Original Investigation

Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010

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IMPORTANCE Opioid analgesic overdose mortality continues to rise in the United States, driven by increases in prescribing for chronic pain. Because chronic pain is a major indication for medical cannabis, laws that establish access to medical cannabis may change overdose mortality related to opioid analgesics in states that have enacted them.

OBJECTIVE To determine the association between the presence of state medical cannabis laws and opioid analgesic overdose mortality.

DESIGN, SETTING, AND PARTICIPANTS A time-series analysis was conducted of medical cannabis laws and state-level death certificate data in the United States from 1999 to 2010; all 50 states were included.

EXPOSURES Presence of a law establishing a medical cannabis program in the state.

MAIN OUTCOMES AND MEASURES Age-adjusted opioid analgesic overdose death rate per 100 000 population in each state. Regression models were developed including state and year fixed effects, the presence of 3 different policies regarding opioid analgesics, and the state-specific unemployment rate.

RESULTS Three states (California, Oregon, and Washington) had medical cannabis laws effective prior to 1999. Ten states (Alaska, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Mexico, Rhode Island, and Vermont) enacted medical cannabis laws between 1999 and 2010. States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95% CI, −37.5% to −9.5%; $P = .003$) compared with states without medical cannabis laws. Examination of the association between medical cannabis laws and opioid analgesic overdose mortality in each year after implementation of the law showed that such laws were associated with a lower rate of overdose mortality that generally strengthened over time: year 1 (−19.9%; 95% CI, −30.6% to −7.7%; $P = .002$), year 2 (−25.2%; 95% CI, −40.6% to −5.9%; $P = .01$), year 3 (−23.6%; 95% CI, −41.1% to −1.0%; $P = .04$), year 4 (−20.2%; 95% CI, −33.6% to −4.0%; $P = .02$), year 5 (−33.7%; 95% CI, −50.9% to −10.4%; $P = .008$), and year 6 (−33.3%; 95% CI, −44.7% to −19.6%; $P < .001$). In secondary analyses, the findings remained similar.

CONCLUSIONS AND RELEVANCE Medical cannabis laws are associated with significantly lower state-level opioid overdose mortality rates. Further investigation is required to determine how medical cannabis laws may interact with policies aimed at preventing opioid analgesic overdose.

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Chronic noncancer pain is common in the United States,[1] and the proportion of patients with noncancer pain who receive prescriptions for opioids has almost doubled over the past decade.[2] In parallel to this increase in prescriptions, rates of opioid use disorders and overdose deaths have risen dramatically.[3,4] Policies such as prescription drug monitoring programs, increased scrutiny of patients and providers, and enhanced access to substance abuse treatment have been advocated to reduce the risk of opioid analgesics[5]; however, relatively less attention has focused on how the availability of alternative nonopioid treatments may affect overdose rates.

As of July 2014, a total of 23 states have enacted laws establishing medical cannabis programs[6] and chronic or severe pain is the primary indication in most states.[7-10] Medical cannabis laws are associated with increased cannabis use among adults.[11] This increased access to medical cannabis may reduce opioid analgesic use by patients with chronic pain, and therefore reduce opioid analgesic overdoses. Alternatively, if cannabis adversely alters the pharmacokinetics of opioids or serves as a "gateway" or "stepping stone" leading to further substance use,[12-14] medical cannabis laws may increase opioid analgesic overdoses. Given these potential effects, we examined the relationship between implementation of state medical cannabis laws and opioid analgesic overdose deaths in the United States between 1999 and 2010.

Methods

The opioid analgesic overdose mortality rate in each state from 1999 to 2010 was abstracted using the Wide-ranging Online Data for Epidemiologic Research interface to multiple cause-of-death data from the Centers for Disease Control and Prevention.[15] We defined opioid analgesic overdose deaths as fatal drug overdoses of any intent (*International Statistical Classification of Diseases, 10th revision* [*ICD-10*], codes X40-X44, X60-X64, and Y10-Y14) where an opioid analgesic was also coded (T40.2-T40.4). This captures all overdose deaths where an opioid analgesic was involved including those involving polypharmacy or illicit drug use (eg, heroin). Analysis of publicly available secondary data is considered exempt by the University of Pennsylvania Institutional Review Board.

Three states (California, Oregon, and Washington) had medical cannabis laws effective prior to 1999.[6] Ten states (Alaska, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Mexico, Rhode Island, and Vermont) implemented medical cannabis laws between 1999 and 2010. Nine states (Arizona, Connecticut, Delaware, Illinois, Maryland, Massachusetts, Minnesota, New Hampshire, and New York) had medical cannabis laws effective after 2010, which is beyond the study period. New Jersey's medical cannabis law went into effect in the last quarter of 2010 and was counted as effective after the study period. In each year, we first plotted the mean age-adjusted opioid analgesic overdose mortality rate in states that had a medical cannabis law vs states that did not.

Next, we determined the association between medical cannabis laws and opioid analgesic-related deaths using linear time-series regression models. For the dependent variable, we used the logarithm of the year- and state-specific age-adjusted opioid analgesic overdose mortality rate. Our main independent variable of interest was the presence of medical cannabis laws, which we modeled in 2 ways.

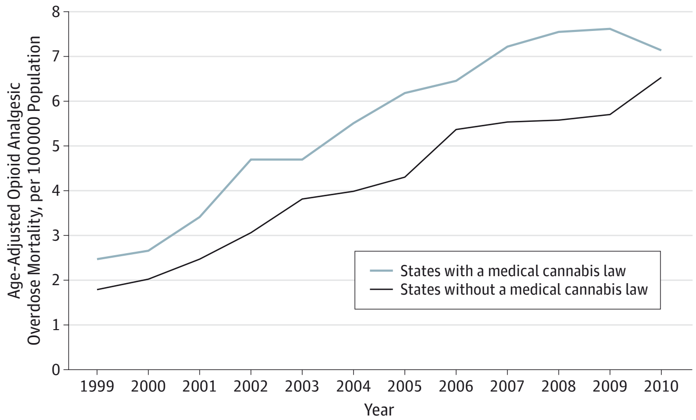
In our first regression model, we included an indicator for the presence of a medical cannabis law in the state and year. All years prior to a medical cannabis law were coded as 0 and all years after the year of passage were coded as 1. Because laws could be implemented at various points in the year, we coded the law as a fraction for years of implementation (eg, 0.5 for a law that was implemented on July 1). The coefficient on this variable therefore represents the mean difference, expressed as a percentage, in the annual opioid analgesic overdose mortality rate associated with the implementation of medical cannabis laws. To estimate the absolute difference in mortality associated with medical cannabis laws in 2010, we calculated the expected number of opioid analgesic overdose deaths in medical cannabis states had laws not been present and subtracted the actual number of overdose deaths recorded.

In our second model, we allowed the effect of medical cannabis laws to vary depending on the time elapsed since enactment, because states may have experienced delays in patient registration, distribution of identification cards, and establishment of dispensaries, if applicable. Accordingly, we coded years with no law present as 0, but included separate coefficients to measure each year since implementation of the medical cannabis law for states that adopted such laws. States that implemented medical cannabis laws before the study period were coded similarly (eg, in 1999, California was coded as 3 because the law was implemented in 1996). This model provides separate estimates for 1 year after implementation, 2 years after implementation, and so forth.

Each model adjusted for state and year (fixed effects). We also included 4 time-varying state-level factors: (1) the presence of a state-level prescription drug monitoring program (a state-level registry containing information on controlled substances prescribed in a state),[16] (2) the presence of a law requiring or allowing a pharmacist to request patient identification before dispensing medications,[17] (3) the presence of regulations establishing increased state oversight of pain management clinics,[18] and (4) state- and year-specific unemployment rates to adjust for the economic climate.[19] Colinearity among independent variables was assessed by examining variance inflation factors; no evidence of colinearity was found. For all models, robust standard errors were calculated using procedures to account for correlation within states over time.

To assess the robustness of our results, we performed several further analyses. First, we excluded intentional opioid analgesic overdose deaths from the age-adjusted overdose mortality rate to focus exclusively on nonsuicide deaths. Second, because heroin and prescription opioid use are interrelated for some individuals,[20-23] we included overdose deaths related to heroin, even if no opioid analgesic was coded. Third, we assessed the robustness of our findings to the inclusion of state-specific linear time trends that can be used to adjust for differential factors that changed linearly over the study period (eg, hard-to-measure attitudes or cultural changes). Fourth, we tested whether trends in opioid analgesic overdose mortality

Figure 1. Mean Age-Adjusted Opioid Analgesic Overdose Death Rate



States with medical cannabis laws compared with states without such laws in the United States, 1999-2010.

Table. Association Between Medical Cannabis Laws and State-Level Opioid Analgesic Overdose Mortality Rates in the United States, 1999-2010

Independent Variable[a]	Percentage Difference in Age-Adjusted Opioid Analgesic Overdose Mortality in States With vs Without a Law: Primary Analysis, Estimate (95% CI)[b]	Secondary Analyses, Estimate (95% CI)[c]	Secondary Analyses, Estimate (95% CI)[d]
Medical cannabis law	−24.8 (−37.5 to −9.5)[e]	−31.0 (−42.2 to −17.6)[f]	−23.1 (−37.1 to −5.9)[e]
Prescription drug monitoring program	3.7 (−12.7 to 23.3)	3.5 (−13.4 to 23.7)	7.7 (−11.0 to 30.3)
Law requiring or allowing pharmacists to request patient identification	5.0 (−10.4 to 23.1)	4.1 (−11.4 to 22.5)	2.3 (−15.4 to 23.7)
Increased state oversight of pain management clinics	−7.6 (−19.1 to 5.6)	−11.7 (−20.7 to −1.7)[e]	−3.9 (−21.7 to 18.0)
Annual state unemployment rate[g]	4.4 (−0.3 to 9.3)	5.2 (0.1 to 10.6)[e]	2.5 (−2.3 to 7.5)

[a] All models adjusted for state and year (fixed effects).

[b] R^2 = 0.876.

[c] All intentional (suicide) overdose deaths were excluded from the dependent variable; opioid analgesic overdose mortality is therefore deaths that are unintentional or of undetermined intent. All covariates were the same as in the primary analysis; R^2 = 0.873.

[d] Findings include all heroin overdose deaths, even if no opioid analgesic was involved. All covariates were the same as in the primary analysis. R^2 = 0.842.

[e] $P \leq .05$.

[f] $P \leq .001$.

[g] An association was calculated for a 1-percentage-point increase in the state unemployment rate.

predated the implementation of medical cannabis laws by including indicator variables in a separate regression model for the 2 years before the passage of the law.[24] Finally, to test the specificity of any association found between medical cannabis laws and opioid analgesic overdose mortality, we examined the association between state medical cannabis laws and age-adjusted death rates of other medical conditions without strong links to cannabis use: heart disease (*ICD-10* codes I00-I09, I11, I13, and I20-I51)[25] and septicemia (A40-A41). All analyses were performed using SAS, version 9.3 (SAS Institute Inc).

Results

The mean age-adjusted opioid analgesic overdose mortality rate increased in states with and without medical cannabis laws during the study period (**Figure 1**). Throughout the study period, states with medical cannabis laws had a higher opioid analgesic overdose mortality rate and the rates rose for both groups; however, between 2009 and 2010 the rate in states with medical cannabis laws appeared to plateau.

In the adjusted model, medical cannabis laws were associated with a mean 24.8% lower annual rate of opioid analgesic overdose deaths (95% CI, −37.5% to −9.5%; *P* = .003) (**Table**), compared with states without laws. In 2010, this translated to an estimated 1729 (95% CI, 549 to 3151) fewer deaths than expected. Medical cannabis laws were associated with lower rates of opioid analgesic overdose mortality, which generally strengthened in the years after passage (**Figure 2**): year 1 (−19.9%; 95% CI, −30.6% to −7.7%; *P* = .002), year 2 (−25.2%; 95% CI, −40.6% to −5.9%; *P* = .01), year 3 (−23.6%; 95% CI, −41.1% to −1.0%; *P* = .04), year 4 (−20.2%; 95% CI, −33.6% to −4.0%; *P* = .02), year 5 (−33.7%; 95% CI, −50.9% to −10.4%; *P* = .008), and year 6 (−33.3%; 95% CI, −44.7% to −19.6%; *P* < .001). The other opioid analgesic policies, as well as state unemployment rates, were not significantly associated with opioid analgesic mortality rates.

In additional analyses, the association between medical cannabis laws and opioid analgesic mortality rates was similar after excluding intentional deaths (ie, suicide) and when including all heroin overdose deaths, even if an opioid analgesic was not involved (Table). Including state-specific linear time trends in the model resulted in a borderline significant association between laws and opioid analgesic overdose mortality (−17.9%; 95% CI, −32.7% to 0.3%; $P = .054$). When examining the years prior to law implementation, we did not find an association between medical cannabis laws and opioid analgesic overdose mortality 2 years prior to law implementation (−13.1%; 95% CI, −45.5% to 38.6%; $P = .56$) or 1 year prior (1.2%; 95% CI, −41.2% to 74.0%; $P = .97$). Finally, we did not find significant associations between medical cannabis laws and mortality associated with heart disease (1.4%; 95% CI, −0.2% to 2.9%; $P = .09$) or septicemia (−1.8%; 95% CI, −7.6% to 4.3%; $P = .55$).

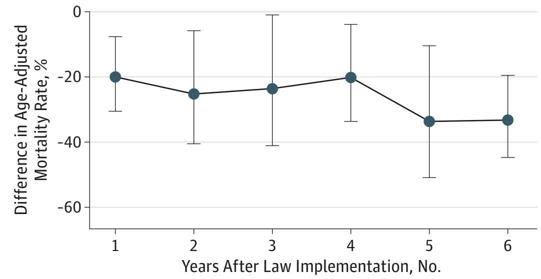
Discussion

In an analysis of death certificate data from 1999 to 2010, we found that states with medical cannabis laws had lower mean opioid analgesic overdose mortality rates compared with states without such laws. This finding persisted when excluding intentional overdose deaths (ie, suicide), suggesting that medical cannabis laws are associated with lower opioid analgesic overdose mortality among individuals using opioid analgesics for medical indications. Similarly, the association between medical cannabis laws and lower opioid analgesic overdose mortality rates persisted when including all deaths related to heroin, even if no opioid analgesic was present, indicating that lower rates of opioid analgesic overdose mortality were not offset by higher rates of heroin overdose mortality. Although the exact mechanism is unclear, our results suggest a link between medical cannabis laws and lower opioid analgesic overdose mortality.

Approximately 60% of all opioid analgesic overdoses occur among patients who have legitimate prescriptions from a single provider.[26] This group may be sensitive to medical cannabis laws; patients with chronic noncancer pain who would have otherwise initiated opioid analgesics may choose medical cannabis instead. Although evidence for the analgesic properties of cannabis is limited, it may provide analgesia for some individuals.[27,28] In addition, patients already receiving opioid analgesics who start medical cannabis treatment may experience improved analgesia and decrease their opioid dose,[29,30] thus potentially decreasing their dose-dependent risk of overdose.[31,32] Finally, if medical cannabis laws lead to decreases in polypharmacy—particularly with benzodiazepines—in people taking opioid analgesics, overdose risk would be decreased. Further analyses examining the association between medical cannabis laws and patterns of opioid analgesic use and polypharmacy in the population as a whole and across different groups are needed.

A connection between medical cannabis laws and opioid analgesic overdose mortality among individuals who misuse or abuse opioids is less clear. Previous laboratory work has shown that cannabinoids act at least in part through an opioid receptor mechanism[33,34] and that they increase dopamine concentrations in the nucleus accumbens in a fashion similar to that of heroin and several other drugs with abuse potential.[33,35] Clinically, cannabis use is associated with modest reductions in opioid withdrawal symptoms for some people,[36,37] and therefore may reduce opioid use. In contrast, cannabis use has been linked with increased use of other drugs, including opioids[14,38-40]; however, a causal relationship has not been established.[14,41] Increased access to cannabis through medical cannabis laws could influence opioid misuse in either direction, and further study is required.

Figure 2. Association Between Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in Each Year After Implementation of Laws in the United States, 1999-2010



Point estimate of the mean difference in the opioid analgesic overdose mortality rate in states with medical cannabis laws compared with states without such laws; whiskers indicate 95% CIs.

Although the mean annual opioid analgesic overdose mortality rate was lower in states with medical cannabis laws compared with states without such laws, the findings of our secondary analyses deserve further consideration. State-specific characteristics, such as trends in attitudes or health behaviors, may explain variation in medical cannabis laws and opioid analgesic overdose mortality, and we found some evidence that differences in these characteristics contributed to our findings. When including state-specific linear time trends in regression models, which are used to adjust for hard-to-measure confounders that change over time, the association between laws and opioid analgesic overdose mortality weakened. In contrast, we did not find evidence that states that passed medical cannabis laws had different overdose mortality rates in years prior to law passage, providing a temporal link between laws and changes in opioid analgesic overdose mortality. In addition, we did not find evidence that laws were associated with differences in mortality rates for unrelated conditions (heart disease and septicemia), suggesting that differences in opioid analgesic overdose mortality cannot be explained by broader changes in health. In summary, although we found a lower mean annual rate of opioid analgesic mortality in states with medical cannabis laws, a direct causal link cannot be established.

This study has several limitations. First, this analysis is ecologic and cannot adjust for characteristics of individuals within the states, such as socioeconomic status, race/ethnicity, or medical and psychiatric diagnoses. Although we found that the association between medical cannabis laws and lower opioid overdose mortality strengthened in the years after implementation, this could represent heterogeneity between states that passed laws earlier in the study period vs those that passed the laws later. Second, death certificate data may not correctly classify cases of opioid analgesic overdose deaths, and reporting of opioid analgesics on death certificates may differ among states; misclassification could bias our results in either direction. Third, although fixed-effects models can adjust for time-invariant characteristics of each state and state-invariant time effects, there may be important time- and state-varying confounders not included in our models. Finally, our findings apply to states that passed medical cannabis laws during the study period and the association between future laws and opioid analgesic overdose mortality may differ.

Conclusions

Although the present study provides evidence that medical cannabis laws are associated with reductions in opioid analgesic overdose mortality on a population level, proposed mechanisms for this association are speculative and rely on indirect evidence. Further rigorous evaluation of medical cannabis policies, including provisions that vary among states,[14,42] is required before their wide adoption can be recommended. If the relationship between medical cannabis laws and opioid analgesic overdose mortality is substantiated in further work, enactment of laws to allow for use of medical cannabis may be advocated as part of a comprehensive package of policies to reduce the population risk of opioid analgesics.

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Drafting of the manuscript: Bachhuber, Saloner.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Bachhuber, Saloner, Barry.
Study supervision: Cunningham, Barry.

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Correction: This article was corrected on August 27, 2014, to fix a typographical error in Figure 1 and on September 10, 2014, to fix an incorrect term in the Discussion.

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Invited Commentary

Legalization of Medical Marijuana and Incidence of Opioid Mortality

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The rapid acceleration of prescription opioid–related overdose deaths in the United States is correlated with the availability of stronger opioid medications, as well as a change in medical practice from withholding opioid medication because of dependence risk[1] to treating patients with chronic pain with opioids. Subsequently, the pendulum of concern has swung again, driven by the public health crisis of rising opioid analgesic addiction, overdose, and death. Opioid medications are problematic as a treatment for chronic pain. Opioid pharmaceuticals cause other adverse effects when used for long periods, such as tolerance, hyperalgesia, and gastrointestinal complications, making this class of drugs a poor choice for long-term use. As is well known, prescription opioids also have great abuse potential due to their influence on stress and reward circuits in the brain, promoting nonmedical use and abuse and diversion of prescription medications.

In this issue, Bachhuber et al[2] examine the link between medical marijuana laws and unintentional overdose mortality in which an opioid analgesic was identified. Using Centers for Disease Control and Prevention data, states with and without medical marijuana laws were contrasted for age-adjusted, opioid-related mortality. Overall, the incidence of opioid analgesic–associated mortality rose dramatically across the study period (1999-2010). States with medical marijuana laws had higher overdose rates than did those without such laws when population-adjusted mortality was analyzed across years, although the rise in deaths over the study period was similar for both groups. In contrast, a convincing protective effect of medical marijuana laws was found in a covariate-adjusted, time-series model in which opioid analgesic mortality declined steadily based on years since medical marijuana laws were enacted, termed *implementation*. The model included an analysis of the impact of critical policies for prescription opioid regulatory efforts: prescription monitoring programs, pharmacist collection of patient information, state and oversight of pain management clinics, as well as state unemployment rates. In states with medical marijuana laws, age-adjusted overdose deaths in which opioids were present declined in yearly estimates since medical marijuana law implementation. Indeed, across the 13 states that approved medical marijuana laws in the study period, the decline in opioid overdose mortality strengthened over time, achieving a mean decline of 24.8%. Worthy of note, a weak contribution was found for state oversight policies such as prescription monitoring and pain management clinics; this finding has been reported previously.[3] The striking implication is that medical marijuana laws, when implemented, may represent a promising approach for stemming runaway rates of nonintentional opioid analgesic–related deaths. If true, this finding upsets the applecart of conventional wisdom regarding the public health implications of marijuana legalization and medicinal usefulness.

The difficulty in endorsing the medical marijuana protective hypothesis is that medical marijuana laws are heterogeneous across states, engender controversy in state legisla-