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Implications of Prescription Drug Monitoring and Medical Cannabis Legislation on Opioid Overdose Mortality

By

Elyse Phillips
Degree to be awarded: Master of Public Health

Global Epidemiology

_________________________________ [Chair's signature]
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Implications of Prescription Drug Monitoring and Medical Cannabis Legislation on Opioid Overdose Mortality

By

Elyse Phillips

B.S., Brandeis University, 2012

Thesis Committee Chair: Julie Gazmararian, PhD, MPH

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Epidemiology
2016

Abstract

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By Elyse Phillips

Background: In response to the opioid epidemic in the United States, medical cannabis laws and expanding prescription drug monitoring programs (PDMPs) have the potential to combat rising rates of opioid overdose.

Methods: This study assessed the effect of legislation on opioid overdose mortality using multivariate repeated measures analysis. State level opioid related mortality rates for 50 states and the District of Columbia from 2011 to 2014 were obtained from CDC WONDER. State PDMPs with mandatory access provision data was obtained from the National Alliance for Model State Drug Laws, and data on state medical cannabis legislation from the National Organization for the Reform of Marijuana Laws. Covariates examined were state level aggregate rates for the population on disability, population living in an urban area, educational attainment, and unemployment from 2011-2014.

Results: Medical cannabis laws were significantly associated with an increase of 21.7% in mean age adjusted opioid related mortality ($p < .0001$). PDMPs with a mandatory access provision were significantly associated with an increase of 11.4% in mean age adjusted opioid related mortality rate ($p=0.005$). When time after enactment was included, for every additional year since enactment, the mean age adjusted opioid related mortality rate increased by 1.7% in states with medical cannabis ($p=0.049$), and 5.8% for states with a PDMP ($p=0.005$). The interaction between both types of legislation produced a borderline significant decrease of 10.1% ($p=0.055$). For every year states had both types of legislation, interaction resulted in a decrease of 0.6% ($p=0.013$).

Conclusions: States with either legal medical cannabis or PDMPs with mandatory access provisions were associated with higher rates of opioid related mortality than states without such laws. When accounting for the amount of time each type of legislation had been enacted, this association was markedly reduced in states with medical cannabis legislation. While PDMPs continue to be underutilized, when combined with the availability of medical cannabis as an alternative analgesic therapy, they may be more effective. Continued follow up of medical cannabis laws over time is important to understand the full effect these new laws may have on opioid related mortality and opioid prescribing trends.

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I. Introduction

The prescription opioid epidemic continues to be one of the most vital public health concerns in the United States today (1). As this public health issue has continued to grow, two types of legislation have been evolving in various states with the potential to combat the rising rates of opioid abuse and overdose. The first is the move towards legalization of medical cannabis, and the second is the creation and improvement of state prescription drug monitoring programs (PDMPs).

As of January 2016, 23 states and the District of Columbia have passed legislation allowing cannabis for medical use upon recommendation by a doctor, and 16 states have legalized cannabidiol (CBD) for medical use, a non-psychoactive extract of cannabis (1). The benefits of medical cannabis and cannabis extracts are best documented for the conditions most often associated with opioid analgesic therapies. Most notably, cannabis has been reported useful in the treatment of cancer, neurological conditions, and chronic non-cancer pain (2). Moreover, several studies have begun to show that cannabinoids act synergistically with opioids, which might allow for lower required doses and fewer side effects from chronic opioid therapy if used in combination (3-6). The replacement or combination of opioid analgesic therapies with medical cannabis may affect opioid overdose rates.

PDMPs have been created in 49 states to collect information on the dispensing of controlled substances like opioids and make that data available to prescribers, pharmacies, and law enforcement (7). Ideally, prescribers would be able to use these databases to learn pertinent information about patients such as how many opioid prescriptions the patient already received in that state, and if that individual has a history of addiction. This information could help the prescriber more effectively dispense opioids and make an informed decision about who might be a patient at high-risk for opioid abuse or overdose.

This study examines the relationship between these two types of legislation and their effect on opioid related mortality in the US. New legislation may be able to reduce the burden of this important public health concern.

II. Background

Prescription drug addiction has become one of the fastest growing public health problems in the US and abroad. Prescribing and use of opioid painkillers in particular has been increasing exponentially over the past two decades as drugs such as oxycodone and hydrocodone have become more widely available (8). These powerful drugs are vital for many people living with chronic pain, yet as physicians prescribe these pain medications more readily, there are more opportunities for individuals to become addicted, misuse or abuse them. By 2009, there were more drug overdose deaths than deaths from motor vehicle crashes, and prescription drug overdose is now the leading cause of accidental death in the US (9). In 2013, over half of all overdose deaths were related to prescription drugs, and opioid analgesics are the most responsible culprit in this trend (8). In 1999, only 30% of overdose deaths involved opioids, but by 2013 this number had climbed to over 70%, far surpassing deaths from any other drug class (8, 10).

With the high rates of opioid addiction brought on by the ubiquitous availability of the drugs is the practice of "doctor shopping". Abusers obtain a disproportionate amount of medications either directly or indirectly through doctor shopping, which is the practice of obtaining opioid prescriptions from multiple prescribers (11). A 2013 retrospective cohort study followed almost 11 million patients in the US that were prescribed opioid painkillers over 18 months and found that 0.7% developed shopping behavior (11). While this is a very small percent of the total number of patients receiving painkillers, the volume of drugs dispensed to shoppers accounted for 8.6% of the total number of opioids dispensed (11). A study from the Centers for Disease Control and Prevention (CDC) indicated that 40% of overdoses involve drug diversion, the practice of patients selling or distributing their prescriptions to individuals who were not prescribed those drugs, or patients that see multiple doctors (12). Among persons who died of opioid overdoses, a significant proportion did not have a prescription in their records for the opioid that killed them (12).

The epidemic of opioid prescription painkiller addiction, misuse and overdose has not gone unnoticed by policymakers. As this public health issue has continued to grow, two types of legislation have been evolving in many states with the potential to combat this issue. The first type of legislation is the move towards legalization of medical cannabis, and the second is the creation and improvement of state prescription drug monitoring programs.

Medical Cannabis and Legislation

The use of medical cannabis remains controversial. Historically, cannabis was studied in conjunction with other illicit street drugs or in combination with tobacco use, and the literature focused on negative effects of cannabis use. Scientists are limited in their ability to study cannabis alone for potential medical benefits due to its legal classification as a schedule I drug (13). Schedule I drugs are defined as "drugs with no currently accepted medical use and a high potential for abuse" (13). As such, to conduct clinical research using cannabis in the U.S., researchers must work through several federal agencies including the Drug Enforcement Administration, the National Institute on Drug Abuse within the National Institutes of Health, and the Food and Drug Administration (14). Due to this restrictive process, few reliable clinical research studies on cannabis have been conducted in the United States. New studies on its potential medical benefits are yet to reach a consensus, as the benefits of its use as a therapeutic treatment are based on only a handful of studies about specific conditions and anecdotal evidence (15).

The benefits of medical cannabis and cannabis extracts are best documented for the conditions most often associated with opioid analgesic therapies. Many of the states that have enacted medical cannabis laws point to chronic or severe pain as the primary medical use for cannabis (16). Most notably, cannabis has been reported useful in the treatment of cancer, neurological conditions, and chronic non-cancer pain (2). Medical cannabis has demonstrated clinical efficacy for the treatment of chemotherapy induced nausea and vomiting, and there have been some early studies suggesting its use for cancer pain management, and its ability to inhibit the growth and spread of cancer cells (3, 17, 18). An extract of cannabis called nabiximol has been studied extensively for treatment of spasticity in individuals with multiple sclerosis, and is currently available in 15 countries, although it is not yet approved for use in the United States (2, 19, 20). Medical cannabis has also been utilized as a form of treatment for epilepsy, although the efficacy of this is still unclear (19).

Numerous studies have demonstrated the analgesic properties of cannabis, and it is reported to be beneficial for various types of chronic non-cancer pain (3, 6, 15, 21). Moreover, several studies have begun to show that cannabinoids act synergistically with opioids, which might allow for lower required doses and fewer side effects from chronic opioid therapy if used in combination (3-6).

As several states have established successful medical cannabis programs since the late 1990s, public opinion and legislation on medical cannabis has moved in favor of legalization of medical cannabis. While medical cannabis is not legal at the federal level, the government has actively allowed this trend as more states have enacted legislation. Despite the continued classification of cannabis as a Schedule I substance, in 2009 the U.S. Justice Department announced that federal prosecutors would not pursue medical cannabis users and distributors if they remained compliant with state laws (22). As of January 2016, a total of 23 states and the District of Columbia have passed legislation allowing cannabis for medical use upon recommendation by a doctor, and 16 states have legalized cannabidiol (CBD) for medical use, a non-psychoactive extract of cannabis (1).

No direct fatalities have ever been attributed to cannabis with either medical or even recreational users, so it stands to reason that cannabis used by patients instead of opioids for the same conditions would lead to fewer drug overdose fatalities (2). A 2014 study published in JAMA examined this relationship, and its findings strongly supported an association between the presence of medical cannabis and a decrease in opioid overdose mortality (16). This study examined data from between 1999 and 2010, and found that states with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate compared with states without medical cannabis laws (16). Researchers evaluated possible trends in opioid overdose that predated enactment of medical cannabis laws, and looked at how the length of time cannabis laws had been enacted effected overdose rates (16). However, since the study period ended in 2010, and as of January 2016, 11 new states passed medical cannabis legislation, and another 16 passed CBD specific laws that did not exist when that study was completed. These new states add to both the number and variety of medical cannabis laws, and may change the effects seen in the older study.

The type of medical cannabis laws in a given state might influence overdose mortality rates, as there is a large difference between state-run medical cannabis programs and the recently adopted CBD specific laws. States with CBD specific laws typically allow doctors to recommend this type of cannabis only for a few very specific conditions, mainly intractable epilepsy, which may not have much of an impact on prescription drug use in the state overall [Appendix A](23). On the other hand, states with fully legal medical cannabis programs allow patients with a variety of qualifying conditions and a doctor's recommendation to possess cannabis up to the state's set legal limit [Appendix A]. This creates the potential for a much larger contingent of people to opt for medical cannabis as a compliment or alternative to prescription opioids. While the push for legalization has not specifically focused on curbing opioid overdose fatalities, cannabis legislation may be a vital tool in changing the current trends of opioid overdose rates in the country.

Prescription Drug Monitoring Programs

States have been creating or improving their existing prescription drug monitoring programs (PDMPs) in response to exponentially increasing prescribing rates of opioid analgesics over the past few decades (7). Currently 49 states have a PDMP in some capacity (24). These databases are created to collect information on the dispensing of controlled substances like opioids and make that data available to prescribers, pharmacies, and law enforcement so the state can manage who is getting their hands on these powerful drugs (7). Ideally, prescribers would be able to use these databases to learn pertinent information about patients such as how many opioid prescriptions he or she has already received in that state, and if that individual has a history of addiction. This information could help the prescriber more effectively dispense opioids and make an informed decision about who might be a patient at high-risk for opioid addiction or abuse.

Numerous studies have examined the efficacy of drug monitoring programs in regards to opioid addiction and abuse, but results are inconsistent. Several studies have found that doctors generally prescribe a different amount of opioid medication after consulting prescription drug monitoring program data (25-28). A 2014 study indicated that implementing PDMPs is associated with lower rates of substance abuse treatment admission, which would also translate to lower rates of substance abuse overdose (29). In a study of PDMP efficacy in an emergency department in Ohio, doctors prescribed a different amount than they would have otherwise in over half of cases after checking PDMP data (25, 30). Despite these positive findings, results are less clear when looking at PDMPs at the state level. One study found that PDMPs appear to decrease the quantity of oxycodone shipments and the admission rate for drug abuse rehabilitation programs for prescription opioid addiction in those states (27). Yet a review of state PDMPs from 1999 to 2008 did not show a significant impact on per-capita opioids dispensed (31). Another study looking at drug overdose mortality rates from 1999-2005 also concluded that PDMPs had only a minimal effect on the overall consumption of opioids, and no impact on mortality rates (32). A more recent study in 2012 examining two prescription monitoring program data sources concluded the opposite, and offered preliminary evidence to support that they are effective in mitigating increasing opioid abuse and misuse over time (33).

These inconsistent results are likely due to a number of factors including the fact that state PDMPs lack the capacity to communicate information over state lines, the vast irregularities between programs, and the lack of prescriber access to PMDP data even within a state. Because PDMPs only keep track of data within their state, and each state's program is different, program communication across state lines is severely lacking. So even if prescribers were fully utilizing a PDMP, they still might not have a way to know if patients were leaving their state to receive additional prescriptions, as is the habit of many doctor shoppers (11). A 2013 study of doctor shopping behavior found patients identified as shoppers travelled a median distance of 83 miles to fill their prescriptions, heavy shoppers travelled a median distance of 199 miles, and any shopping behavior was associated with visiting more than one state to fill opioid prescriptions (11).

The second part of the problem is that there is no standardized methodology for identifying opioid misuse based on prescription claims information (34). This means that depending on the state, a prescriber may or may not be alerted to the same situation of potential opioid misuse, which could significantly change the effectiveness of a particular state's program (26, 34). Dosages with opioid prescribing can also vary drastically depending on the patient and his or her condition, and there is potential for physicians to settle on medical solutions that do not reflect the science, but rather their own personal biases or guidelines (34-36). This is evident in the inexplicably large variation of prescribing rates between states. Alabama and Tennessee have the highest rates, dispensing over 142 prescriptions for opioid pain relievers per 100 people, while states with the lowest rates such as California and Hawaii dispense less than 60 prescriptions for opioid pain relievers per 100 people (37).

Despite variation in state prescribing habits, a prescriber will almost always prescribe less when informed about a high-risk patient. A recent study showed that providing actionable information to prescribers about patients who received an excessive number of prescriptions within a 3-month period resulted in significant reductions in the number of prescribers, dispensing pharmacies and filled opioid prescriptions over the study period (26). More often than not, the issue is that prescribers simply do not receive the alert or take the time to look up the communication they received on a secure website—that is, if that state issues alerts in general (26).

It was only recently that states even allowed prescribers to access PDMPs. In 1998, less than a third of states permitted physicians or pharmacists to access patient-identifiable data (34). By 2011, this had increased to 43 out of 46 states with PDMPs allowing access to physicians, and 41 allowing access to pharmacists (34). Even with the availability of drug monitoring data, physicians often do not take the time to take that information into consideration. Many physicians feel these programs are a burden as accessing them takes extra time, the systems do not always work properly and data might be incomplete (7). This underutilization of

PDMPs is a major issue for opioid overdose mortality. Prescribers are regularly unaware if their patient has had a nonfatal opioid overdose, and in the vast majority of cases will continue to prescribe that same patient opioids (38).

To make PDMPs more effective in actually getting the pertinent information to prescribers, 29 states now require that prescribers and sometimes dispensers have to access these databases prior to or at initiation of a new course of opioid treatment (24, 28). The circumstances during which a prescriber must access the database vary by state, and some are more stringent than others. In 2014, researchers at the Center of Prescription Monitoring Program Excellence at Brandeis University examined these requirements in Kentucky, Ohio, New York and Tennessee, and reported that the increased PDMP use was associated with a decrease in opioid prescribing in all four states, and a decrease in doctor shopping in three (28). However, more research is still needed as most of these mandates took effect within the last 5 years, and the scope of their impact is still unknown (39).

Contributions to the Literature

This study will contribute to the scientific literature in four key areas. First, it takes into account newly enacted medical cannabis legislation in the 11 states that have passed laws since 2010 and through 2014 (40). Second, it differentiates between legal medical cannabis programs and the new cannabidiol specific legislation that has been passed in 16 states since the beginning of 2014 (10 of which passed in 2014), which are much more limited in their ability to provide cannabis based therapies to individuals (23). The study explores how these two different types of medical cannabis legislation influence opioid overdose mortality when compared to states without medical cannabis during 2011 to 2014.

Third, this study will help determine how PDMP laws affect the relationship between medical cannabis and opioid overdose mortality. The previously mentioned JAMA study by Bachhuber et al. that explored the relationship between medical cannabis and opioid related mortality rates did not fully account for PDMP laws aimed at mitigating high rates of opioid overdose (16). That study follows the common assumption in the literature that all PDMPs can be considered the same regardless of their operational characteristics, which is severely limiting (34). These previous studies on the effect of PDMPs on overdose mortality are unreliable since they do not deal with the wide variation in state PDMP programs such as the type of data required to be reported to the databases and who can access the data (34). These differences can significantly impact the effectiveness of state programs on curbing overdose rates, as some states still do not allow prescribers access to the information collected in their PDMPs (41). The Bachhuber et al. study differentiated between states that allowed prescribers access to PDMP information and those that do not, but this study takes it one step further and delineates between states that mandate medical professionals to access PDMPs in certain circumstances and states that do not. This distinction will attempt to further avoid the assumption that simply the presence of a state PDMP means that the program is being utilized by prescribers to prevent opioid overdose and misuse.

Fourth, several other potential confounders are also being considered that may have an effect on the relationship between cannabis and PDMP legislation and opioid overdose mortality (Appendix B). The first is the rates of Americans receiving disability benefits, as studies have found almost half of Americans on disability are prescribed opioid painkillers (around 40%) (42). Among this population the prevalence of one or more musculoskeletal diseases was as high as 65.5% in 2011, and of the almost half that had taken opioid painkillers, 20% were considered chronic users and were at increased risk of opioid overdose death (42).

The percent of urban population in a state may also relate to overdose morality rates through several avenues. Access to medical care in general varies widely among urban and rural areas of the country, and urban centers offer better access and more choice of care for residents. In states where medical cannabis is legal, this affects utilization of cannabis, as doctors willing to prescribe cannabis and dispensaries are distributed mainly in and around urban centers (43) . Doctors in rural areas are less inclined to recommend medical cannabis, even in states where it is legal, and lean towards more traditional medical interventions such as opioids for their patients (43). Aside from better access to medical cannabis, the visibility of dispensaries may create more awareness of cannabis as a medical option in urban areas. Rural residency is associated with higher prevalence of chronic pain, higher pain frequency and intensity, and more pain-related disability compared to people with pain living in urban areas (44, 45). The increase in opioid prescribing in recent years combined with the fact that rural areas have less access to illicit street drugs may contribute to the findings of several studies that found patterns of greater opioid misuse in rural areas (44-47). Nevertheless, there is disagreement in the literature on this association, as other findings such as a 2009 study using US poison center surveillance data suggest there is no association between population density and opioid misuse (48).

Education is another important potential confounder, as the quality and type of education may vary drastically depending on the state or area, and educational attainment can influence an individual's risk of opioid addiction and overdose. Rural residents are found to have lower educational attainment compared to urban residents, and lower educational attainment has been associated with a higher likelihood of prescription opioid misuse, in addition to higher risk for addiction in general (48-51). Lower educational attainment has also been associated with a higher risk of relapse after receiving treatment for substance use disorders, which is important to note in light of the fact that most patients who have a nonfatal opioid overdose are dispensed opioids again (38, 52). It is possible education levels may also be associated with the likelihood of an individual seeking and/or using medical cannabis instead of opioids, which would decrease their risk of opioid overdose mortality. Scientific literature on cannabis use that has historically studied recreational cannabis users, grouped together with users of other illicit substances, found that substance dependence was associated with lower educational attainment. However, a recent study of medical cannabis patients in California found that 61% of patients had more than a high school education, and it remains that very little is currently known about the demographics of these patients (53). Unemployment may be another confounder in this study as higher unemployment rates are consistent with lower levels of education, and may represent individuals who are uninsured. Both education and unemployment have been associated with addiction and opioid misuse and overdose (12, 48, 51, 54).

III. Methods

Study design: This analysis was an ecological study.

Study population: The study population included residents of the 50 United States and the District of Columbia with available death certificate data for the years 2011, 2012, 2013, and 2014.

Data sources: This study utilized public data obtained through all cause mortality data available from CDC Wonder (55). The data included total opioid related deaths for each state, and the age adjusted opioid related overdose mortality rates per 100,000 people by state for the years 2011, 2012, 2013, and 2014.

Data on prescription drug monitoring program (PDMP) legislation was obtained from the National Alliance for Model State Drug Laws (NAMSDL). Data collected was a list of states that require prescribers and/or dispensers to access PDMP database in certain circumstances, and the date of enactment in which the earliest mandatory access provision went into effect for those states where available. In North Carolina there was no specific statute, but NAMSDL were informed by the former administrator of North Carolina's prescription monitoring program that medical directors of opioid treatment programs are required to access the PDMP. This correspondence occurred sometime between 2011 or 2012 so for this analysis the date of enactment was assumed to be 7/1/2011. The date for Delaware was obtained via email correspondence with a representative of the Delaware Prescription Monitoring Program (56).

Data on medical cannabis legislation was obtained from the NORML Foundation at norml.org, and procon.org (1, 40). The data included the type of legislation each state had surrounding medical cannabis for the study period of 2011, 2012, 2013 and 2014, and what date any legislation about cannabis was enacted. The time since enactment of PDMP and Medical Cannabis legislation was calculated in SAS 9.4 statistical software.

Covariate data is obtained from a variety of sources: Rates for state urban populations are obtained from the US Census Bureau's statistics from the 2010 census. This measure is determined by the percent of a state's population living in an urban area, as reported from data collected during the 2010 census. An urban area is defined as a densely settled area that encompasses "at least 2,500 people, at least 1,500 of which reside outside institutional group quarters" (57). Rates for state population on disability, and education attainment were obtained from the US Census Bureau's American Community Survey for the years 2011, 2012, 2013, and 2014. Disability rates are determined by an estimate of the percentage of people in a given state that encompass the survey's definition of disability. The survey attempts to capture people under the age of 65 years old with serious difficulty with 6 aspects of disability: hearing, vision, cognition, ambulation, self-care and independent living (58). Education rates are determined by the percentage of the state's population that attained a high school diploma, its equivalent, or higher (59). Annual unemployment data is obtained from the US Department of Labor Statistics. Rates are the percentage of the civilian labor force in each state that is unemployed. The Bureau of Labor Statistics defines unemployment as "all people who had no employment during the reference week, were available for work—except for temporary illness—and made specific efforts to find employment sometime during the 4-week period ending with the reference week. People who were waiting to be recalled to a job from which they had been laid off need not have been looking for work to be classified as unemployed" (60).

Data measures (be clear on what is your outcome, exposure and covariates): The outcome variable of this study is the logarithm of the age adjusted opioid related mortality for each state and year. Opioid related mortality was defined using ICD-10 codes T40.2-T40.4, X40-X44, X60-X64, and Y10-Y14. This captured all overdose deaths where an opioid analgesic was involved including those involving polypharmacy or illicit drug use, and intentional overdose.

This study had two exposure variables, PDMPs and medical cannabis. For PDMPs, states were dichotomized into two categories: those with legislation that require prescribers and/or dispensers to access PDMP database in certain circumstances, and those without such legislation. Only states in this category with PDMP legislation enacted prior to December 31, 2014 are considered to have a PDMP in this study. Medical cannabis legislation was grouped into three categories for analysis: states with legal medical cannabis upon recommendation from a physician, states with legal cannabidiol (CBD) therapies only upon recommendation from a physician, and states with no legal medical cannabis. States with any type of medical cannabis legislation enacted after December 31, 2014 were not considered to have medical cannabis legislation in this study. The time since enactment of the legislation was calculated using the date of enactment as the start date, and December 31st of each year of the study period as the cutoff point.

The covariates included in this study were state level aggregate rates for the population on disability, population living in an urban area, educational attainment, and unemployment from 2011-2014. All covariates are rates calculated as continuous variables based on population percentages.

Analysis plan: Analysis was performed using SAS 9.4 statistical software. The association between medical cannabis, PDMP laws, and opioid related mortality rate was assessed using multivariate repeated measure analysis, with age adjusted mortality rate as the outcome of interest. The mortality rate was log transformed for analysis to account for non-normality.

The presence of relevant legislation was modeled in two ways. The first regression model used an indicator variable for the presence of legislation in each state for each year of the study. All years prior to the enactment of legislation for medical cannabis, CBD, or a PDMP were coded as 0 for each of the three types of legislation, and all years during which or after legislation was passed were coded as 1. The second regression model used the time since enactment of each type of legislation to account for the presence of legislation. Time since enactment of each of the three types of legislation was calculated as the time elapsed between the date of enactment and December 31st of each year of the study period. If no legislation was enacted, time since enactment was coded as 0. This model was run once using time since enactment of medical cannabis laws that included both medical cannabis and CBD laws, and then again including a time since enactment variable that only incorporated states with full medical cannabis legislation.

In addition to the main exposures, each model also adjusted for education, unemployment, percent of population on disability, and the interaction between the presence of medical cannabis and a PDMP. Percent of the population living in an urban area was not significantly associated with opioid related mortality, and was not included in the final models. Significance was considered at alpha=0.05, and results of the regression analyses were back transformed for interpretability.

IV. Results

Between 2011 and 2014, the mean age-adjusted opioid related mortality rate increased nationwide from 15.3 deaths per 100,000 people in 2011 to 17.2 deaths per 100,000 people in 2014 (Table 1). The mean age-adjusted opioid related mortality rate was higher in states with a PDMP with a mandatory access provision, compared to those without one, but the mortality rate increased in both groups over the four year period. During the study period, the mean age-adjusted opioid related mortality rate was also higher in states with medical cannabis legislation than in states without. Opioid mortality rates in both groups increased over the course of the study period, although states without medical cannabis legislation saw a greater mean increase in rate (0.8 additional deaths per 100,000 in states with medical cannabis vs. 2.5 additional deaths per 100,000 in states without).

Model 1- Indicator variables for the effect of presence of legislation

In the first adjusted model, CBD legislation did not have a significant association with the mean age adjusted opioid related mortality rate (Table 2). The presence of medical cannabis laws was significantly associated with an increase of 21.7% in mean annual age adjusted opioid related mortality ($p < .0001$). The presence of a PDMP with a mandatory access provision was significantly associated with an increase of 11.4% in mean annual age adjusted opioid related mortality rate ($p=0.005$). The percent of the population on disability in a given state was also significantly associated with an increase in mean annual age adjusted opioid related mortality rate. For every 1% increase in population on disability, there was a mean opioid related mortality increase of 4.9% ($p= 0.008$). There was a borderline significant protective effect of the interaction between the presence of medical cannabis and the presence of PDMP legislation. In states with both types of legislation there was a decrease of 10.1% in mean opioid related mortality rate (p=0.06). State unemployment rates and education were not significantly associated with opioid related mortality rates.

Model 2- Time since enactment variables for the effect of legislation over time

In the second adjusted model, there was a significant association between both exposures and the age-adjusted opioid related mortality rate. For every additional year since enactment of medical cannabis legislation, the mean opioid related mortality rate increased by 1.7% compared with states without medical cannabis (p=0.05)(Table 3). For every additional year since enactment of a mandatory access provision for a state PDMP, the mean opioid related mortality rate increased by 5.8% compared with states without a PDMP with mandatory access provisions (p=0.005). This model also had a significant association between percent of population on disability in a given state and the mean annual age adjusted opioid related mortality (increase of 4.6%; p= 0.02). There was a significant protective effect of the interaction between the time since enactment of medical cannabis legislation and the time since enactment of PDMP legislation. For every year states had both types of legislation there was a decrease of 0.6% in mean opioid related mortality rate (p=0.01). State unemployment rates and education were not significantly associated with opioid related mortality rates.

In the adjusted model using time, when the medical cannabis variable only incorporated states with full medical cannabis legislation, the associations did not change from those seen in Table 3 (Appendix C).

V. Discussion

This study found that states with either legal medical cannabis or PDMPs with mandatory access provisions were associated with higher rates of opioid related mortality than states without such laws. When accounting for the amount of time each type of legislation had been in place, these associations persisted although the effects of both laws were markedly lessened. There was no significant association between CBD only legislation and opioid related mortality. This is most likely due to the fact that that type of legislation went into effect starting in the last year of the study period, and had not been enacted long enough for any effects to emerge. The exact mechanism causing the association between the two types of legislation and increased opioid related mortality is unclear.

One possibility for the association between medical cannabis laws and opioid overdose comes from a recent finding by the CDC, which linked abuse of certain substances to an increased risk of heroin use disorder (61). Individuals who abused cannabis were found to be three times more likely to abuse heroin than those who did not (61). It is possible that states with legal medical cannabis may have higher rates of cannabis use in the general population due to cannabis' expanded availability from the legal market. This may lead to higher rates of heroin overdose deaths in those states, which were included in the rates of opioid overdose mortality for this study. Nevertheless, the increase in opioid related mortality is lessened by 20% (from 21.7% to 1.7%) once time is considered, implying that the longer medical cannabis is available in a state, the more protective it becomes.

This study found an association between PDMPs with mandatory access provisions and an increased rate of opioid overdose mortality, but there is no reason the presence of a PDMP in a state would cause opioid overdoses to increase. While the majority of states had a PDMP during the study period at varying levels of functionality, states with the worst issues related to doctor shopping and drug diversion would seemingly be more inclined to include mandatory access provisions to their monitoring programs. This could potentially be inflating the association between PDMPs and opioid related mortality in this study. However, when examining the effect that the time mandatory access provisions have been in place has on this relationship, the increase in opioid related mortality persisted at a rate of 5.8% per year in those states compared to states without those provisions.

When comparing the effect of the two types of legislation, the results indicate that medical cannabis legislation does more on average to slow the rising opioid related mortality rates over time than PDMPs with mandatory access provisions do. The potential benefit of medical cannabis laws becomes more compelling when considering the protective effect of the interaction between medical cannabis laws and PDMPs in both regression models. Despite the connection between heroin and cannabis, states with both a medical cannabis law and a PDMP with mandatory access provisions saw a diminished rate of increase in mean opioid related mortality. Prescribers may be more inclined to access a PDMP in those states if they know there is an alternative analgesic therapy to offer patients who are at high risk for opioid abuse, and patients themselves might be seeking out cannabis as an alternative to opioid analgesics. More research is necessary to understand the prevalence and trends of medical cannabis use in the United States, and to determine the extent to which it is perceived as a viable alternative to opioids by both patients and prescribers.

The increase in opioid related mortality rates in states with either legislation may be partially explained by the overall increase in mortality throughout the study period. Opioid related mortality rates rose steadily between 2011 and 2014, so these associations may simply be reflecting national trends. Heroin deaths are also an important factor in these results. Individuals who are dependent on or abuse prescription opioid painkillers are 40 times more likely to abuse heroin, and heroin related deaths nearly doubled in the United States between 2011 and 2013 (61). Because of this, it is difficult to determine the extent prescription opioids are to blame for this trend, and further study would be useful to look at the relationship between polypharmacy use of prescription opioids and illicit drugs (61).

The results of the 2014 JAMA study differ somewhat from the findings of this study. Their findings suggest medical cannabis laws are associated with reductions in opioid related mortality on a population level, which strengthened in the years after passage (16). Our study did show a protective effect of cannabis laws in the interaction between cannabis laws and PDMPs, but did not find a reduction in opioid related mortality in those states. Part of this discrepancy may be explained by the different years considered in their study period, which ended in 2010. Our study looked at the years following 2010, which saw the total number of states with medical cannabis nearly double, as 11 new states passed medical cannabis legislation (1). The JAMA study found that over time, the beneficial effect of medical cannabis laws on opioid related mortality strengthened with each year after passage. This association may have been washed out in the current study by the large influx of new cannabis programs. Further analyses is needed to determine how these new cannabis programs affect opioid related mortality over time as they become more established in the healthcare culture of their given state.

Strengths and Limitations

This study had four main strengths. First, it takes into account newly enacted medical cannabis legislation in the 11 states that have passed laws since 2010 and through 2014 (40). Second, it differentiates between legal medical cannabis programs and the new cannabidiol specific legislation that has been passed in 16 states since the beginning of 2014 (10 of which passed in 2014), which are much more limited in their ability to provide cannabis based therapies to individuals (23). Third, this study differentiates between simply the presence of a PDMP, and PDMPs that require prescribers to access the systems. This helps avoid the common assumption in the literature that all PDMPs can be considered the same regardless of their operational characteristics, which is severely limiting (34). These previous studies on the effect of PDMPs on overdose mortality are unreliable since they do not deal with the wide variation in state PDMP programs such as the type of data required to be reported to the databases and who can access the data (34). Fourth, the covariates being considered are able to act as proxies for traits like socioeconomic status, that were not assessed in previous literature on this topic such as in the Bachhuber et al. study.

There were four limitations in this study. First, as an ecological study the analysis was only able to look at population level data, and the aggregated data act as a proxy for individual level data. Heterogeneity between states in death certificate reporting of opioid overdose deaths may cause a misclassification bias in the results. Differences between state laws, particularly with PDMPs, may also cause confounding that was not accounted for in the models. By differentiating between CBD and medical cannabis laws, and examining PDMPs with mandatory access provisions, this study tried to address some of the variability between state laws. However, this variability means the dates of enactment for PDMP mandatory access provisions may not represent the exact time enforcement or action of that law began, as each state did not add their provisions in the same way. Second, this study included heroin deaths in the opioid related mortality rate even if no opioid analgesic was present due to the strong relationship between the two substances. Third, is that the study period was relatively short in an attempt to assess the large shifts in legislation in recent years for both medical cannabis and PDMP legislation. Many states had newly adopted these laws, and CBD legislation was only enacted in the last year of the study period. A longer follow-up time would allow any effects these laws might have to become more apparent in the data. Fourth, the models used in the analysis assumed a compound symmetry covariance structure because of limitations with degrees of freedom and loss of power.

VI. Conclusion

This study found that states with either medical cannabis legislation or a PDMP that requires prescribers/dispensers to access PDMP database in certain circumstances were associated with an increase in mean opioid related mortality rate compared to states without those laws. However, there was evidence that when a state had both medical cannabis and a PDMP, the effect on mean opioid related mortality rate was protective. This is likely due to the availability of medical cannabis as an alternative to prescription opioids in those states when a high-risk patient is identified in a PDMP. However, this possible mechanism is speculative and further research is necessary to fully explore the effect of medical cannabis on opioid analgesic prescribing patterns. More research is also needed to explore why PDMPs with mandatory access provisions are still unable to reduce the opioid related mortality rates in their states, as mandatory access provisions are explicitly put in place to prevent drug diversion, doctor shopping and opioid abuse. While PDMPs continue to be underutilized by prescribers, when combined with the availability of medical cannabis as an alternative analgesic therapy, they may be more effective in reducing opioid overdose deaths. The time after enactment of both types of legislation had a strong mitigating effect of the association with an increase in mean opioid related mortality rate, particularly in states with medical cannabis. Continued follow up of medical cannabis legislation over time will be important to understand the full effect these new laws have on opioid related mortality and the culture of opioid prescribing in those states.

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VIII. Tables

Table 1. Summary Statistics of Exposures

		Mandatory PDMP Access[1]		Medical Cannabis Legislation		
Opioid Related Mortality		Yes	No	Yes	CBD[2] Only	No
Year	No. Deaths Nationwide	No. States		No. States		
2011	44,764	7	44	17	0	34
2012	45,068	10	41	18	0	33
2013	47,649	19	32	20	0	31
2014	50,785	22	29	24	10	17
Total (N) 2011-2014	188,266	-	-	-	-	-
Opioid Related Mortality Rate[3]						
Year	Mean (SD)					
2011	15.31 (5.97)	18.88 (4.75)	14.83 (6.00)	16.66 (4.69)	-	14.64 (6.47)
2012	15.17 (5.78)	21.95 (7.69)	13.51 (3.80)	15.73 (4.44)	-	14.85 (6.43)
2013	15.98 (5.56)	19.59 (6.65)	14.18 (3.91)	16.92 (3.97)	-	15.38 (6.36)
2014	17.19 (5.98)	19.34 (7.18)	15.56 (4.34)	17.43 (4.80)	16.79 (5.09)	17.09 (7.98)
Overall Mean 2011-14	15.91 (5.83)	19.84 (6.77)	14.46 (4.70)	16.74 (4.46)	16.79 (5.09)	15.26 (6.63)

[1] Prescription Drug Monitoring Program (PDMP) that requires prescribers and/or dispensers to access PDMP database in certain circumstances
[2] Cannabidiol
[3] Age-Adjusted Opioid Related Mortality Rate per 100,000 people

Table 2. Association Between any Medical Cannabis and PDMP[1] Legislation and Age-Adjusted Opioid Related Mortality in the United States, 2011-2014

Independent Variable	β-Estimate	Standard Error	t-Value	Pr > |t|
CBD[2]	0.0330	0.0423	0.78	0.4369
Medical Cannabis	0.1962	0.0452	4.34	< .0001
PDMP	0.1078	0.0381	2.83	0.0053
Unemployment	-0.0048	0.0120	-0.40	0.6917
Education	-0.0012	0.0146	-008	0.9368
Disability	0.0482	0.0178	2.71	0.0076
Medical Cannabis*PDMP	-0.1065	0.0550	-1.93	0.0550

[1] Prescription Drug Monitoring Program
[2] Cannabidiol

Table 3. Association Between the Time Since Enactment of Medical Cannabis and PDMP[1] Legislation and Age-Adjusted Opioid Related Mortality in the United States, 2011-2014

Independent Variable	β-Estimate	Standard Error	t-Value	Pr > |t|
Time Medical Cannabis[2]	0.0165	0.0083	1.99	0.0488
Time PDMP[3]	0.0561	0.0196	2.86	0.0048
Unemployment	-0.0057	0.0125	-0.45	0.6510
Education	-0.0001	0.0154	-0.00	0.9968
Disability	0.0450	0.0187	2.40	0.0175
Time Medical Cannabis * Time PDMP	-0.0064	0.0025	-2.52	0.0126

[1] Prescription Drug Monitoring Program
[2] Time in years since the enactment of a medical cannabis law (includes states with only legal CBD)
[3] Time in years since the enactment of a state's PDMP provision requiring a prescriber and/or dispenser to access PDMP database in certain circumstances

Appendices

Appendix A

Appendix A.I. Commonly Approved Conditions for Medical Cannabis Use by State, 2015

State	Year[1]	Cancer	HIV/AIDS	Chronic/ Severe Pain	Epilepsy/ Seizure Disorders	Glaucoma	MS[2]/ Spasms	Nausea	Chrohn's Disease
Alaska	1999	yes	yes	yes	yes	yes	yes	yes	no[3]
Arizona	2010	yes	yes	yes	yes	yes	yes	yes	yes
California	1996	yes	yes	yes	yes	yes	yes	yes	no
Colorado	2001	yes	yes	yes	yes	yes	yes	yes	no
Connecticut	2012	yes	yes	no	yes	yes	yes	no	yes
Delaware	2011	yes	yes	yes	yes	yes	yes	yes	no
Hawaii	2015	yes	yes	yes	yes	yes	yes	yes	yes
Illinois	2014	yes	yes	yes	yes	yes	yes	no	yes
Maine	1999	yes	yes	no	yes	yes	yes	yes	no
Maryland	2014	no	no	yes	yes	no	yes	yes	no
Massachusetts	2013	yes	yes	no	no	yes	yes	no	yes
Michigan	2008	yes	yes	yes	yes	yes	yes	yes	yes
Minnesota	2014	yes	yes	yes	yes	yes	yes	yes	yes
Montana	2004	yes	yes	yes	yes	no	yes	yes	yes
Nevada	2001	yes	yes	yes	yes	yes	yes	yes	no
New Hampshire	2013	yes	yes	yes	yes	yes	yes	yes	yes
New Jersey	2010	yes	yes	yes	yes	yes	yes	yes	yes
New Mexico	2007	yes	yes	yes	yes	yes	yes	yes	yes
New York	2014	yes	yes	no	yes	no	yes	no	yes
Oregon	1998	yes	yes	yes	yes	yes	yes	yes	no
Rhode Island	2006	yes	yes	yes	yes	yes	yes	yes	yes
Vermont	2004	yes	yes	yes	yes	no	yes	yes	no
Washington	1998	yes	yes	yes	yes	yes	yes	yes	yes
Washington DC	2010	yes	yes	no	no	no	yes	no	no

[1] Year medical cannabis legislation was enacted
[2] Multiple Sclerosis
[3] no signifies that the state's law does not explicitly state that condition, but cannabis may still be allowed for that condition on a case by case basis

(40)

Appendix A.II. Commonly Approved Conditions for Medical Cannabidiol Use by State, 2015

State	Year[1]	Intractable Epilepsy	Cancer	MS[2]/ Muscle Spasms	Chrohn's Disease
Alabama	2014	yes	no	no	no
Delaware	2015	yes	no	yes	no
Florida	2014	yes	yes	yes	no
Georgia	2015	yes	yes	yes	yes
Iowa	2014	yes	no	no	no
Kentucky	2014	yes	no	no	no
Mississippi	2014	yes	no	no	no
Missouri	2014	yes	no	no	no
North Carolina	2014	yes	no	no	no
Oklahoma	2015	yes	no	no	no
South Carolina	2014	yes	no	no	no
Tennessee	2014	yes	no	no	no
Texas	2015	yes	no	no	no
Utah	2014	yes	no	no	no
Virginia	2014	yes	no	no	no
Wisconsin	2014	yes	no	no	no

[1] Year medical cannabidiol legislation was enacted
[2] Multiple Sclerosis

(23)

Appendix B

Appendix B. Summary Statistics of Covariates

	Overall	Mandatory PDMP Access[1]		Medical Cannabis Legislation		
		Yes	No	Yes	CBD[2] Only	No
Variable	Mean (SD)	Mean (SD)		Mean (SD)		
Urban Pop. (%)						
2011	74.10 (14.89)	77.91 (11.88)	73.59 (15.28)	78.96 (18.80)	-	71.67 (12.09)
2012	74.10 (14.89)	70.38 (16.93)	75.08 (14.16)	79.46 (18.36)	-	71.18 (11.92)
2013	74.10 (14.89)	73.21 (16.88)	74.54 (14.03)	79.13 (18.14)	-	70.86 (11.54)
2014	74.10 (14.89)	73.24 (15.29)	74.75 (14.81)	79.97 (16.81)	68.55 (13.32)	69.07 (9.41)
Overall Mean 2011-2014	74.10 (14.78)	73.17 (15.67)	74.44 (14.47)	79.42 (17.59)	68.55 (13.32)	70.92 (11.42)
Unemployment Rate (%)						
2011	8.17 (1.93)	9.22 (2.42)	8.03 (1.84)	8.95 (1.96)	-	7.77 (1.82)
2012	7.37 (1.71)	7.65 (1.80)	7.30 (1.71)	8.15 (1.64)	-	6.95 (1.62)
2013	6.77 (1.55)	7.22 (1.41)	6.54 (1.58)	7.20 (1.48)	-	6.49 (1.55)
2014	5.80 (1.27)	6.01 (1.27)	5.63 (1.26)	6.15 (1.20)	5.97 (1.16)	5.19 (1.27)
Overall Mean 2011-2014	7.03 (1.84)	7.03 (1.83)	7.03 (1.85)	7.47 (1.86)	5.97 (1.16)	6.81 (1.80)
Education[3] (%)						
2011	87.48 (3.28)	85.25 (2.00)	87.78 (3.32)	88.06 (3.34)	-	87.20 (3.26)
2012	88.01 (3.12)	86.42 (2.51)	88.40 (3.16)	88.69 (3.05)	-	87.63 (3.14)
2013	88.23 (3.13)	86.88 (2.93)	88.89 (3.10)	89.03 (2.99)	-	87.71 (3.15)
2014	88.52 (3.06)	87.38 (2.94)	89.39 (2.91)	89.21 (2.94)	87.55 (3.26)	88.11 (3.07)
Overall Mean 2011-2014	88.06 (3.15)	86.82 (2.74)	88.52 (3.17)	88.80 (3.03)	87.55 (3.26)	87.60 (3.14)
Pop. On Disability (%)						
2011	12.54 (2.16)	13.37 (1.80)	12.43 (2.20)	12.04 (1.57)	-	12.79 (2.38)
2012	12.66 (2.15)	14.30 (2.26)	12.21 (1.91)	12.20 (1.62)	-	12.91 (2.36)
2013	13.07 (2.18)	13.91 (2.43)	12.58 (1.88)	12.61 (1.70)	-	13.37 (2.42)
2014	13.16 (2.17)	13.84 (2.36)	12.66 (1.91)	12.44 (1.68)	14.01 (2.50)	13.69 (2.38)
Overall Mean 2011-2014	12.86 (2.16)	13.90 (2.27)	12.45 (1.98)	12.34 (1.64)	14.01 (2.50)	13.12 (2.38)

[1] Prescription Drug Monitoring Program (PDMP) that requires prescribers and/or dispensers to access PDMP database in certain circumstances
[2] Cannabidiol
[3] Percent of the population that has attained a high school diploma, its equivalent, or higher

Appendix C

Appendix C. Association Between the Time Since Enactment of Medical Cannabis and PDMP Legislation and Age-Adjusted Opioid Related Mortality in the United States, 2011-2014

Independent Variable	β-Estimate	Standard Error	t-Value	Pr > |t|
Time Medical Cannabis[1]	0.0159	0.0083	1.92	0.0573
Time PDMP[2]	0.0549	0.0195	2.82	0.0055
Unemployment	-0.0062	0.0125	-0.49	0.6215
Education	0.0003	0.0154	0.02	0.9836
Disability	0.0452	0.0187	2.41	0.0170
Time Medical Cannabis * Time PDMP	-0.0062	0.0025	-2.46	0.0152

[1] This is the time in years since the enactment of a medical cannabis law not including states with cannabidiol only legislation
[2] Time in years since the enactment of a state's prescription drug monitoring program provision requiring a prescriber and/or dispenser to access PDMP database in certain circumstances