicians per 100,000 Population	Association of American Medical Colleges database
Alcohol consumption	The gallons of ethanol consumed each year per population aged 14 and older	National Institute on Alcohol Abuse and Alcoholism
Gender	The percentage of males in a state in a particular year	United States Census Bureau database
Marriage rate	Population aged 15 years and older who are married per 100,000 persons	
Race	The percent of the population that is Hispanic	
Population density	Population per square mile	
Unemployment rate	Total number of individuals of working age group unemployed to the total working age group	Bureau of Economic Analysis

RESULTS AND DISCUSSION

The policy under investigation is legalization of recreational marijuana use. Colorado is among the few states to have legalized recreational marijuana use. Colorado passed the law legalizing recreational marijuana use in 2012 and began retail sales in 2014. Therefore, the treatment period for the study is the year 2014. The donor pool comprised of U.S. states that had not legalized marijuana prior to 2018 (the end of the post-treatment period for this study). About this time, forty (40) U.S. states had not legalized recreational marijuana use in any form. The States of Alaska, California, Maine, Massachusetts, Nevada, Oregon, Vermont, Washington and District of Columbia were dropped because by 2014, these states had legalized recreational marijuana. Further, the synthetic control method requires a balanced panel, and any state which lacks complete annual data was dropped. In this case, North Dakota was excluded.

Table 2 presents the descriptive statistics of the variables used for the analysis. The outcome variable (opioid overdose death rates) had a minimum value of 0.65 and maximum value of 49.602, with a mean value of 9.917.

Table 2. Descriptive Statistics

Variable	Mean	Std. Dev.	Min	Max
Opioid overdose deaths	9.917	7.181	.65	49.602
Oxycodone prescriptions	19.126	8.551	3.946	66.39
Hydrocodone prescriptions	12.177	7.247	1.294	42.276
Health insurance	88.356	4.231	76.2	96.5
Physician rate	246.688	45.806	172.9	377.8
Alcohol consumption	23758.469	5222.881	13250	47618
Gender	.496	.046	.482	1.034
Marriage rate	7.084	2.054	4.0	21.9
Race	.104	.094	.01	.494
Population density	73.273	12.686	46.1	94.7
Unemployment rate	5.868	2.125	2.433	13.608

Table 3 and Figure 1 present a comparison of predictor means between actual Colorado and synthetic Colorado as well as the population-weighted averages of the 40 states in the donor pool. From Table 3, it is observed that the weighted averages of the 40 states that did not legalize recreational marijuana in 2014-2018 does not seem to match closely the weighted averages of the actual Colorado and thus, cannot serve as a suitable control group for the state of Colorado. Particularly, opioid death rates were lower in the average of the 40 control states than in Colorado, and prior to the legalization of recreational marijuana, on average, the rates were higher than in Colorado (see Figure 1).

Table 3. Predictor Balance

Variables	Colorado			
	Actual	Synthetic	Difference (actual vs synthetic)	Average of 40 states
Oxycodone	20.00	21.72	1.72	19.11
Hydrocodone	7.89	9.42	1.53	12.30
Health insurance	84.62	85.27	0.65	88.37
Physician rate	259.15	251.93	7.22	246.24
LN (Alcohol consumption)	10.22	10.18	0.04	10.05
Percent male	0.50	0.49	0.01	0.50
Percent Hispanic	0.20	0.20	0.00	0.10
Marriage rate	7.01	7.25	0.24	7.08
Population density	85.35	83.78	1.57	72.96
Unemployment rate	6.50	6.79	0.29	5.88
Overdose deaths (2013)	8.03	8.06	0.03	9.11
Overdose deaths (2011)	8.05	8.01	0.04	8.21
Overdose deaths (2009)	7.67	7.66	0.01	7.02
Overdose deaths (2007)	7.05	7.06	0.01	6.58

Table note. Predictors are averaged over: 2006 2007 2008 2009 2010 2011 2012 2013

Further, it is noted from Table 3 that the weighted averages of actual Colorado and synthetic Colorado are just as close to each other. The closer the weighted average of each variable is, the more appropriate the variable is for constructing the counterfactual. The predictor means (as shown in Table 3) for almost all the indicator variables exhibited differences of less than 1. Thus, it is certain that the synthetic Colorado would match closely the actual Colorado. In

order words, the synthetic Colorado would be a better counterfactual. The synthetic control method enables the researcher to see what the counterfactual is. i.e., if Colorado had not legalized recreational marijuana, what would have been the results. King and Zeng (2006) note that synthetic control method "safeguards against estimation of extreme counterfactuals."

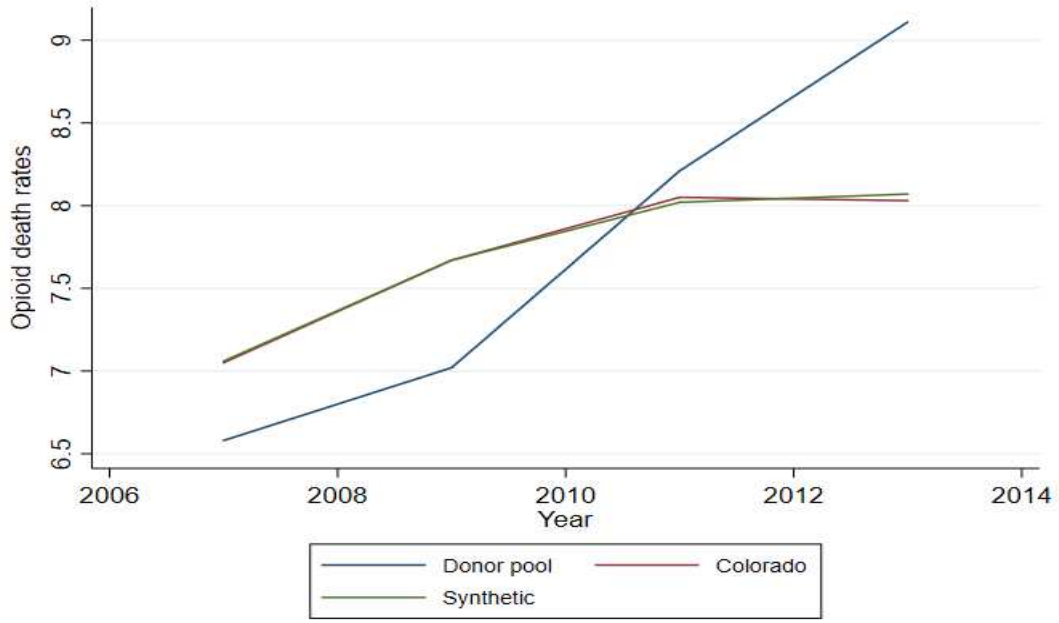

Figure 1. Opioid Death Rates for Colorado vs Synthetic Colorado vs Donor Pool

Table 4 presents the potential control states (donor pool) and the states which had weight loadings. These states were the states used for producing the synthetic Colorado. The synthetic Colorado was a combination of Arizona (37.3%), Illinois (14.9%), New Hampshire (16.3%), Texas (9.3%), Hawaii (7.7%), New York (6.5%), New Jersey (4.0%), Florida (2.4%), Nebraska (0.9%), and Delaware (0.7%). All other states in the donor pool obtained zero weights. It is observed that no single state weighs 50% or more and the weights sum up to 1 or 100%. The three largest states that served as controls were Arizona, Illinois, and New Hampshire. These three states are compared to Colorado in Figure 3.

Table 4. State Weights in the Synthetic Colorado

State	Weight	State	Weight
Alabama	0	Montana	0
Arizona	0.373	Nebraska	0.009
Arkansas	0	New Hampshire	0.163
Connecticut	0	New Jersey	0.04
Delaware	0.007	New Mexico	0
Florida	0.024	New York	0.065
Georgia	0	North Carolina	0
Hawaii	0.077	Ohio	0
Idaho	0	Oklahoma	0
Illinois	0.149	Pennsylvania	0
Indiana	0	Rhode Island	0
Iowa	0	South Carolina	0
Kansas	0	South Dakota	0
Kentucky	0	Tennessee	0
Louisiana	0	Texas	0.093
Maryland	0	Utah	0
Michigan	0	Virginia	0
Minnesota	0	West Virginia	0
Mississippi	0	Wisconsin	0
Missouri	0	Wyoming	0

I compared the opioid death rates for Colorado to the U.S. Figure 2 shows the change in opioid death rates across the U.S. and Colorado from 2006 to 2018. From the figure, it is observed that even before the legalization of recreational marijuana use in 2014, Colorado and the rest of U.S. differed notably. The opioid death rates were very similar for Colorado and the rest of U.S. in the early 2000's. However, the trend began to diverge in the late 2000's. In 2014, when recreational marijuana use was legalized, opioid death rates was about 13% higher in the rest of U.S relative to Colorado and 71% in 2018.

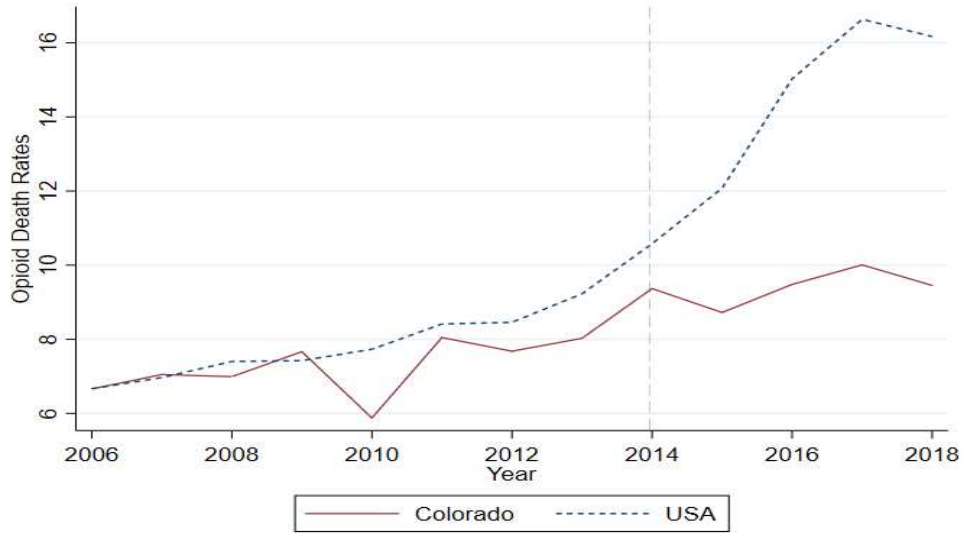

Figure 2. Opioid Death Rates for Colorado vs U.S.

The closest counterfactual states were Arizona, Illinois, and New Hampshire, contributing weights of 37.3%, 14.9%, and 16.3% respectively. Figure 3 shows their relationship to Colorado's opioid death rates from 2006 to 2018. One would have expected that New Hampshire would contribute the highest weight because opioid death rates was on the rise in New Hampshire. It can only be said that New Hampshire is among the few states that is driving the opioid death crisis in the U.S. The closest counterfactual states on their own, however, do not make for suitable counterfactuals, despite their relevant similarities to the treated unit. The root mean squared prediction error (RMSPE) is 1.76 for Arizona, 0.91 for Illinois and 2.81 for New Hampshire. These scores show a worse fit than the synthetic control, whose RMSPE is 0.711. Hence, the synthetic control method provides a more suitable counterfactual for comparative scientific analysis in a world without one that is readily available. A graph of opioid death rates from 2006 to 2018 for each state in the donor pool is presented in the Appendix.

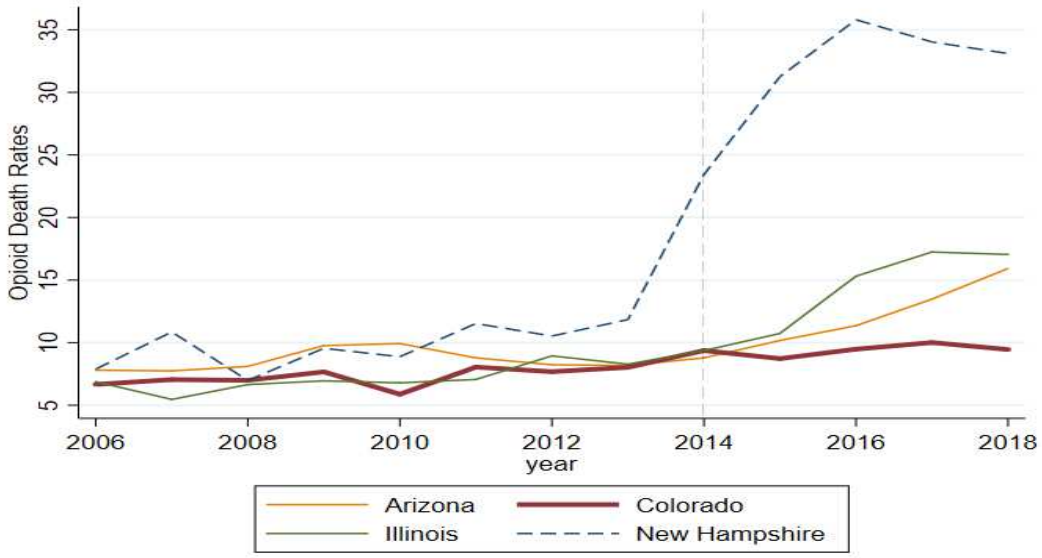

Figure 3. Opioid Death Rates for Colorado vs Arizona vs Illinois vs New Hampshire

To understand the effect of legalizing recreational marijuana use in Colorado in 2014, the synthetic control method provides a better causal link. The question to be answered is 'what would have happened in Colorado after 2014 in the absence of recreational marijuana legalization. Figure 4 presents a graph of the synthetic control estimate. The synthetic Colorado closely match actual Colorado during the pre-treatment period, with a Root Mean Squared Prediction Error (RMSPE) of 0.711. Leading up to the treatment period around the year 2013, synthetic Colorado's opioid death rates began to outpace actual Colorado. This effect can be observed because Colorado had passed the law on legalization in November 2012 even though retail sales began in the year 2014. The passage of the law might have had some reduction effect as it was legal to use marijuana for recreational use. Figure 4 suggests that the legalization of recreational marijuana had a large effect on opioid abuse/death rate and this effect increased with time. The results suggest that opioid death rates from 2014-2018 was an average of about 53.71% lower than the synthetic counterfactual. This constitutes the average treatment effect. During the pre-treatment period, the difference in average death rates was about 3.08%. The results summary is presented in Table 6. Further, from Figure 5, it is noted that the opioid death

rates declined sharply for Colorado after the treatment (legalization of recreational marijuana use).

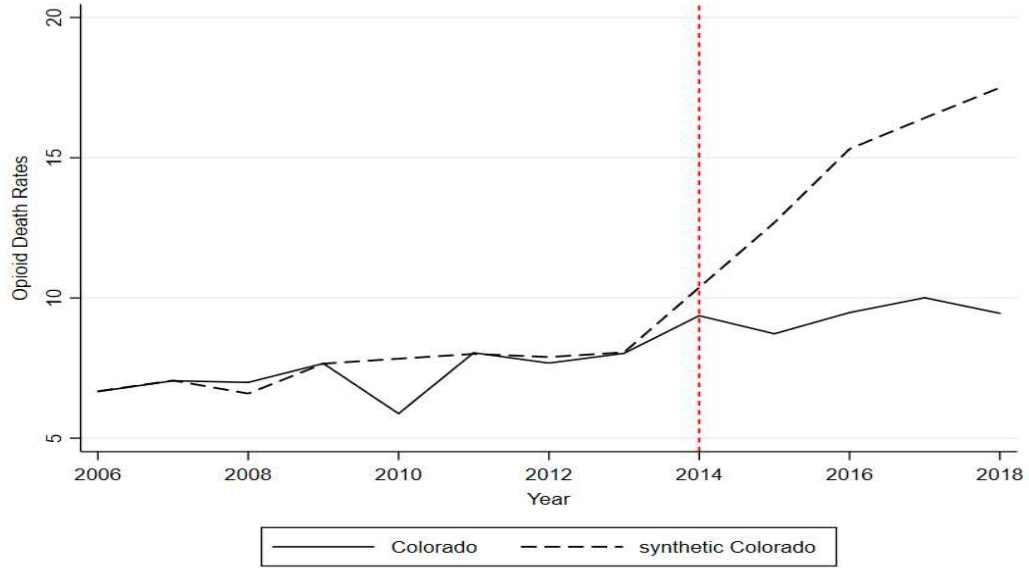

Figure 4. Primary Experiment

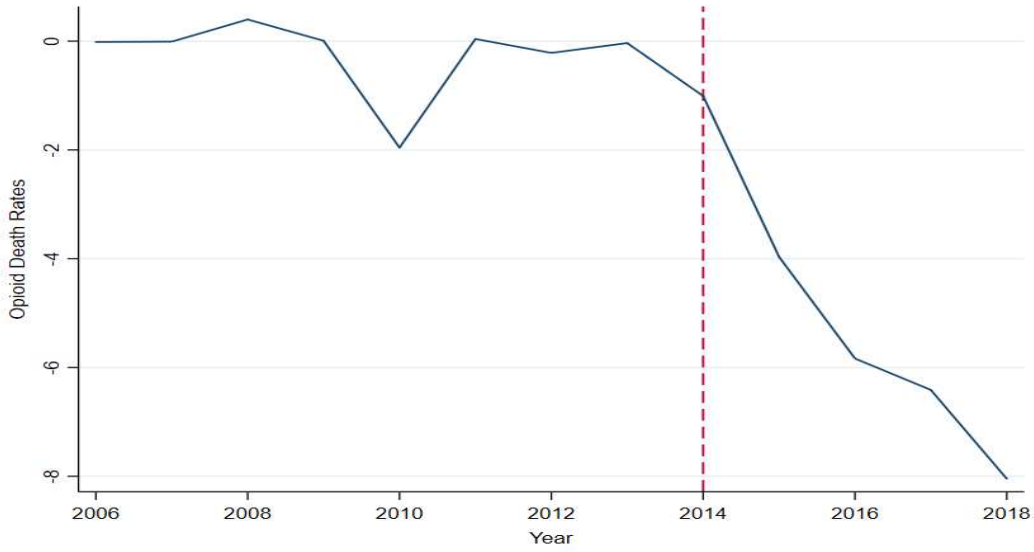

Figure 5. Effects Graph

Significance Test

Because there is no significance test for the synthetic control method, permutation tests must be conducted to determine if post-treatment deviations are due to chance or the result of the

treatment. To achieve this, placebo tests are performed on states that have not legalized recreational marijuana from 2014 to 2018. Since these states did not receive the treatment (recreational marijuana legalization), I would not expect the same results, provided that the treatment in Colorado had any effect on opioid death rates.

The placebo test shows how a state lies within or outside the donor pool. From the placebo tests presented in Figure 6, it is seen that many of the donor pool states exhibit the same pattern as the synthetic Colorado. That is, the opioid overdose death rates increased significantly during the post-treatment period. This is expected, given what is understood about the opioid crisis. Notice further that Colorado is not one of those states that is increasing. Its path is centered somewhere in the middle. What this means is that it will be difficult to obtain any significant p-values from the placebo tests. This is because relative to the other donor pool units, it is not significantly different. The trend does not fall outside of the other states. It is right in the middle. But it is also not increasing upward like many of the other states.

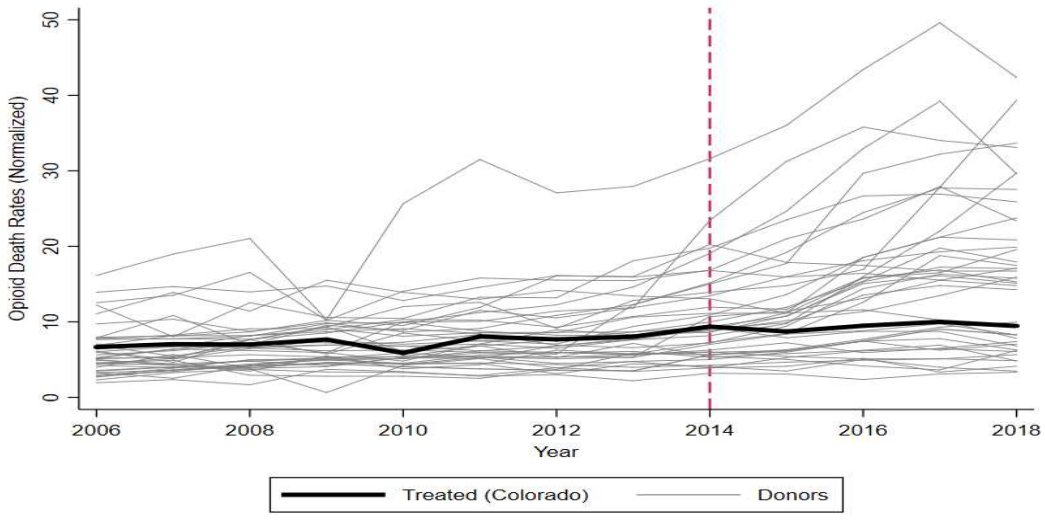

Figure 6. Placebo Test

The placebo test for the synthetic control creates a unique p-value for each post-treatment period, to measure the changes in the significance of the effect over time. P-values are calculated

for each time period i by gathering each placebo's estimated treatment effect for the ith period and dividing them by their respective pre-treatment RMSPE. This minimizes the possibility of a poor pre-treatment fit influencing the estimated post-treatment effect. After the statistics are collected, p-value estimates are created for each period i by counting the number of placebos with greater effects than that of the treated unit (i.e. Colorado) and divided by the number of total units (Colorado and all other states in the donor pool). Iterations of this process are conducted for all post-treatment periods.

Particularly, the p-value is an estimate of the probability that the effect of the treatment (legalization of recreational marijuana) on the outcome variable (opioid death rates) happened by chance. The p-values are presented in Figures 7 and 8. From the Figures, it is evident that significance was not achieved. This confirms the earlier assertion made from the placebo graph shown in Figure 6. However, the probability that opioid death rates reducing after the treatment period is by chance is very low. The final measure of the p-values is the standard p-values, and on average it is 0.235. I can therefore not confidently state that the legalization of recreational marijuana did not have any effect on the opioid death rates or did it happen by chance.

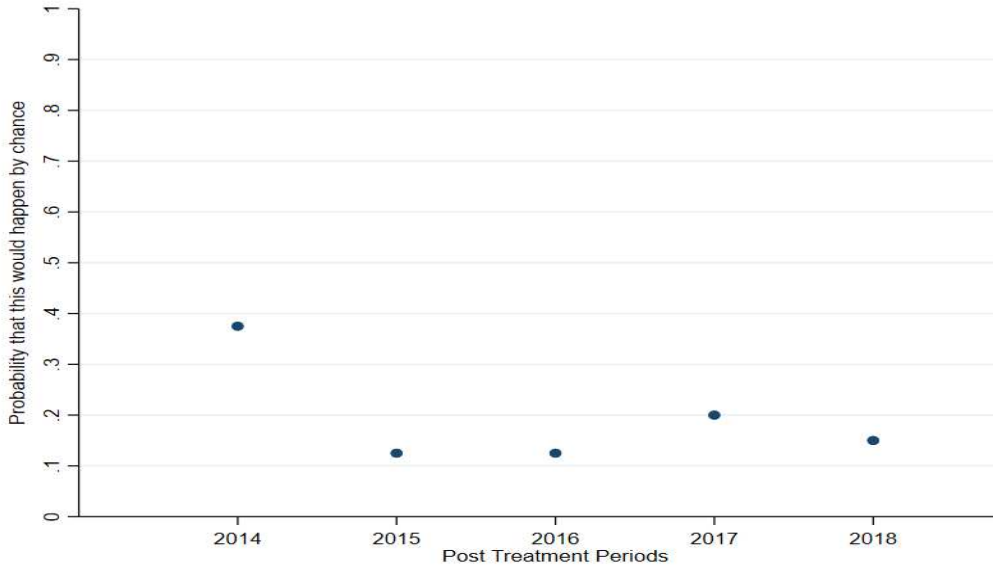

Figure 7. P-Values of Primary Experiment

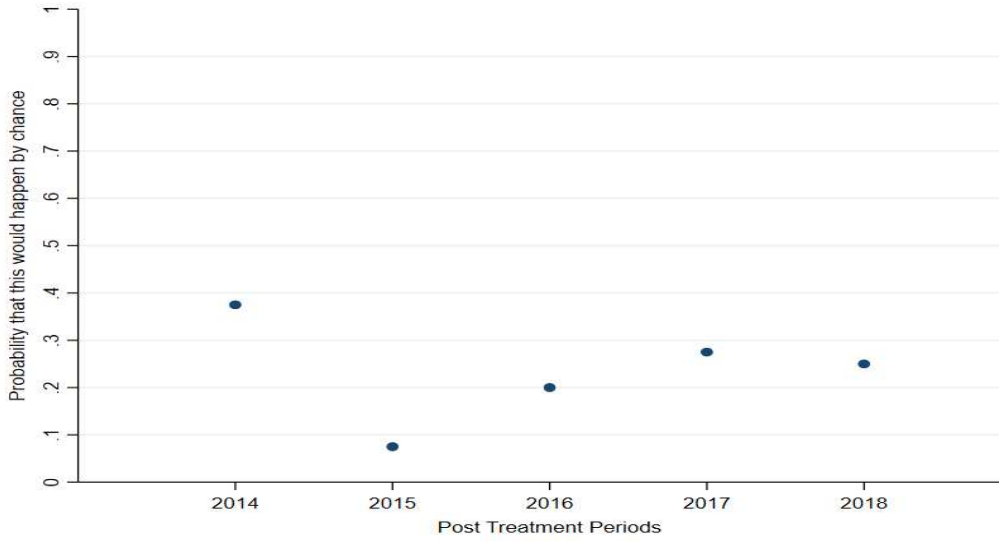

Figure 8. Standard P-Values of Primary Experiment

Robustness Check

To test the validity of the results and to determine whether the results was not driven entirely by chance, two robustness checks were done. First was dropping the states with highest loadings. The states with highest loadings as noted earlier were Arizona with loading of 37.3%, Illinois with 14.9%, and New Hampshire with 16.3%. When the states with highest loadings are dropped, the result is expected to be same or similar with the result of the primary experiment. If this is the case, it implies that the earlier results hold, and it is valid.

Eliminating these states leaves a less than an ideal choice of donors to contribute to the construction of synthetic Colorado. It is possible that our original results were driven primarily by the selection of these states. Table 5 displays the new selection of donors and their respective weights. With Arizona, Illinois, and New Hampshire eliminated from the donor pool, the new synthetic Colorado's largest donors are Florida (32.6%), Minnesota (20.9%), and Texas (13.3%).

Table 5. Estimated Weights: “Drop Largest Donors” Experiment

State	Weight
Delaware	0.074
Florida	0.326
Hawaii	0.054
Maryland	0.071
Minnesota	0.209
New Mexico	0.096
Rhode Island	0.025
Texas	0.133
Utah	0.012

Figure 9 presents the synthetic control graph of dropping the largest donors. It is observed that the new synthetic counterfactual track well as in the primary experiment. Comparing the p-values of Figures 10 and 11 to the p-values of the earlier results, it is seen that the results hold. Though some significance is lost, the p-values are just as same as the earlier results and the probability of chance is still low. This means that Arizona, Illinois, and New Hampshire though have the highest loadings, it does not only determine the outcome of the results.

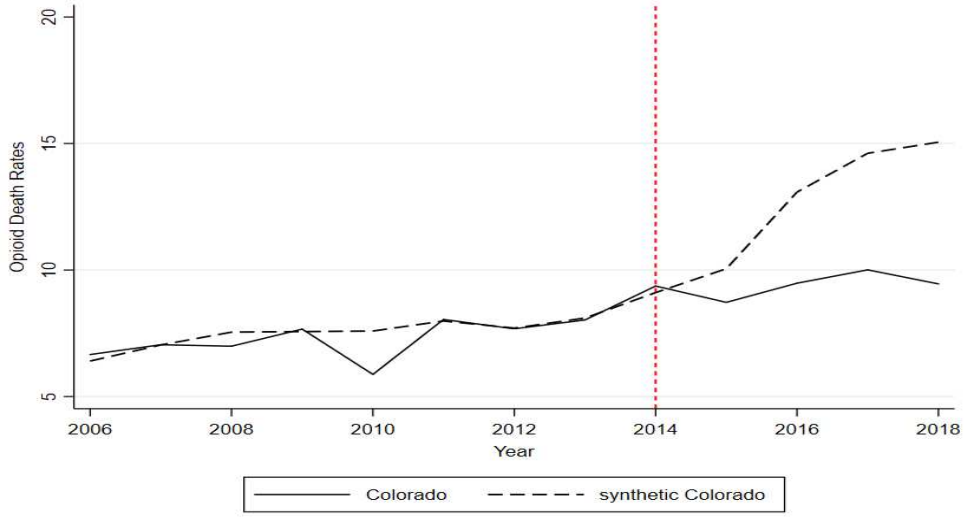

Figure 9. Synthetic Control: “Drop Largest Donors” Experiment

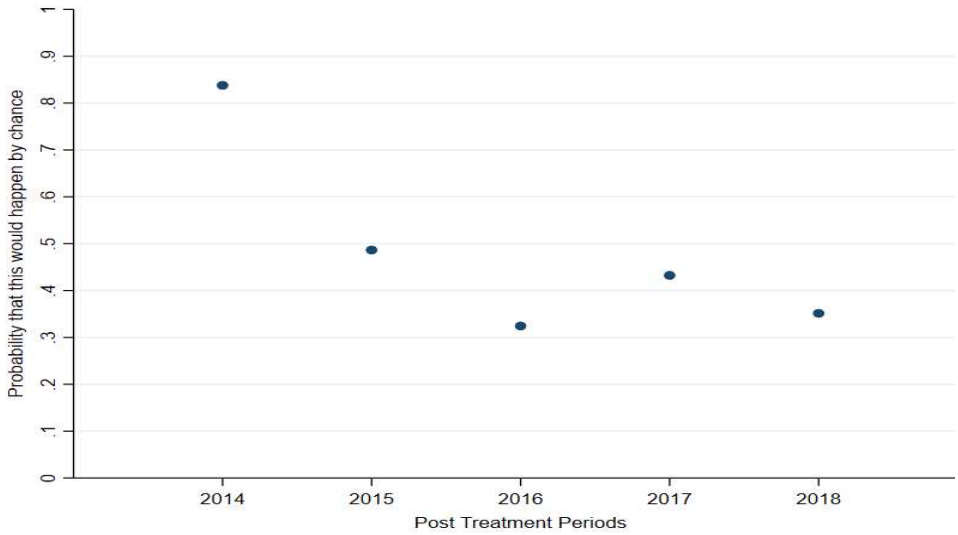

Figure 10. P-Values of Dropping Largest Donors

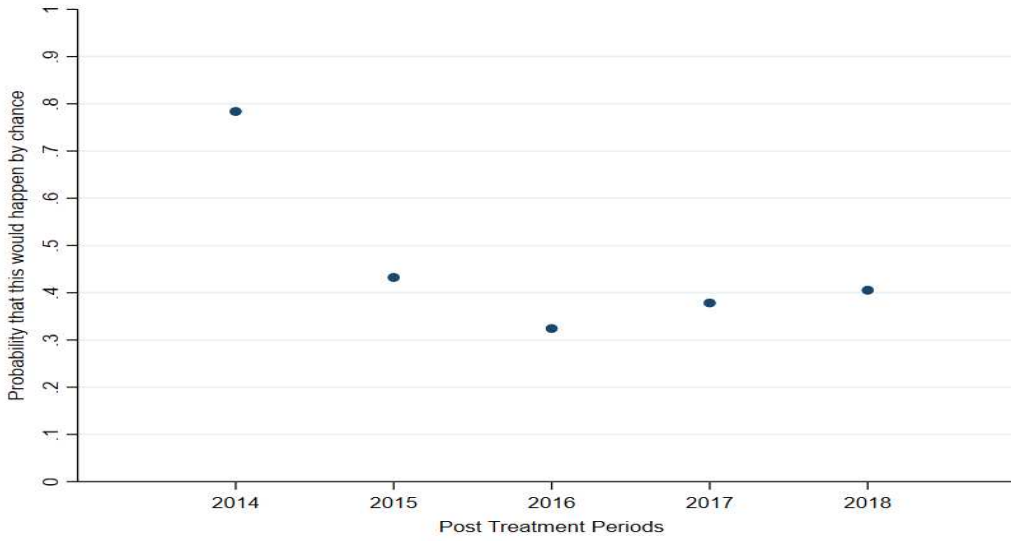

Figure 11. Standard P-Values of Dropping Largest Donors

The second robustness check was shifting the treatment period to 2012, creating a "false" treatment. The idea is that I want to see if the results of the primary experiment are valid. If I get the same results at a different period, then I have cause to worry. The results should not be the same at all. This adds confidence to the results from my original experiment, showing that the actual treatment date is responsible for the divergence observed, and that there is not some peculiar factor associated with the treatment date, which is driving the results. The treatment period is chosen to be 2012 because the law on legalizing recreational marijuana was passed in

2012, and therefore, it is imperative to examine if passing the legislation had any effect even before the retail sale began in 2014. Comparing the p-values of Figures 13 and 14 to the p-values of the primary experiment, it is seen that the result does not hold. It is observed that the p-values were highest for 2012 and 2013 but dropped sharply after the year 2013. The p-values were lowest from 2014 to 2018 just as in the primary experiment, suggesting a lower probability of chance in the reduction of opioid death rates. This suggests that the treatment period (i.e. year 2014) caused a greater influence in the gap between Colorado and its synthetic counterfactual.

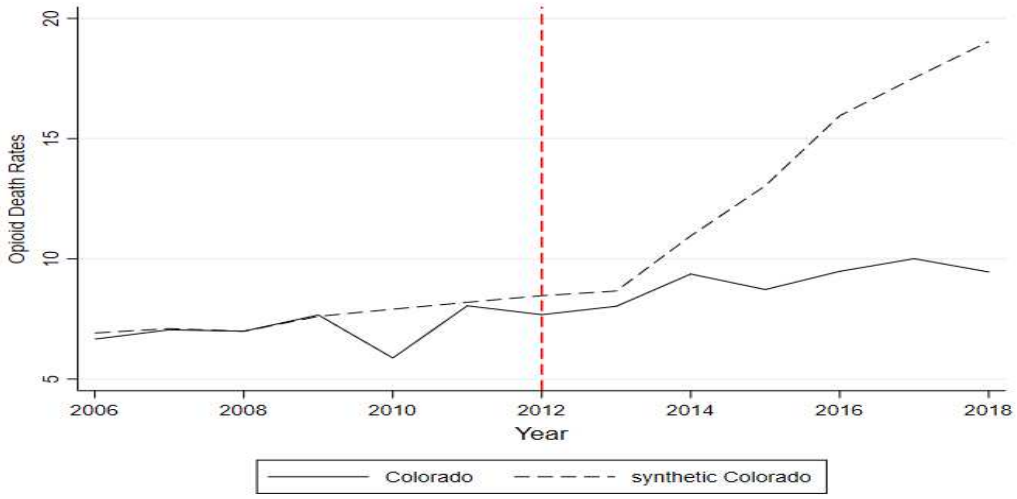

Figure 12. Synthetic Control: Shifting Treatment Period to 2012

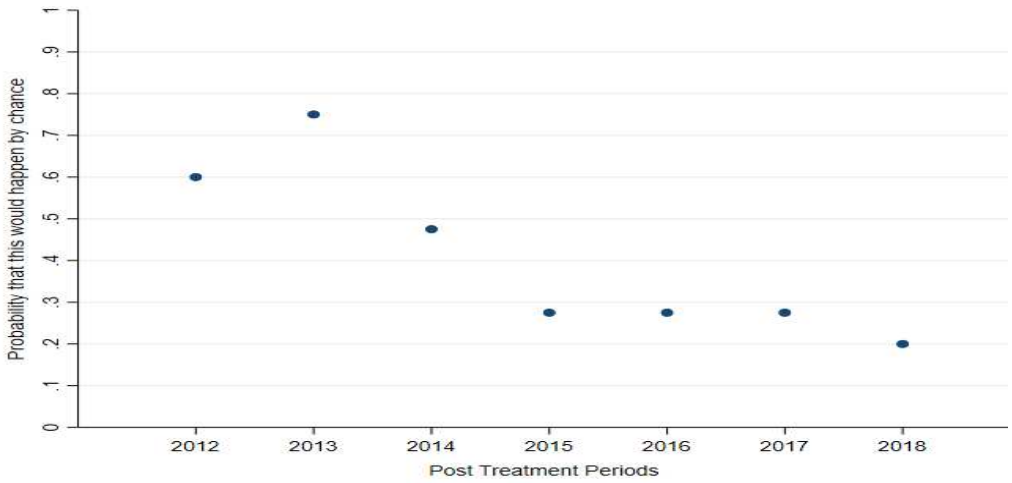

Figure 13. P-Values from Shifting Treatment Period to 2012

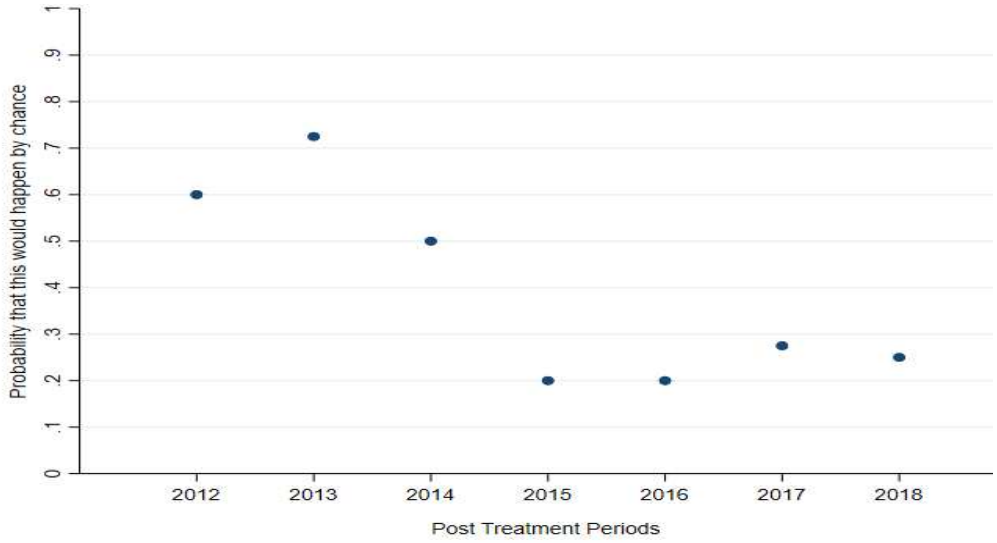

Figure 14. Standard P-Values from Shifting Treatment Period to 2012

Overall, the results from these experiments reveal that our original results were not due to the donors selected, nor were they the result of some unique events that took place in 2014 alongside the treatment. However, our pusedo t-stats indicate the treatment effects estimated from our synthetic control are insignificant. Thus, the effects of recreational marijuana legalization on opioid overdose deaths could be the result of random chance. The results of my primary experiment and robustness checks are summarized in Table 6.

Table 6. Summary Results

Experiment	RMSPE (ratio)	Average Treatment Effect	Minimum Treatment Effect	Maximum Treatment Effect
Primary	0.711 (9.90%)	-5.05 (-53.71%)	-1.65 (-18.94%)	-7.49 (-74.85%)
Drop Donor	0.645 (9.12%)	-2.98 (-31.64%)	-0.39 (-4.42%)	-5.05 (-50.42%)
In-time Placebo	0.838 (11.67%)	-4.41 (-49.26%)	-0.79 (-10.27%)	-9.03 (-90.24%)

CONCLUSION AND POLICY IMPLICATIONS

My research estimates the effect of recreational marijuana legalization on opioid abuse using a synthetic control method on Colorado State. Synthetic controls allow for an estimation of a counterfactual event (treatment) for comparative case studies purposes. I use this method to compare the effects of recreational marijuana legalization on opioid abuse by comparing the post-treatment periods for Colorado and a synthetically constructed counterfactual Colorado State. The synthetic control utilized data from 2006 to 2018. With 2014 serving as the treatment period, I was able to analyze four years of post-treatment observations. The primary experiment revealed a strong pre-treatment match of the synthetic Colorado with Colorado State (RMSPE of 0.711). The synthetic control also indicated lower opioid death rates during the post-treatment period in Colorado State compared to the synthetic counterfactual. The post-treatment average effect indicated that Colorado State had 53.71% opioid deaths lower than the synthetic counterfactual. However, the results produced weak pseudo t-stats, indicating the divergence between Colorado and the synthetically constructed Colorado could be due to random chance.

I performed additional robustness checks on the synthetic counterfactual by dropping the three largest donors (in terms of weighted contributions to the counterfactual Colorado) and with an in-time placebo test which changed the treatment period. Both checks reduced the closeness of fit as demonstrated through an increased RMSPE. However, the synthetic Colorado remained a robust comparison to Colorado State. The robustness checks provided further evidence of the validity of the synthetic control developed in this study.

Implications for Drug and Public Policy

My research findings pose a challenge to many studies and policy recommendations which argue that marijuana, for both medicinal and recreational use can provide a means to

reduce opioid abuse. My results specifically find considerable differences to those findings (Blake 2020; Kropp et al., 2019; Powell et al., 2018; Livingston et al., 2017; Bachhuber et al., 2014).

Few of the previous studies examining the effects of marijuana legalization provided utilized quasi-experimental methods to arrive at policy recommendations. For instance, Blake (2020) finds opioid prescribing rates in 15 of 19 states examined experienced decreases in opioid prescribing rates one year after marijuana legalization.[11] While an important contribution, the author's findings indicate a substitution between marijuana and opioid use than provide a drug and health policy analysis. Similarly, Kropp et al. (2019) find that recreational marijuana legalization significantly decreased opioid prescription but their analysis was not able to incorporate confounding variables and provide a causality argument to their proposed relationship. Related studies had similar limitations (Powell, Pacula and Jacobson, 2018; Livingston et al., 2017).

My results moreso overlap with studies utilizing richer data. Degenhardt et al. (2015) using large samples of chronic pain patients revealed that opioid doses do not reduce among marijuana users compared to non-marijuana users. A recent study which used the U.S. National Epidemiologic Survey on Alcohol and Related Conditions revealed that marijuana users including those with severe pain and opioid use in the baseline study had a higher likelihood of opioid use disorder 3 years later (Olfson, Wall, Liu, & Blanco, 2018).

Though these studies have attempted to establish a relationship between marijuana and opioid abuse, these studies are limited in their approach and draw conclusions from self-reports,

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[11] New Jersey, New Mexico, Michigan and Arizona were the four states which had an increase in opioid prescribing rate.

lack of robust techniques to assess causality. Studies (Bachhuber et al., 2014; Caputi, 2019; Shover, Davis, Gordon, & Humphreys, 2019) have cautioned against methodological flaws and spurious results and recommend a causal analysis for researches related to marijuana and opioid use disorder.

My research contributes to a divided policy literature and avoids many of the methodological flaws previous authors have noted. The method used in this study is robust and establishes a causal link between recreational marijuana legalization and opioid overdose deaths. Further, my findings strongly indicate marijuana legalization was not a statistically significant factor in reducing opioid abuse in Colorado State. This provides important implications for states designing policies to provide opioid addicts with marijuana substitutes and states hoping to address concerning rises in opioid abuse. For example, medical examining boards in Pennsylvania, New York, New Jersey and New Mexico include opioid use disorder among conditions that qualify a person to access marijuana for medical purposes (Shover et al., 2020). Based on my findings, these and other states planning on legalizing marijuana for similar reasons might exercise greater discretion. States might explore other options which could provide greater assistance to reduce opioid deaths than recreational marijuana.

However, as indicated before, marijuana likely has other medical benefits (Grinspoon & Bakalar, 1998; Hartman & Huestis, 2013; National Academies of Sciences, Engineering, and Medicine, 2017; Ogborne et al., 2000; Porter & Jacobson, 2013), making it a strong possibility to assist with other pressing drug policy questions.[12] The results of my study only imply a lack of evidence that recreational marijuana legalization can reliably reduce opioid overdose deaths.

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[12] The debates about its therapeutic benefit, side effects and abuses have been inconclusive. However, that is beyond the scope of this study.

Research Limitations

Drug and related public policy disagreements often involve political means to change or modify existing laws or regulations. For example, Shover et al. (2019) note that lower opioid death rates may be the results of something peculiar about the states which legalized recreational marijuana. States which are comparatively wealthier are also typically more politically liberal. Consequently, states more likely to legalize recreational marijuana access could provide greater access to addiction treatment and to naloxone, which reverses the effect of opioids and can prevent overdose fatalities. In his letter to the editor of the journal '*Addiction,*' Caputi (2019) notes that the reduction in opioid overdose rates, obesity rate and Medicaid and Medicare prescriptions reported by studies are "probably too grand to even possibly be ascribed to medical marijuana use" (p. 1128). These political heterogeneities between states are not part of my synthetic control. However, using synthetic control methods on a historically politically divided state like Colorado help mitigate these concerns.

The use of opioid overdose deaths as a measure of opioid abuse which does not account for individuals recovered from its adverse effects, the inability to measure black market operations for opioid abuse, only four years of post-treatment period to observe the trend in opioid overdose deaths, other established policies and technologies that may help curb addiction but are not accounted for in the synthetic control method are some of the limitations of this study.

Implications for Future Research

How does the effects of recreational marijuana legalization on opioid overdoses in other states compare to Colorado? Is the trend similar to the findings of this study? What are the effects of recreational marijuana legalization on prescription opioids? What is the causal

relationship between recreational marijuana use and emergency department visits or hospitalization due to opioid use? Future studies should investigate the causal link between recreational marijuana legalization and opioid abuse in other states. Since synthetic control method is mostly for case studies (Abadie et al., 2010), further synthetic control studies are needed to develop a robust understanding. Further research should use emergency department visits or hospitalization as a measure of opioid abuse to explore the causal relationship between recreational marijuana legalization and opioid abuse. Such a measure is difficult to obtain if not impossible due to lack of data. Future research might consider the causal relationship between recreational marijuana use and crime rates, crashes, etc. Finally, studies should explore the effects of recreational marijuana on other health outcomes.

REFERENCES

Abadie, A. (2019). Using synthetic controls : feasibility, data requirements, and methodological aspects. *Journal of Economic Literature*.

Abadie, A., Diamond, A., & Hainmueller, A. J. (2010). Synthetic control methods for comparative case studies: estimating the effect of California's tobacco control program. *Journal of the American Statistical Association*, *105*(490), 493–505. https://doi.org/https://doi.org/10.1198/jasa.2009.ap08746

Abadie, A., Diamond, A., & Hainmueller, J. (2015). Comparative politics and the synthetic control method. *American Journal of Political Science*, *59*(2), 495–510. https://doi.org/10.1111/ajps.12116

Abadie, A., & Gardeazabal, J. (2003). The economic costs of conflict: A case study of the Basque country. *American Economic Review*, *93*(1), 113–132. https://doi.org/10.1257/000282803321455188

Abrams, D. I., Jay, C. A., Shade, S. B., Vizoso, H., Reda, H., Press, S., … Petersen, K. L. (2007). Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial. *Neurology*, *68*(7), 515–521. https://doi.org/10.1212/01.wnl.0000253187.66183.9c

Acemoglu, D., Johnson, S., Kermani, A., Kwak, J., & Mitton, T. (2016). The value of connections in turbulent times: evidence from the United States. *Journal of Financial Economics*, *121*(2), 368–391. https://doi.org/10.1016/j.jfineco.2015.10.001

Anderson, K. O., Green, C. R., & Payne, R. (2009). Racial and ethnic disparities in pain: causes and consequences of unequal care. *Journal of Pain*, *10*(12), 1187–1204. https://doi.org/10.1016/j.jpain.2009.10.002

Andreae, M. H., Carter, G. M., Shaparin, N., Suslov, K., Ellis, R. J., Ware, M. A., … Sacks, H. S. (2015). Inhaled cannabis for chronic neuropathic pain: A meta-analysis of individual patient data. *Journal of Pain*, *16*(12), 1221–1232. https://doi.org/10.1016/j.jpain.2015.07.009

Angrist, J. D., & Pischke, J. S. (2010). The credibility revolution in empirical economics: How better research design is taking the con out of econometrics. *Journal of Economic Perspectives*, *24*(2), 3–30. https://doi.org/10.1257/jep.24.2.3

Azagba, S., Shan, L., Manzione, L., Qeadan, F., & Wolfson, M. (2019). Trends in opioid misuse among marijuana users and non-users in the U.S. from 2007–2017. *International Journal of Environmental Research and Public Health*, *16*(22). https://doi.org/10.3390/ijerph16224585

Bachhuber, M. A., Saloner, B., Cunningham, C. O., & Barry, C. L. (2014). Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Internal Medicine*, *174*(10), 1668–1673. https://doi.org/10.1001/jamainternmed.2014.4005

Bao, Y., Pan, Y., Taylor, A., Radakrishnan, S., Luo, F., Pincus, H. A., & Schackman, B. R. (2016). Prescription drug monitoring programs are associated with sustained reductions in opioid prescribing by physicians. *Health Affairs*, *35*(6), 1045–1051. https://doi.org/10.1377/hlthaff.2015.1673

Bauhoff, S. (2014). The effect of school district nutrition policies on dietary intake and overweight: a synthetic control approach. *Economics and Human Biology*, *12*(1), 45–55. https://doi.org/10.1016/j.ehb.2013.06.001

Bhattacharyya, S., Morrison, P. D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., … McGuire, P. K. (2010). Opposite effects of δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology*, *35*(3), 764–774. https://doi.org/10.1038/npp.2009.184

Birnbaum, H. G., White, A. G., Reynolds, J. L., Greenberg, P. E., Zhang, M., Vallow, S., … Katz, N. P. (2006). Estimated costs of prescription opioid analgesic abuse in the United States in 2001: a societal perspective. *Clinical Journal of Pain*, *22*(8), 667–676. https://doi.org/10.1097/01.ajp.0000210915.80417.cf

Birnbaum, H. G., White, A. G., Schiller, M., Waldman, T., Cleveland, J. M., & Roland, C. L. (2011). Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain Medicine*, *12*(4), 657–667. https://doi.org/10.1111/j.1526-4637.2011.01075.x

Blake, D. K. (2020). Medical marijuana reduces opioid prescribing rate. Retrieved May 29, 2020, from American Marijuana website: https://americanmarijuana.org/medical-marijuana-solution-to-opioid-epidemic/?msID=f48579d4-5eef-4767-a07f-e424773ac84e

Blake, D. R., Robson, P., Ho, M., Jubb, R. W., & McCabe, C. S. (2006). Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology*, *45*(1), 50–52. https://doi.org/10.1093/rheumatology/kei183

Boehnke, K. F., Litinas, E., & Clauw, D. J. (2016). Medical cannabis use Is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. *Journal of Pain*, *17*(6), 739–744. https://doi.org/10.1016/j.jpain.2016.03.002

Bohn, S., Lofstrom, M., & Raphael, S. (2014). Did the 2007 legal Arizona workers act reduce the state's unauthorized immigrant population? *Review of Economics and Statistics*, *96*(2), 258–269. https://doi.org/10.1162/REST_a_00429

Bonham, V. L. (2001). Race, ethnicity, and pain treatment: striving to understand the causes and solutions to the disparities in pain treatment. *Journal of Law, Medicine & Ethics*, *29*, 52–68.

Bradford, A. C., Bradford, W. D., Abraham, A., & Adams, G. B. (2018). Association between U.S. state medical cannabis laws and opioid prescribing in the medicare part D population. *JAMA Internal Medicine*, *178*(5), 667–673. https://doi.org/10.1001/jamainternmed.2018.0266

Brady, J. E., Wunsch, H., DiMaggio, C., Lang, B. H., Giglio, J., & Li, G. (2014). Prescription drug monitoring and dispensing of prescription opioids. *Public Health Reports*, *129*(2), 139–147. https://doi.org/10.1177/003335491412900207

Buckner, J. D., Ecker, A. H., & Cohen, A. S. (2010). Mental health problems and interest in marijuana treatment among marijuana-using college students. *Addictive Behaviors*, *35*(9), 826–833. https://doi.org/10.1016/j.addbeh.2010.04.001

Caputi, T. L. (2019). Medical marijuana, not miracle marijuana: some well-publicized studies about medical marijuana do not pass a reality check. *Addiction*, *114*(6), 1128–1129. https://doi.org/https://doi.org/10.1111/add.14580

Caputi, T. L., & Humphreys, K. (2018). Medical marijuana users are more likely to use prescription drugs medically and nonmedically. *Journal of Addiction Medicine*, *12*(4), 295–299. https://doi.org/10.1097/ADM.0000000000000405

Caspi, A., Moffitt, T. E., Cannon, M., McClay, J., Murray, R., Harrington, H. L., … Craig, I. W. (2005). Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: Longitudinal evidence of a gene X environment interaction. *Biological Psychiatry*, *57*(10), 1117–1127. https://doi.org/10.1016/j.biopsych.2005.01.026

Castelli, G. B., & Frazier, W. T. (2018). Opioids. In T. S. Schepis (Ed.), *The prescription drug abuse epidemic: Incidence, treatment, prevention, and policy*. Retrieved from http://ebookcentral.proquest.com

Centers for Disease Control and Prevention. (2016). *Health, United States 2015: Special feature on racial and ethnic health disparities* (No. 39). Retrieved from https://www.cdc.gov/nchs/hus/previous.htm

Centers for Disease Control and Prevention. (2018a). 2018 annual surveillance drug-related risks and outcomes- United States. In *Surveillance Special Report*. Retrieved from https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf

Centers for Disease Control and Prevention. (2018b). U.S. opioid prescribing rate maps. Retrieved from https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html

Chou, R., Cruciani, R. A., Fiellin, D. A., Compton, P., Farrar, J. T., Haigney, M. C., … Zeltzer, L. (2014). Methadone safety: a clinical practice guideline from the american pain society and college on problems of drug dependence, in collaboration with the heart rhythm society. *Journal of Pain*, *15*(4), 321–337. https://doi.org/10.1016/j.jpain.2014.01.494

Chou, R., Fanciullo, G. J., Fine, P. G., Adler, J. A., Ballantyne, J. C., Davies, P., … Miaskowski, C. (2009). Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *Journal of Pain*, *10*(2), 113-130.e22. https://doi.org/10.1016/j.jpain.2008.10.008

Chou, R., Turner, J. A., Devine, E. B., Hansen, R. N., Sullivan, S. D., Blazina, I., … Deyo, R. A. (2015). The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a national institutes of health pathways to prevention workshop. *Annals of Internal Medicine*, *162*(4), 276–286. https://doi.org/10.7326/M14-2559

Chu, Y. W. L., & Townsend, W. (2019). Joint culpability: the effects of medical marijuana laws on crime. *Journal of Economic Behavior and Organization*, *159*, 502–525. https://doi.org/10.1016/j.jebo.2018.07.003

Coben, J. H., Davis, S. M., Furbee, P. M., Sikora, R. D., Tillotson, R. D., & Bossarte, R. M. (2010). Hospitalizations for poisoning by prescription opioids, sedatives, and tranquilizers. *American Journal of Preventive Medicine*, *38*(5), 517–524. https://doi.org/10.1016/j.amepre.2010.01.022

Cohen, P. J. (2009). Medical marijuana: The conflict between scientific evidence and political ideology. Part one of two. *Journal of Pain and Palliative Care Pharmacotherapy*, Vol. 23, pp. 4–25. https://doi.org/10.1080/15360280902727973

Colorado Department of Education. (2019). Marijuana tax revenue and education. Retrieved December 28, 2019, from https://www.cde.state.co.us/communications/2019marijuanarevenue

Colorado Department of Public Health and Environment. (2019a). *Monitoring health concerns related to marijuana in Colorado: 2018*. Retrieved from https://www.colorado.gov/pacific/marijuanahealthinfo/summary

Colorado Department of Public Health and Environment. (2019b). Qualifying medical conditions medical marijuana registry. Retrieved December 28, 2019, from https://www.colorado.gov/pacific/cdphe/qualifying-medical-conditions-medical-marijuana-registry

Colorado Department of Regulatory Agencies. (2015). *Implementation status of HB 14-1283 (Concerning modifications to the Prescription Drug Monitoring Program)*. Retrieved from https://dpo.colorado.gov/PDMP/DrugAbuse

Colorado Department of Revenue. (2018). *Retail marijuana rules*. Retrieved from https://www.colorado.gov/pacific/sites/default/files/Amalgamated Retail Marijuana Rules 01012018.pdf

Compton, W. M., Boyle, M., & Wargo, E. (2015). Prescription opioid abuse: Problems and responses. *Preventive Medicine*, *80*, 5–9. https://doi.org/10.1016/j.ypmed.2015.04.003

Compton, W. M., Jones, C. M., & Baldwin, G. T. (2016). Relationship between nonmedical prescription-opioid use and heroin Use. *New England Journal of Medicine*, *374*(2), 154–163. https://doi.org/10.1056/NEJMra1508490

Cunningham, S., & Shah, M. (2018). Decriminalizing indoor prostitution: implications for sexual violence and public health. *Review of Economic Studies*, *85*(3), 1683–1715. https://doi.org/10.1093/restud/rdx065

Dahlhamer, J. M., Lucas, J., Zelaya, C., Nahin, R., Mackey, S., Debar, L., … Helmick, C. (2018). Prevalence of chronic pain and high-impact chronic pain among adults — United States, 2016. *Morbidity and Mortality Weekly Report*, *67*(36), 1001–1006. https://doi.org/10.15585/mmwr.mm6736a2

Dansak, D. A. (1997). Medical use of recreational drugs by AIDS patients. *Journal of Addictive Diseases*, *16*(3), 25–30. https://doi.org/http://dx.doi.org/10.1300/J069v16n03_03

Dasgupta, N., Freifeld, C., Brownstein, J. S., Menone, C. M., Surratt, H. L., Poppish, L., … Dart, R. C. (2013). Crowdsourcing black market prices for prescription opioids. *Journal of Medical Internet Research*, *15*(8), 1–11. https://doi.org/10.2196/jmir.2810

Daubresse, M., Chang, H. Y., Yu, Y., Viswanathan, S., Shah, N. D., Stafford, R. S., … Alexander, G. C. (2013). Ambulatory diagnosis and treatment of nonmalignant pain in the united states, 2000-2010. *Medical Care*, *51*(10), 870–878. https://doi.org/10.1097/MLR.0b013e3182a95d86

Davis, J. M., Mendelson, B., Berkes, J. J., Suleta, K., Corsi, K. F., & Booth, R. E. (2016). Public health effects of medical marijuana legalization in Colorado. *American Journal of Preventive Medicine*, *50*(3), 373–379. https://doi.org/10.1016/j.amepre.2015.06.034

DeBonis, M. (2009, July 20). Bob Barr lauds demise of Barr Amendment. *Washington City Paper*. Retrieved from https://www.washingtoncitypaper.com/news/city-desk/blog/13059132/bob-barr-lauds-demise-of-barr-amendment

Degenhardt, L., Lintzeris, N., Campbell, G., Bruno, R., Cohen, M., Farrell, M., & Hall, W. D. (2015). Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the pain and opioids in treatment (POINT) study. *Drug and Alcohol Dependence*, *147*, 144–150. https://doi.org/10.1016/j.drugalcdep.2014.11.031

Deyo, R. A., Irvine, J. M., Millet, L. M., Beran, T., O'Kane, N., Wright, D. A., & McCarty, D. (2013). Measures such as interstate cooperation would improve the efficacy of programs to track controlled drug prescriptions. *Health Affairs*, *32*(3), 603–613. https://doi.org/10.1377/hlthaff.2012.0945

Donohue, J. J., Aneja, A., & Weber, K. D. (2019). Right-to-carry laws and violent crime: a comprehensive assessment using panel data and a state-level synthetic control analysis. *Journal of Empirical Legal Studies*, *16*(2), 198–247. https://doi.org/10.1111/jels.12219

Dowell, D., Haegerich, T. M., & Chou, R. (2016). CDC guideline for prescribing opioids for chronic pain-United States, 2016. *JAMA - Journal of the American Medical Association*, *315*(15), 1624–1645. https://doi.org/10.1001/jama.2016.1464

Drwecki, B. B., Moore, C. F., Ward, S. E., & Prkachin, K. M. (2011). Reducing racial disparities in pain treatment: the role of empathy and perspective-taking. *Pain*, *152*(5), 1001–1006. https://doi.org/10.1016/j.pain.2010.12.005

Ellis, R. J., Toperoff, W., Vaida, F., Van Den Brande, G., Gonzales, J., Gouaux, B., … Atkinson, J. H. (2009). Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology*, *34*(3), 672–680. https://doi.org/10.1038/npp.2008.120

Esposito, G., De Filippis, D., Cirillo, C., Iuvone, T., Capoccia, E., Scuderi, C., … Steardo, L. (2013). Cannabidiol in inflammatory bowel diseases: a brief overview. *Phytotherapy Research*, *27*(5), 633–636. https://doi.org/10.1002/ptr.4781

Fink, D. S., Schleimer, J. P., Sarvet, A., Grover, K. K., Delcher, C., Kim, J. H., … Martins, S. S. (2018). Promoting prescription drug monitoring programs for population health: research and policy implications. In Ty. S. Schepis (Ed.), *The Prescription Drug Abuse Epidemic: Incidence, Treatment, Prevention, and Policy* (pp. 1–321). Retrieved from http://ebookcentral.proquest.com

Florence, C., Luo, F., Xu, L., & Zhou, C. (2016). The economic burden of prescription opioid overdose, abuse and dependence in the United States, 2013. *Medical Careare*, *54*(10), 901–906. https://doi.org/10.1097/MLR.0000000000000625

Franklin, G. M., Mai, J., Wickizer, T., Turner, J. A., Fulton-Kehoe, D., & Grant, L. (2005). Opioid dosing trends and mortality in Washington State workers' compensation, 1996-2002. *American Journal of Industrial Medicine*, *48*(2), 91–99. https://doi.org/10.1002/ajim.20191

Furton, G. (2018). High crimes? the effect of marijuana legalization on crime in Colorado. *SSRN Electronic Journal*. https://doi.org/10.2139/ssrn.3271993

G. (2016). j. *Journal of American Medical Association*, *315*(15), 1624–1645. https://doi.org/10.1001/jama.2016.1464

Gaskin, D. J., & Richard, P. (2012). The economic costs of pain in the United States. *Journal of Pain*, *13*(8), 715–724. https://doi.org/10.1016/j.jpain.2012.03.009

Gietel-Basten, S., Han, X., & Cheng, Y. (2019). Assessing the impact of the "one-child policy" in China: a synthetic control approach. *PLoS ONE*, *14*(11), 1–17. https://doi.org/10.1371/journal.pone.0220170

Grant, I., Atkinson, H. J., Mattison, A., & Coates, T. J. (2010). *Purported therapeutic usages of marijuana*. Retrieved from http://www.cmcr.ucsd.edu/images/PDFs/CMCR_REPORT_FEB17.pdf

Green, B. E. ., & Ritter, C. (2000). Marijuana use and depression. *Journal of Health and Social Behavior*, *41*(1), 40–49.

Grinspoon, L., & Bakalar, J. B. (1993). *Marihuana: the forbidden medicine*. New Haven, CT: Yale University Press.

Grinspoon, L., & Bakalar, J. B. (1998). The use of cannabis as a mood stabilizer in bipolar disorder: anecdotal evidence and the need for clinical research. *Journal of Psychoactive Drugs*, *30*(2), 171–177. https://doi.org/10.1080/02791072.1998.10399687

Gureje, O., Von Korff, M., Simon, G. E., & Gater, R. (1998). Persistent pain and well-being. *JAMA - Journal of American Medical Association*, *280*(2), 147. https://doi.org/10.1001/jama.280.2.147

Haffajee, R. L., Jena, A. B., & Weiner, S. G. (2015). Mandatory use of prescription drug monitoring programs. *JAMA - Journal of the American Medical Association*, *313*(9), 891–892. https://doi.org/10.1001/jama.2014.18514

Haffajee, R. L., Mello, M. M., Zhang, F., Zaslavsky, A. M., Larochelle, M. R., & Wharam, J. F. (2018). Four states with robust prescription drug monitoring programs reduced opioid dosages. *Health Affairs*, *37*(6), 964–974. https://doi.org/10.1377/hlthaff.2017.1321

Hall, A. J., Logan, J. E., Toblin, R. L., Kaplan, J. A., Kraner, J. C., & Crosby, A. E. (2008). Pharmaceutical overdose fatalities. *JAMA - Journal of the American Medical Association*, *300*(22), 2613–2620. https://doi.org/10.1001/jama.2008.802

Hall, W., & Lynskey, M. (2016). Evaluating the public health impacts of legalizing recreational cannabis use in the United States. *Addiction*, *111*(10), 1764–1773. https://doi.org/10.1111/add.13428

Hansen, R. N., Oster, G., Edelsberg, J., Woody, G. E., & Sullivan, S. D. (2011). Economic costs of nonmedical use of prescription opioids. *Clinical Journal of Pain*, *27*(3), 194–202. https://doi.org/10.1097/AJP.0b013e3181ff04ca

Harris, G. (2006, April 21). F.D.A. dismisses medical benefit from marijuana. *The New York Times*. Retrieved from https://www.nytimes.com/2006/04/21/health/fda-dismisses-medical-benefit-from-marijuana.html

Harris, L. S., Dewey, W. L., & Rasdan, R. K. (1997). Cannabis: its chemistry, pharmacology and toxicology. In W. R. Martin (Ed.), *Handbook of Experimental Pharmacology.* (pp. 371–429). New York, NY: Springer-verlag.

Hartman, R. L., & Huestis, M. A. (2013). Cannabis effects on driving skills. *Clinical Chemistry*, *59*(3), 478–492. https://doi.org/10.1373/clinchem.2012.194381

Hill, K. P. (2015). Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. *JAMA - Journal of the American Medical Association*, *313*(24), 2474–2483. https://doi.org/10.1001/jama.2015.6199

Hoffmann, D. E., & Weber, E. (2010). Medical marijuana and the law. *New England Journal of Medicine*, *362*(16), 1453–1457. https://doi.org/10.1056/NEJMp1000695

Hopfer, C. (2014). Implications of marijuana legalization for adolescent substance use. *Substance Abuse*, *35*(4), 331–335. https://doi.org/10.1080/08897077.2014.943386

Johannes, C. B., Le, T. K., Zhou, X., Johnston, J. A., & Dworkin, R. H. (2010). The prevalence of chronic pain in United States adults: results of an internet-based survey. *Journal of Pain*, *11*(11), 1230–1239. https://doi.org/10.1016/j.jpain.2010.07.002

Kane, B. (2001). Medical marijuana: the continuing story. *Annals of Internal Medicine*, *134*(12), 1159–1162. https://doi.org/10.7326/0003-4819-134-12-200106190-00035

King, G., & Zeng, L. (2006). The dangers of extreme counterfactuals. *Political Analysis*, *14*(2), 131–159. https://doi.org/10.1093/pan/mpj004

Kleven, H. J., Landais, C., & Saez, E. (2013). Taxation and international migration of superstars: evidence from the european football market. *American Economic Review*, *103*(5), 1892–1924. https://doi.org/10.1257/aer.103.5.1892

Kolodny, A., Courtwright, D. T., Hwang, C. S., Kreiner, P., Eadie, J. L., Clark, T. W., & Alexander, G. C. (2015). The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annual Review of Public Health*, *36*(1), 559–574. https://doi.org/10.1146/annurev-publhealth-031914-122957

Kondrad, E. (2013). Medical marijuana for chronic pain. *North Carolina Medical Journal*, *74*(3), 210–211.

Koppel, B. S., Brust, J. C. M., Fife, T., Bronstein, J., Youssof, S., Gronseth, G., & Gloss, D. (2014). Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the guideline development subcommittee of the American Academy of Neurology. *Neurology*, *82*(17), 1556–1563. https://doi.org/10.1212/WNL.0000000000000363

Kropp, A. K., Nichols, S. D., Chung, D. Y., McCall, K. L., & Piper, B. J. (2019). Prescription opioid distribution after the legalization of recreational marijuana in Colorado, 2007-2017. *BioRxiv*, *702811*, 1–24. https://doi.org/https://doi.org/10.1101/702811

Kuo, Y. F., Raji, M. A., Chen, N. W., Hasan, H., & Goodwin, J. S. (2016). Trends in opioid prescriptions among Part D medicare recipients from 2007 to 2012. *American Journal of Medicine*, *129*(2), 221-e21–e30. https://doi.org/10.1016/j.amjmed.2015.10.002

Kurz, C. F., Rehm, M., Holle, R., Teuner, C., Laxy, M., & Schwarzkopf, L. (2019). The effect of bariatric surgery on health care costs: a synthetic control approach using Bayesian structural time series. *Health Economics (United Kingdom)*, *28*(11), 1293–1307. https://doi.org/10.1002/hec.3941

Lake, S., Walsh, Z., Kerr, T., Cooper, Z. D., Buxton, J., Wood, E., … Milloy, M. J. (2019). Frequency of cannabis and illicit opioid use among people who use drugs and report chronic pain: a longitudinal analysis. *PLoS Medicine*, *16*(11), e1002967. https://doi.org/10.1371/journal.pmed.1002967

Lalley, P. M. (2008). Opioidergic and dopaminergic modulation of respiration. *Respiratory Physiology and Neurobiology*, *164*(1–2), 160–167. https://doi.org/10.1016/j.resp.2008.02.004

Leweke, F., Leichsenring, F., Kruse, J., & Hermes, S. (2011). Is alexithymia associated with specific mental disorders? *Psychopathology*, *45*(1), 22–28. https://doi.org/10.1159/000325170

Lin, H. C., Wang, Z., Boyd, C., Simoni-Wastila, L., & Buu, A. (2018). Associations between statewide prescription drug monitoring program (PDMP) requirement and physician patterns of prescribing opioid analgesics for patients with non-cancer chronic pain. *Addictive Behaviors*, *76*, 348–354. https://doi.org/10.1016/j.addbeh.2017.08.032

Lindo, J. M., & Packham, A. (2017). How much can expanding access to long-acting reversible contraceptives reduce teen birth rates? *American Economic Journal: Economic Policy*, *9*(3), 348–376. https://doi.org/https://doi.org/10.1257/pol.20160039

Livingston, M. D., Barnett, T. E., Delcher, C., & Wagenaar, A. C. (2017). Recreational cannabis legalization and opioid-related deaths in Colorado, 2000-2015. *American Journal of Public Health*, *107*(11), 1827–1829. https://doi.org/10.2105/AJPH.2017.304059

Lyketsos, C. G., Garrett, E., Liang, K. Y., & Anthony, J. C. (1999). Cannabis use and cognitive decline in persons under 65 years of age. *American Journal of Epidemiology*, *149*(9), 794–800. https://doi.org/10.1093/oxfordjournals.aje.a009894

Marijuana Policy Project. (2012). Marijuana now being sold, legally, in our nation's capital. Retrieved October 25, 2019, from http://www.mpp.org/states/district-of-columbia/

Marijuana Work Group. (2016). *Initiative 71*. Retrieved from https://dchealth.dc.gov/sites/default/files/dc/sites/doh/publication/attachments/Marijuana-Task-Force-Status-Report_v2.pdf

Marret, E., Remy, C., Bonnet, F., Breivik, H., Curatolo, M., Gomar, C., … Tramèr, M. (2007). Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. *British Journal of Surgery*, *94*(6), 665–673. https://doi.org/10.1002/bjs.5825

McAuliffe, W. E., Rohman, M., Feldman, B., & Launer, E. K. (1985). The role of euphoric effects in the opiate addictions of heroin addicts, medical patients and impaired health professionals. *Journal of Drug Issues*, *15*(2), 203–224.

Medina, J. L., & Diamond, S. (1977). Drug dependency in patients with chronic headaches. *Headache: The Journal of Head and Face Pain*, *17*(1), 12–14. https://doi.org/10.1111/j.1526-4610.1977.hed1701012.x

Miron, J., Sollenberger, G., & Nicolae, L. (2019). Overdosing on regulation: how government caused the opioid epidemic. In *Cato Institute Policy Analysis*. Retrieved from https://www.cato.org/publications/policy-analysis/overdosing-regulation-how-government-caused-opioid-epidemic

Monfort, S. S. (2018). *Effect of recreational marijuana sales on police-reported crashes in Colorado, Oregon, and Washington*. Insurance Institute for Highway Safety.

Monte, A. A., Zane, R. D., & Heard, K. J. (2015). The implications of marijuana legalization in Colorado. *JAMA - Journal of the American Medical Association*, *313*(3), 241–242. https://doi.org/10.1001/jama.2014.17057

Moyo, P., Simoni-Wastila, L., Griffin, B. A., Onukwugha, E., Harrington, D., Alexander, G. C., & Palumbo, F. (2017). Impact of prescription drug monitoring programs (PDMPs) on opioid utilization among Medicare beneficiaries in 10 U.S. States. *Addiction*, *112*(10), 1784–1796. https://doi.org/10.1111/add.13860

Murthy, V. H. (2016). Ending the opioid epidemic — A call to action. *New England Journal of Medicine*, *375*(25), 2413–2415. https://doi.org/10.1056/NEJMp1612578

Narang, S., Gibson, D., Wasan, A. D., Ross, E. L., Michna, E., Nedeljkovic, S. S., & Jamison, R. N. (2008). Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *Journal of Pain*, *9*(3), 254–264. https://doi.org/10.1016/j.jpain.2007.10.018

National Academies of Sciences, Engineering, and Medicine. (2017a). The health effects of cannabis and cannabinoids: committee's conclusions. In Mandlowitz, J. (2017). Cannabis and cannabinoids in the workplace. *The Official Publication of the Ontario Occupational Health Nurses Association*, *36*(2), 5–7.

National Academies of Sciences, Engineering, and Medicine. (2017b). *The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research*. Washington D.C.: The National Academies Press.

Ogborne, A. C., Smart, R. G., Weber, T., & Birchmore-Timney, C. (2000). Who is using cannabis as a medicine and why: an exploratory study. *Journal of Psychoactive Drugs*, *32*(4), 435–443. https://doi.org/10.1080/02791072.2000.10400245

Olfson, M., Wall, M. M., Liu, S. M., & Blanco, C. (2018). Cannabis use and risk of prescription opioid use disorder in the United States. *American Journal of Psychiatry*, *175*(1), 47–53. https://doi.org/10.1176/appi.ajp.2017.17040413

Pacula, R. L., & Smart, R. (2017). Medical marijuana and marijuana legalization. *Annual Review of Clinical Psychology*, *13*(1), 397–419. https://doi.org/10.1146/annurev-clinpsy-032816-045128

Patrick, S. W., Fry, C. E., Jones, T. F., & Buntin, M. B. (2016). Implementation of prescription drug monitoring programs associated with reductions in opioid-related death rates. *Health Affairs*, *35*(7), 1324–1332. https://doi.org/10.1377/hlthaff.2015.1496

Pattinson, K. T. S. (2008). Opioids and the control of respiration. *British Journal of Anaesthesia*, *100*(6), 747–758. https://doi.org/10.1093/bja/aen094

Patton, G. C., Coffey, C., Carlin, J. B., Degenhardt, L., Hall, W., & Lynskey, M. (2002). Cannabis use and mental health in young people: cohort study. *British Medical Journal*, *325*, 1195–1198. https://doi.org/10.1136/bmj.325.7374.1195

Peirce, G. L., Smith, M. J., Abate, M. A., & Halverson, J. (2012). Doctor and pharmacy shopping for controlled substances. *Medical Care*, *50*(6), 494–500. https://doi.org/10.1097/MLR.0b013e31824ebd81

Pieters, H., Curzi, D., Olper, A., & Swinnen, J. (2016). Effect of democratic reforms on child mortality: a synthetic control analysis. *The Lancet Global Health*, *4*(9), e627–e632. https://doi.org/10.1016/S2214-109X(16)30104-8

Pinotti, P. (2015). The Economic costs of organised crime: evidence from Southern Italy. *Economic Journal*, *125*(586), F203–F232. https://doi.org/10.1111/ecoj.12235

Pinsger, M., Schimetta, W., Volc, D., Hiermann, E., Riederer, F., & Pölz, W. (2006). Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain--a randomized controlled trial. *Wiener Klinische Wochenschrift*, *118*(11–12), 327–335. https://doi.org/10.1007/s00508-006-0611-4

Pletcher, M. J., Kertesz, S. G., Kohn, M. A., & Gonzales, R. (2008). Trends in opioid prescribing by race/ethnicity for patients seeking care in U.S. emergency departments. *JAMA - Journal of the American Medical Association*, *299*(1), 70–78. https://doi.org/10.1001/jama.2007.64

Pollini, R., Garfein, Banta-Green, Cuevas-Mota, Metzner, & Teshale. (2011). Problematic use of prescription-type opioids prior to heroin use among young heroin injectors. *Substance Abuse and Rehabilitation*, 173. https://doi.org/10.2147/sar.s24800

Portenoy, R. K., & Foley, K. M. (1986). Chronic use of opioid analgesics in non-malignant pain. *Pain*, *25*(2), 171–186.

Porter, B. E., & Jacobson, C. (2013). Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy and Behavior*, *29*(3), 574–577. https://doi.org/10.1016/j.yebeh.2013.08.037

Porter, J., & Jick, H. (1980). Addiction rare in patients treated with narcotics. *The New England Journal of Medicine*, *302*(2), 123.

Powell, D., Pacula, R. L., & Jacobson, M. (2018). Do medical marijuana laws reduce addictions and deaths related to pain killers? *Journal of Health Economics*, *58*, 29–42. https://doi.org/10.1016/j.jhealeco.2017.12.007

Quinton, S. (2019, August 13). *Where doctors can recommend marijuana to replace opioids*. Retrieved from https://www.pewtrusts.org/en/research-and-analysis/blogs/stateline/2019/08/13/where-doctors-can-recommend-marijuana-to-replace-opioids

Ramsin, B., Trescot, A. M., Datta, S., Buenaventura, R., Adlaka, R., Sehgal, N., … Vallejo, R. (2008). Opioid complications and side effects. *Pain Physician*, *11*(11:S105-S120), 105–120. https://doi.org/10.1007/978-3-540-35423-9_14

Reifler, L. M., Droz, D., Bailey, J. E., Schnoll, S. H., Fant, R., Dart, R. C., & Bartelson, B. B. (2012). State trends in opioid abuse/misuse ? *Pain Medicine*, *13*(3), 434–442. https://doi.org/https://doi.org/10.1111/j.1526-4637.2012.01327.x

Reisman, R. M., Shenoy, P. J., Atherly, A. J., & Flowers, C. R. (2009). Prescription opioid usage and abuse relationships: an evaluation of state prescription drug monitoring program efficacy. *Substance Abuse: Research and Treatment*, *3*(1), 41–51. https://doi.org/10.4137/sart.s2345

Reissig, J. E., & Rybarczyk, A. M. (2005). Pharmacologic treatment of opioid-induced sedation in chronic pain. *Annals of Pharmacotherapy*, *39*(4), 727–731. https://doi.org/10.1345/aph.1E309

Rieger, M., Wagner, N., & Bedi, A. S. (2017). Universal health coverage at the macro level: synthetic control evidence from Thailand. *Social Science and Medicine*, *172*, 46–55. https://doi.org/10.1016/j.socscimed.2016.11.022

Rudd, R. A., Aleshire, N., Zibbell, J. E., & Gladden, R. M. (2016). Increases in drug and opioid overdose deaths - United States, 2000-2014. *American Journal of Transplantation*, *16*(4), 1323–1327. https://doi.org/10.1111/ajt.13776

Ryan, A. M., Burgess, J. F., & Dimick, J. B. (2015). Why we should not be indifferent to specification choices for difference-in-differences. *Health Services Research*, *50*(4), 1211–1235. https://doi.org/10.1111/1475-6773.12270

Sabia, J. J., Swigert, J., & Young, T. (2015). The effect of medical marijuana laws on body weight. *Health Economics*, *26*(1), 6–34. https://doi.org/https://doi.org/10.1002/hec.3267

Sallan, S. E., Zinberg, N. E., & Frei III, E. (1975). Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. *The New England Journal of Medicine*, *293*(16), 795–797.

Schatman, M. E. (2011). The role of the health insurance industry in perpetuating suboptimal pain management. *Pain Medicine*, *12*(3), 415–426. https://doi.org/10.1111/j.1526-4637.2011.01061.x

Scholl, L., Seth, P., Kariisa, M., Wilson, N., & Baldwin, G. (2018). Drug and opioid-involved overdose deaths — United States, 2013–2017. *MMWR. Morbidity and Mortality Weekly Report*, *67*(5152), 2013–2017. https://doi.org/10.15585/mmwr.mm6751521e1

Schulz, K. F. (1995). Subverting randomization in controlled trials. *JAMA: The Journal of the American Medical Association*, *274*(18), 1456–1458. https://doi.org/10.1001/jama.274.18.1456

Sera, L., McPherson, M. L., & Holmes, H. M. (2014). Commonly prescribed medications in a population of hospice patients. *American Journal of Hospice and Palliative Medicine*, *31*(2), 126–131. https://doi.org/10.1177/1049909113476132

Shei, A., Rice, J. B., Kirson, N. Y., Bodnar, K., Birnbaum, H. G., Holly, P., & Ben-Joseph, R. (2015). Sources of prescription opioids among diagnosed opioid abusers. *Current Medical Research and Opinion*, *31*(4), 779–784. https://doi.org/https://doi.org/10.1185/03007995.2015.1016607

Shepherd, K. (2020, January 7). 'It's a lot happening all at once': Illinois shops run out of marijuana just six days after start of legalization. Retrieved from https://www.washingtonpost.com/nation/2020/01/07/illinois-runs-out-recreational-marijuana-first-week-legalized/

Shi, Y. (2017). Medical marijuana policies and hospitalizations related to marijuana and opioid pain reliever. *Drug and Alcohol Dependence*, *173*, 144–150. https://doi.org/10.1016/j.drugalcdep.2017.01.006

Shi, Y., Liang, D., Bao, Y., An, R., Wallace, M. S., & Grant, I. (2018). Recreational marijuana legalization and prescription opioids received by Medicaid enrollees. *Drug and Alcohol Dependence*, *194*, 13–19. https://doi.org/10.1016/j.drugalcdep.2018.09.016

Shover, C. L., Davis, C. S., Gordon, S. C., & Humphreys, K. (2019). Association between medical cannabis laws and opioid overdose mortality has reversed over time. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(26), 12624–12626. https://doi.org/10.1073/pnas.1903434116

Shover, C. L., Vest, N. A., Chen, D., Stueber, A., Falasinnu, T. O., Hah, J. M., … Humphreys, K. (2020). Association of state policies allowing medical cannabis for opioid use disorder with dispensary marketing for this indication. *JAMA Network Open*, *3*(7), 1–8. https://doi.org/10.1001/jamanetworkopen.2020.10001

Simeone, R., & Holland, L. (2006). An evaluation of prescription drug monitoring programs. *Washington, DC: US Dept of Justice, Office of Justice Programs; 2006.*, *12210*(2005).

Simoni□Wastila, L., & Qian, J. (2012). Influence of prescription monitoring programs on analgesic utilization by an insured retiree population. *Pharmacoepidemiology and Drug Safety*, *21*(12), 1261–1268. https://doi.org/10.1002/pds.3342

Skrabek, R. Q., Galimova, L., Ethans, K., & Perry, D. (2008). Nabilone for the treatment of pain in fibromyalgia. *Journal of Pain*, *9*(2), 164–173. https://doi.org/10.1016/j.jpain.2007.09.002

Smith, B. H., Elliott, A. M., Alastair Chambers, W., Smith, W. C., Hannaford, P. C., & Penny, K. (2001). The impact of chronic pain in the community. *Family Practice*, *18*(3), 292–299. https://doi.org/10.1093/fampra/18.3.292

Spruk, R., & Kovac, M. (2020). Does a ban on trans fats improve public health: synthetic control evidence from Denmark. *Swiss Journal of Economics and Statistics*, *156*(1). https://doi.org/10.1186/s41937-019-0048-0

Strang, J., Witton, J., & Hall, W. (2000). Improving the quality of the cannabis debate: defining the different domains. *British Medical Journal*, *320*(7227), 108–110. https://doi.org/10.1136/bmj.320.7227.108

Sun, B. C., Charlesworth, C. J., Lupulescu-Mann, N., Young, J. I., Kim, H., Hartung, D. M., … McConnell, K. J. (2018). Effect of automated prescription drug monitoring program queries on emergency department opioid prescribing. *Annals of Emergency Medicine*, *71*(3), 337-347.e6. https://doi.org/10.1016/j.annemergmed.2017.10.023

Swegle, J. M., & Logemann, C. (2006). Management of common opioid-induced adverse effects. *American Family Physician*, *74*(8), 1347–1354.

Tamayo-Sarver, J. H., Hinze, S. W., Cydulka, R. K., & Baker, D. W. (2003). Racial and ethnic disparities in emergency department analgesic prescription. *American Journal of Public Health*, *93*(12), 2067–2073.

Thorn, C. F., Klein, T. E., & Altman, R. B. (2009). Codeine and morphine pathway. *Pharmacogenetics and Genomics*, *19*(7), 556–558. https://doi.org/10.1097/FPC.0b013e32832e0eac

Tiersky, M. (1998). Medical marijuana: putting the power where it belongs. *Northwestern University Law Review*, *93*(2), 547–595.

Todd, K. H., Samaroo, N., & Hoffman, J. R. (1993). Ethnicity as a risk factor for inadequate emergency department analgesia. *JAMA - Journal of American Medical Association*, *269*(12), 1537–1539. https://doi.org/10.1001/jama.1993.03500120075029

Tsang, A., Von Korff, M., Lee, S., Alonso, J., Karam, E., Angermeyer, M. C., … Watanabe, M. (2008). Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *Journal of Pain*, *9*(10), 883–891. https://doi.org/10.1016/j.jpain.2008.05.005

Vigil, J. M., Stith, S. S., Adams, I. M., & Reeve, A. P. (2017). Associations between medical cannabis and prescription opioid use in chronic pain patients: a preliminary cohort study. *PLoS ONE*, *12*(11), 1–13. https://doi.org/10.1371/journal.pone.0187795

Volkow, N. D., Baler, R. D., Compton, W. M., & Weiss, S. R. B. (2014). Adverse health effects of marijuana use. *New England Journal of Medicine*, *370*(23), 2219–2227. https://doi.org/10.1056/NEJMra1402309

Wang, G. S., Davies, S. D., Halmo, L. S., Sass, A., & Mistry, R. D. (2018). Impact of marijuana legalization in Colorado on adolescent emergency and urgent care visits. *Journal of Adolescent Health*, *63*(2), 239–241. https://doi.org/10.1016/j.jadohealth.2017.12.010

Weiss, A. J., Elixhauser, A., Barrett, M. L., Steiner, C. A., Bailey, M. K., & O'Malley, L. (2017). Opioid-Related Inpatient Stays and Emergency Department Visits by State, 2009–2014: Statistical Brief #219. In *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/28682575

Welch, S. P., & Martin, B. R. (2003). The pharmacology of marijuana. In A. W. Graham, T. K. Schultz, M. E. Mayo-Smith, R. K. Ries, & B. B. Wilford (Eds.), *Principles of Addiction Medicine* (3rd ed., pp. 249–270). Chevy Chase, MD: American Society of Addiction Medicine.

Wen, H., & Hockenberry, J. M. (2018). Association of medical and adult-use marijuana laws with opioid prescribing for medicaid enrollees. *JAMA Internal Medicine*, *178*(5), 673–679. https://doi.org/10.1001/jamainternmed.2018.1007

Wen, H., Schackman, B. R., Aden, B., & Bao, Y. (2017). States with prescription drug monitoring mandates saw a reduction in opioids prescribed to medicaid enrollees. *Health Affairs*, *36*(4), 733–741. https://doi.org/10.1377/hlthaff.2016.1141

Wilsey, B., Marcotte, T., Tsodikov, A., Millman, J., Bentley, H., Gouaux, B., & Fishman, S. (2008). A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *Journal of Pain*, *9*(6), 506–521. https://doi.org/10.1016/j.jpain.2007.12.010

Wingerter, J. (2019, May 23). Coloradans can soon get medical marijuana in place of opioids. *The Denver Post*. Retrieved from https://www.denverpost.com/2019/05/23/medical-marijuana-opioid-painkillers-colorado/

Yaksh, T. L., & Wallace, M. S. (2011). Opioids, analgesia, and pain management. In L. L. Brunton, B. A. Chabner, & B. C. Knollman (Eds.), *Goodman and Gilman's the Pharmacological Basis of Therapeutics* (12th ed., pp. 481–526). New York: McGraw-Hill Medical.

Yang, Z., Wilsey, B., Bohm, M., Weyrich, M., Roy, K., Ritley, D., … Melnikow, J. (2015). Defining risk of prescription opioid overdose: pharmacy shopping and overlapping prescriptions among long-term opioid users in medicaid. *Journal of Pain*, *16*(5), 445–453. https://doi.org/10.1016/j.jpain.2015.01.475

Yarbrough, C. R. (2018). Prescription drug monitoring programs produce a limited impact on painkiller prescribing in medicare Part D. *Health Services Research*, *53*(2), 671–689. https://doi.org/10.1111/1475-6773.12652

Yuan, C. S., & Foss, J. F. (2000). Antagonism of gastrointestinal opioid effects. *Regional Anesthesia and Pain Medicine*, *25*(6), 639–642. https://doi.org/10.1053/rapm.2000.8658

Zajicek, J. P., Hobart, J. C., Slade, A., Barnes, D., & Mattison, P. G. (2012). Multiple sclerosis and extract of cannabis: results of the MUSEC trial. *Journal of Neurology, Neurosurgery and Psychiatry*, *83*(11), 1125–1132. https://doi.org/10.1136/jnnp-2012-302468

Zhong, W., Maradit-Kremers, H., St. Sauver, J. L., Yawn, B. P., Ebbert, J. O., Roger, V. L., … Rocca, W. A. (2013). Age and sex patterns of drug prescribing in a defined american population. *Mayo Clinic Proceedings*, *88*(7), 697–707. https://doi.org/10.1016/j.mayocp.2013.04.021

APPENDIX

Figure A1. Opioid Death Rates for each State in the Donor Pool and Colorado