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Medical cannabis legalization and opioid prescriptions: evidence on US Medicaid enrollees during 1993–2014

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Abstract

Background and Aims—While the United States has been experiencing an opioid epidemic, 29 states and Washington DC have legalized cannabis for medical use. This study examined whether state-wide medical cannabis legalization was associated with reduction in opioids received by Medicaid enrollees.

Design—Secondary data analysis of state-level opioid prescription records from 1993–2014 Medicaid State Drug Utilization Data. Linear time–series regressions assessed the associations between medical cannabis legalization and opioid prescriptions, controlling for state-level time-varying policy covariates (such as prescription drug monitoring programs) and socio-economic covariates (such as income).

Setting—United States.

Participants—Drug prescription records for patients enrolled in fee-for-service Medicaid programs that primarily provide health-care coverage to low-income and disabled people.

Measurements—The primary outcomes were population-adjusted number, dosage and Medicaid spending on opioid prescriptions. Outcomes for Schedule II opioids (e.g. hydrocodone, oxycodone) and Schedule III opioids (e.g. codeine) were analyzed separately. The primary policy variable of interest was the implementation of state-wide medical cannabis legalization.

Findings—For Schedule III opioid prescriptions, medical cannabis legalization was associated with a 29.6% ($P = 0.03$) reduction in number of prescriptions, 29.9% ($P = 0.02$) reduction in dosage and 28.8% ($P = 0.04$) reduction in related Medicaid spending. No evidence was found to support the associations between medical cannabis legalization and Schedule II opioid prescriptions. Permitting medical cannabis dispensaries was not associated with Schedule II or Schedule III opioid prescriptions after controlling for medical cannabis legalization. It was

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Declaration of interests

None.

estimated that, if all the states had legalized medical cannabis by 2014, Medicaid annual spending on opioid prescriptions would be reduced by 17.8 million dollars.

Conclusion—State-wide medical cannabis legalization appears to have been associated with reductions in both prescriptions and dosages of Schedule III (but not Schedule II) opioids received by Medicaid enrollees in the United States.

Keywords

Cannabis; legalization; medicaid; medical cannabis; opioid; opioid prescription; Prescription Drug Monitoring Program

INTRODUCTION

The opioid epidemic is a global problem faced by many European, North American and Oceania countries. In 2016, opioid addiction accounted for more than 55% of years of life lost due to premature death caused by drug abuse [1]. The opioid epidemic in the United States is particularly alarming. It was declared a 'National Public Health Emergency' in October 2017 [2,3]. The number of opioid prescriptions quadrupled from 76 million to 207 million during 1991–2013 [4]. There was also a parallel escalation in opioid-related mortality rates, hospitalizations and emergency department visits [5,6]. It was estimated that opioid abuse and overdose imposed 56 billion dollars of annual costs to US society [7].

Paralleling the opioid epidemic, there was a rapid expansion of medical cannabis legalization in the United States and other countries globally. Since 1996, 29 states and Washington DC in the United States have legalized cannabis for medical use at state level. Country-wide medical cannabis legalization was adopted in Australia, Colombia, Czech Republic, Canada, Uruguay and several other countries. A large body of work examined the impacts of medical cannabis legalization on cannabis-related public health outcomes in the United States, such as cannabis-related perceptions and attitudes, illicit cannabis use, cannabis dependence and abuse, traffic fatalities and health-care utilization, but there is a lack of consistent evidence supporting the associations [8,9]. The spillover effects of medical cannabis legalization on other drug use has received much less attention.

There is increasing evidence that cannabis has therapeutic effects on pain. Its effectiveness was suggested by systematic reviews of randomized controlled trials [10–14] and the US National Academies 2017 report [15]. In the United States, where medical cannabis is legal, pain is one of the most commonly approved conditions for patients to request cannabis [16]. Recent research hypothesized that patients may substitute cannabis for pain medications in these states and opioid prescriptions may be impacted as a result [16–21]. These studies reported emerging evidence in the United States that medical cannabis legalization was associated with considerable reductions in opioid-related outcomes [16–21]. In particular, two studies utilized administrative records of Medicare and Medicaid enrollees to examine the impacts on drug prescriptions [16,18]. In the United States, Medicare is a federal health insurance program primarily covering senior people aged 65 years or older, and Medicaid is a joint federal and state program primarily covering people with low income or disabilities. Using Medicare prescription records from 2010 to 2013, in 2016 Bradford & Bradford

found that state-wide implementation of medical cannabis legalization was associated with reductions in prescriptions of most drug classes for which cannabis could serve as substitutes, including pain medications [18]. In 2017, Bradford & Bradford provided similar evidence using Medicaid prescription records from 2007 to 2014 [16]. Despite the comprehensive evaluations in these two studies, they categorized pain medications broadly, including not only opioid and non-opioid analgesics but also drugs used primarily to treat other conditions[1] [16,18]. The specific associations of medical cannabis legalization with opioid prescriptions are unknown.

We investigated state-level aggregate prescription drug records from 1993 to 2014, covering almost all years of state-wide legislative activities in medical cannabis legalization in the United States. We tested the hypothesis that legalizing medical cannabis was associated with reductions in opioids received by Medicaid enrollees, a priority group with an excessive burden of chronic pain and high risks for opioid misuse and overdose [22,23]. We explored the heterogeneity in policy responses by drug schedules. Potential impacts on Medicaid spending were also estimated.

METHODS

Data

This is a secondary data analysis of state-level opioid prescriptions in the United States. The primary data were obtained from 1993–2014 Medicaid State Drug Utilization Data published by the US Centers for Medicare and Medicaid Services (CMS) [24]. The data included quarterly records of out-patient drugs reimbursed by each state's Medicaid program, excluding drugs dispensed in emergency departments or in-patient settings and those paid with cash [24]. Because states' reporting to CMS is required in the Medicaid Drug Rebate Program, the prescription drug records were almost complete in each state and quarter [24]. The 1993–2014 data included 61 million drug records in total.

Study population

The study was restricted to records for Medicaid enrollees who enrolled in fee-for-service programs during 1993–2014. Records for patients enrolled in managed care Medicaid programs were excluded because states' regular reporting on managed care programs did not start until 2010. In the United States, Medicaid covered services are paid directly by the state under the fee-for-service model, whereas the state pays managed care organizations on a per capita basis and the managed care organizations pay providers for all Medicaid-covered services under the managed care model. The Medicaid managed care penetration rate has risen from less than 50% in the 1990s to more than 70% in the 2010s [25]. We excluded the most recent data after 2014, because fee-for-service enrollees for those years were not published at the time of this study.

[1]These drugs included antimalarial agents, anti-convulsants, anti-emetic/anti-vertigo agents, muscle relaxants, adrenal cortical steroids, respiratory inhalant products, anti-rheumatics, antidepressants and functional bowel disorder agents.

Measures

Outcome measures—The three primary outcomes were the number of filled opioid prescriptions (including both new prescriptions and refills), dosage of filled opioid prescriptions [in oral morphine milligram equivalents (MME)] [26] and Medicaid spending on opioid prescriptions (in 2014 US dollars). All outcomes were population-adjusted to values per quarter per 100 Medicaid enrollees [27]. The number of Medicaid enrollees in fee-for-service programs in each state was obtained from yearly Medicaid Managed Care Enrollment Reports [25]. To identify opioid prescriptions, the National Drug Code numbers from Medicaid State Drug Utilization Data were linked with drug information [26] in the Approved Drug Products with Therapeutic Equivalence Evaluations published by the US Food and Drug Administration (FDA) [28]. Following previous research [29], we excluded buprenorphine drugs used commonly to treat opioid use disorder (e.g. Suboxone®, Subutex®) and included those prescribed generally for pain management (e.g. Butrans®, Belbuca®). Methadone was included because it was prescribed typically for pain management in our data source. Nominal Medicaid spending was inflation-adjusted to 2014 constant US dollars [27]. Schedule II and Schedule III opioids were identified based on the current classifications by the US Drug Enforcement Agency and analyzed respectively [30]. Following previous research [26,27], hydrocodone-combination drugs such as Vicodin and Lortab were classified as Schedule II opioids in this study to reflect the recent reclassification of these drugs from Schedule III to Schedule II [31]. In our analyses, Schedule II opioids accounted for 94.5% of all opioid prescriptions in 2014. The top Schedule II opioids were those containing hydrocodone and oxycodone (48 and 27% of all Schedule II opioids, respectively); the top Schedule III opioids were those containing codeine (99% of all Schedule III opioids). According to classifications by the Single Convention on Narcotic Drugs, US-standard Schedule II opioids are mainly Schedule I drugs in other countries and US-standard Schedule III opioids are Schedules II or III drugs in other countries [32]. More detailed information about US drug schedules can be found in Supporting information, Technical note S1.

Cannabis policy measures—The primary policy variable of interest was the presence of state-wide medical cannabis legalization. The dichotomous policy indicator took the value of 1 if the state had medical cannabis legalization in effect in that quarter and 0 otherwise. During the study period, 23 states and Washington DC implemented medical cannabis legalization. The models also controlled for two additional cannabis-related dichotomous policy indicators: the presence of cannabis decriminalization, under which cannabis use is no longer a criminal offense, and the presence of recreational cannabis legalization, under which the production, sale and consumption of cannabis for recreational purpose is legal. During the study period, two states (Colorado and Washington) had recreational cannabis legalization in effect. Because permitting medical cannabis dispensaries is the major provision that increases direct access to cannabis [33], we also considered a dichotomous indicator for the presence of any active medical cannabis dispensary. During the study period, 14 states and Washington DC opened their first medical cannabis dispensaries. The effective dates of these policies were obtained from various sources of legal and policy reviews [34–38] (Supporting information, Table S1).

Other state-level covariates—The models also controlled for state-level policy and socioeconomic covariates, including a dichotomous indicator for the presence of the Prescription Drug Monitoring Program that provides a state-wide electronic database to track controlled substances, a dichotomous indicator for the implementation of Medicaid expansion under the Affordable Care Act that expanded Medicaid coverage to all adults with income up to 138% of the federal poverty level, median household income in 2014 constant dollars, the number of active physicians per 1000 population, the percentage of residents with household income below the federal poverty level and unemployment rate [39–41] (see details in Supporting information, Technical note S2).

Statistical analyses

The data were aggregated and analyzed at state-quarter level. The final state-quarter observations were approximately 4100 for both Schedule II and Schedule III opioids analysis. The descriptive statistics were provided to compare the 23 states and Washington DC that implemented medical cannabis legalization[2] and the 27 states that had not implemented the legalization[3] during the study period. Two sets of linear time–series regressions (models 1 and 2) were used to assess the associations of implementing medical cannabis legalization with the three opioid prescription outcomes, which were log-transformed to obtain normal distributions [16]. The coefficient of the dichotomous indicator of medical cannabis legalization can be interpreted as the average percentage change in the outcome associated with legalization implementation. Specifically, model 1 examined the implementation of medical cannabis legalization, controlling for state-level time-varying cannabis policies and other policy and socio-economic covariates. To assess the additional effects of permitting medical cannabis dispensaries after controlling for medical cannabis legalization, model 2 further included the presence of any active medical dispensaries. Both models also included the following regressors: state indicators to control for unobserved time-invariant state-level fixed effects such as political preferences; year and quarter indicators to control for national-level shocks applying to all the states at the same time such as the 2006 introduction of Medicare Part D, a federal program to subsidize costs and insurance premiums of prescription drugs for Medicare enrollees; and state-specific linear time trends to control for state-level trends in outcomes. Because Medicaid saw a sharp decline in prescriptions filled by Medicare and Medicaid dually eligible enrollees after 2006 when Medicare Part D covered most of their prescriptions, we allowed separate state-specific time trends before and after 2006. The standard errors in the regressions were clustered at the state level. Detailed information about model specifications can be found in Supporting information, Technical note S2. A few state-quarter pairs were excluded where the outcome variables had obvious data errors (Supporting information, Technical note S3).

To test the robustness of the results, we replaced the dates of implementing medical cannabis legalization with law-passing dates. We added back data outliers to the regressions.

[2]These 23 states included Alaska, Arizona, California, Colorado, Connecticut, Delaware, Hawaii, Illinois, Maine, Maryland, Massachusetts, Michigan, Minnesota, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, Oregon, Rhode Island, Vermont and Washington.

[3]These 27 states included Alabama, Arkansas, Florida, Georgia, Idaho, Indiana, Iowa, Kansas, Kentucky, Louisiana, Mississippi, Missouri, Nebraska, North Carolina, North Dakota, Ohio, Oklahoma, Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Utah, Virginia, West Virginia, Wisconsin and Wyoming.

Following Bradford & Bradford [16,18], we conducted falsification tests on the four classes of drugs used to treat conditions for which cannabis had no proven beneficial (or harmful) effects.[4]

To estimate the potential Medicaid cost savings associated with medical cannabis legalization, we calculated the statistically significant changes in Medicaid spending from regressions, then multiplied the annualized changes with the number of fee-for-service enrollees in states that had implemented medical cannabis legalization by the end of 2014. To project nation-wide cost savings, we extrapolated the estimates to all the 50 states and Washington DC, assuming that they all had implemented legalization by 2014. The cost savings were allocated to the federal government and state governments based on Federal Medical Assistance Percentages in 2014 [42]. Cost savings for enrollees in managed care programs were not included in the estimation.

RESULTS

Descriptive statistics

Unadjusted descriptive outcomes for opioid prescriptions per quarter per 100 Medicaid enrollees are presented in Table 1 and Fig. 1. In terms of the average rates during the 21-year study period, the rates of Schedule II opioids were higher compared to Schedule III opioids and the rates of opioids in states without cannabis legalization were higher compared to those that did adopt cannabis legalization. For Schedule II opioids, there was a downward trend over time in states that did not adopt cannabis legalization and a slight upward trend for states with legalization. For Schedule III opioids, these trends were reversed; sates without legalization had an upward trend while states with legalization showed a slight downward trend.

Regression results

Table 2 shows regression results for Schedule II opioids (full results shown in Supporting information, Table S2). In model 1, no associations were found between medical cannabis legalization and number of prescriptions, dosage or Medicaid spending on Schedule II opioids. Model 2 reported further that permitting medical cannabis dispensaries was not associated with Schedule II opioid outcomes after controlling for medical cannabis legalization.

Table 3 shows regression results for Schedule III opioids (full results shown in Supporting information, Table S3). Model 1 reported that implementing medical cannabis legalization was associated with a 29.6% (95% confidence interval: 2.4–56.7%; $P = 0.03$) reduction in number of prescriptions, a 29.9% (4.8–55.0%; $P = 0.02$) reduction in dosage of prescriptions and a 28.8% (1.4–56.1%; $P = 0.04$) reduction in Medicaid spending related to Schedule III opioid prescriptions. Model 2 reported further that permitting dispensaries was not associated with Schedule III opioid prescriptions after controlling for medical cannabis legalization.

[4]These drug classes were blood-thinning agents, phosphorous-stimulating agents for patients with end-stage renal disease and anti-virals used to treat influenza and antibiotics.

Cannabis decriminalization, recreational cannabis legalization, and Prescription Drug Monitoring Programs were not associated with either Schedule II or Schedule III opioid prescriptions. State Medicaid expansion was associated with increased Schedule II and Schedule III opioid prescriptions by 30–45%, depending on model specifications.

Figure 2 presents the estimated Medicaid cost savings for fee-for-service enrollees associated with medical cannabis legalization based on model 1 results (details are illustrated in Supporting information, Table S4). It was estimated that, in states that had implemented medical cannabis legalization by 2014, Medicaid annual spending on opioids would be reduced by 7.46 million dollars for the federal government and 6.54 million dollars for state governments. Assuming that all the 50 states and Washington DC in the United States had implemented medical cannabis legalization by 2014 would yield cost savings of 10.03 million dollars for the federal government and 7.78 million dollars for state governments (17.8 million in total).

Sensitivity analysis results

The significant results reported above remained significant in the regressions replacing implementation dates of legalization with law-passing dates (Supporting information, Table S5) and in the regressions adding outliers back (Supporting information, Table S6). In the falsification tests (Supporting information, Table S7), no associations were found between medical cannabis legalization and the number of prescriptions in any of the four drug classes.

DISCUSSION

The findings of this study added to the still limited literature [16–21], supporting the hypothesis that state-wide medical cannabis legalization in the United States was associated with reduced opioids received by Medicaid enrollees. Compared to Bradford & Bradford [16], this study focused specifically on opioid prescriptions and explored the heterogeneity in policy responses by drug classes. The long time-span (1993–2014) included early legalization period in the late 1990s and the early 2000s. Thus, estimates of this study represented the overall policy associations with opioids in both early and late policy adopters.

Our results suggested that medical cannabis legalization was associated with nearly 30% reductions in Schedule III opioids, within the range of estimates in previous research [16–21]. Nonetheless, there was no evidence supporting legalization's association with Schedule II opioids, which constituted approximately 95% of all opioid prescriptions in the data. With the absence of individual-level information, we were not able to explore the mechanisms underlying the differential associations. Here, we provided tentative explanations for discussions. In the United States, Schedule III opioids are used typically to treat mild to moderate pain and refillable within 6 months without new prescriptions [43]. In contrast, Schedule II opioids must be refilled with new monthly prescriptions because of their higher potential of dependence and abuse, such that patients prescribed Schedule II opioids are required to receive regular monitoring and evaluations from physicians. In addition, evidence suggested that cannabis provides mild to moderate relief from pain, on par with

codeine [15], making cannabis a better alternative to Schedule III opioids. Although there is emerging evidence suggesting that cannabis is effective in treating severe pain [44–48], no studies compared the analgesic efficacy of the cannabinoids with Schedule II opioids. Due to the concern of cannabis' lack of efficacy on severe pain symptoms, patients prescribed Schedule II opioids might be less likely to switch to medical cannabis and physicians might be less likely to recommend medical cannabis to these patients.

Consistent with previous research [20,21], we found no evidence that permitting medical cannabis dispensaries had association with opioid prescriptions after controlling for medical cannabis legalization. One plausible explanation is the co-occurrence of the two policy variables. Of the 23 states and Washington DC, that legalized medical cannabis during the study period, 14 states and Washington DC had active dispensaries and most of these states opened their first dispensaries within 3 years of legalization. The lack of additional variations in policy adoption and timing may have made it challenging to discern statistically the effects of dispensaries independent of the legalization. An alternative explanation is that patients were responsive to the change in the legal status of medical cannabis use but less so to the increased access to cannabis provided in the dispensaries. This hypothesis is unfortunately not testable in the aggregate analyses of this study.

It is worth noting that despite the significant associations with Schedule III opioid prescriptions, medical cannabis legalization had limited implications about Medicaid spending on opioids. This is largely because Schedule III opioids, mostly codeine, only accounted for less than 5% of Medicaid spending on opioid prescriptions. Even if we extrapolated the estimated savings for fee-for-service enrollees to managed care program enrollees, the total annual savings combined would be only $34 million, a modest portion in the total Medicaid spending of $497 million in 2014 [49]. This number would be even smaller if patients' out-of-pocket costs to pay cannabis were considered negative welfare transfer.

Our data did not find a significant association between Prescription Drug Monitoring Programs and opioid prescriptions. This is likely because mandates, enforcement and awareness in early adopters were generally weak [27]. The non-significant findings were also reported in some previous studies [50–52], but not all [53,54]. The research using most recent data sources, however, consistently suggested the program effectiveness in states that adopted best practices [27,53–57].

The study has limitations. First, the findings suggested associations but not causality. Even after we controlled for a rich set of state-level time varying covariates, state and time fixed effects and state-specific time trends, some important differences between states with different legalization status may not be captured successfully [58].

Secondly, we relied upon aggregate state-level records. Despite the common application in studies of this kind [5,8,17,23,27,52], aggregate data are subject to ecological fallacy, as pointed out by Hall *et al.* [58]. Without direct observations on individual physician or patient behaviors, inferences cannot be made regarding whether and how individual behaviors

responded to policy changes. In particular, the hypothesis that patients substituted medical cannabis for opioid prescriptions cannot be tested explicitly.

Thirdly, following Bradford & Bradford [16], we focused on fee-for-service Medicaid enrollees and excluded patients enrolled in managed care programs, which constituted the majority (70% or more) of Medicaid enrollees. It is unknown whether our findings would generalize to managed care enrollees. Note, however, that Medicaid cost savings associated with medical cannabis legalization would be underestimated if our results are applicable to that population.

Lastly, the findings may not be generalizable to opioids dispensed in emergency departments or in-patient settings, to Medicaid enrollees in managed care programs or to the general population in the United States. They may not be generalizable to other countries facing similar challenges from opioid epidemic or cannabis legalization, given the differences in drug schedules, prescribing and drug use behaviors, social norms and legal and policy contexts. In particular, the significant results on US-standard Schedule III opioids, most of which were codeine, may not be replicated in countries where codeine was classified into other drug schedules or not commonly used. Furthermore, cannabis for recreational use may be associated with an increased risk of opioid misuse and opioid use disorder [59], and the findings of this study may be altered after recreational cannabis was legalized.

CONCLUSION

In this study, we found that state-wide medical cannabis legalization implemented in 1993–2014 in the United States was associated with close to 30% reductions in Schedule III opioids received by Medicaid enrollees. The legalization was not associated with changes in Schedule II opioids, resulting in modest overall savings of Medicaid spending. Future research is warranted to utilize individual-level data to understand the causal mechanisms of the findings and replicate the analysis in other countries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Nations United. World Drug Report 2016. Vienna, Austria: United Nations Office on Drugs and Crime; 2017.
2. Drash W, Merica D Trump: ‘The opioid crisis is an emergency’. Available at: http://www.cnn.com/2017/08/10/health/trump-opioid-emergency-declaration-bn/index.html (accessed 30 April 2018) (Archived at http://www.webcitation.org/6z4oJknn0).

3. Merica D Trump declares opioid epidemic a national public health emergency. Available at: http://www.cnn.com/2017/10/26/politics/donald-trump-opioid-epidemic/index.html (accessed 30 April 2018) (Archived at http://www.webcitation.org/6z4ym1Ii7).
4. Volkow ND America's Addiction to Opioids: Heroin and Prescription Drug Abuse. Available at: https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse (accessed 30 April 2018) (Archived at http://www.webcitation.org/6z4z3Hqvt).
5. Warner M, Hedegaard H, Chen LH Trends in drug-poisoning deaths involving opioid analgesics and heroin: United States, 1999–2012 NCHS Health E-Stat. Atlanta, GA: Centers for Disease Control and Prevention; 2014.
6. Substance Abuse and Mental Health Services Administration (SAMHSA). Drug Abuse Warning Network, 2011 National Estimates of Drug-Related Emergency Department Visits. Rockville, MD: SAMHSA; 2013.
7. Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL Societal costs of prescription opioid abuse, dependence, and misuse in the United States. Pain Med (Malden, MA) 2011; 12: 657–67.
8. Sznitman SR, Zolotov Y Cannabis for therapeutic purposes and public health and safety: a systematic and critical review. Int J Drug Policy 2015; 26: 20–9. [PubMed: 25304050]
9. Sarvet AL, Wall MM, Fink DS, Greene E, Le A, Boustead AE et al. Medical marijuana laws and adolescent marijuana use in the United States: a systematic review and meta-analysis. Addiction 2018; 113: 1003–16. [PubMed: 29468763]
10. Hill KP Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. JAMA 2015; 313: 2474–83. [PubMed: 26103031]
11. Lynch ME, Campbell F Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. Br J Clin Pharmacol 2011; 72: 735–44. [PubMed: 21426373]
12. Lynch ME, Ware MA Cannabinoids for the treatment of chronic non-cancer pain: an updated systematic review of randomized controlled trials. J Neuroimmune Pharmacol 2015; 10: 293–301. [PubMed: 25796592]
13. Martin-Sanchez E, Furukawa TA, Taylor J, Martin JL Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med (Malden, MA) 2009; 10: 1353–68.
14. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA 2015; 313: 2456–73. [PubMed: 26103030]
15. National Academies of Sciences, Engineering and Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington, DC: National Academies Press; 2017.
16. Bradford AC, Bradford WD Medical marijuana laws may be associated with a decline in the number of prescriptions for Medicaid enrollees. Health Affairs (Project Hope) 2017; 36: 945–51. [PubMed: 28424215]
17. Bachhuber MA, Saloner B, Cunningham CO, Barry CL Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999–2010. JAMA Intern Med 2014; 174: 1668–73. [PubMed: 25154332]
18. Bradford AC, Bradford WD Medical marijuana laws reduce prescription medication use in Medicare Part D. Health Affairs (Project Hope) 2016; 35: 1230–6. [PubMed: 27385238]
19. Kim JH, Santaella-Tenorio J, Mauro C, Wrobel J, Cerda M, Keyes KM et al. State medical marijuana laws and the prevalence of opioids detected among fatally injured drivers. Am J Public Health 2016; 106: 2032–7. [PubMed: 27631755]
20. Powell D, Pacula RL, Jacobson M Do medical marijuana laws reduce addictions and deaths related to pain killers? J Health Econ 2018; 58: 29–42. [PubMed: 29408153]
21. Shi Y Medical marijuana policies and hospitalizations related to marijuana and opioid pain reliever. Drug Alcohol Depend 2017; 173: 144–50. [PubMed: 28259087]
22. Shmagel A, Foley R, Ibrahim H Epidemiology of chronic low back pain in US adults: data from the 2009–2010 National Health and Nutrition Examination Survey. Arthritis Care Res 2016; 68: 1688–94.

23. Mack KA, Zhang K, Paulozzi L, Jones C Prescription practices involving opioid analgesics among Americans with Medicaid, 2010. J Health Care Poor Underserved 2015; 26: 182–98. [PubMed: 25702736]
24. Centers for Medicare and Medicaid Services (CMS). Medicaid State Drug Utilization Data. Available at: https://www.medicaid.gov/medicaid/prescription-drugs/state-drug-utilization-data/index.html (accessed 30 April 2018) (Archived at http://www.webcitation.org/6z4zvK6PH).
25. Centers for Medicare and Medicaid Services (CMS). Medicaid Managed Care Enrollment Report. Washington, DC: Centers for Medicare and Medicaid Services; 2017.
26. Centers for Disease Control and Prevention (CDC). CDC Compilation of Benzodiazepines, Muscle Relaxants, Stimulants, Zolpidem, and Opioid Analgesics With Oral Morphine Milligram Equivalent Conversion Factors, 2016 version. Atlanta, GA: National Center for Injury Prevention and Control; 2016.
27. Wen H, Schackman BR, Aden B, Bao Y States with prescription drug monitoring mandates saw a reduction in opioids prescribed to Medicaid enrollees. Health Affairs (Project Hope) 2017; 36: 733–41. [PubMed: 28373340]
28. Food and Drug Administration (FDA). Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). Silver Spring, MD: FDA; 2017.
29. Volkow ND, Frieden TR, Hyde PS, Cha SS Medication-assisted therapies—tackling the opioid-overdose epidemic. New Engl J Med 2014; 370: 2063–6. [PubMed: 24758595]
30. Drug Enforcement Administration (DEA). Controlled Substance Schedules. Available at: https://www.deadiversion.usdoj.gov/schedules/ (accessed 30 April 2018) (Archived at http://www.webcitation.org/6z4zaaxMC).
31. Drug Enforcement Administration (DEA). Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products From Schedule III to Schedule II. Available at: https://www.deadiversion.usdoj.gov/fed_regs/rules/2014/fr0822.htm (accessed 30 April 2018) (Archived at http://www.webcitation.org/6z50K00G9).
32. United Nations Office on Drugs and Crime (UNODC). The International Drug Control Conventions. New York: UNODC; 2013.
33. Pacula RL, Powell D, Heaton P, Sevigny EL Assessing the effects of medical marijuana laws on marijuana use: the devil is in the details. J Policy Anal Manage 2015; 34: 7–31. [PubMed: 25558490]
34. ProCon.org. 29 Legal Medical Marijuana States and DC—Laws, Fees, and Possession Limits. Available at: https://medicalmarijuana.procon.org/view.resource.php?resourceID=000881 (accessed 30 April 2018) (Archived at http://www.webcitation.org/6z50b5lqY).
35. NORML.org. Marijuana Law Status in the United States. Available at: http://norml.org/states (accessed 30 April 2018) (Archived at http://www.webcitation.org/6z50ovy8d).
36. NCSL.org. Marijuana overview. National Conference of State Legalization. Available at: http://www.ncsl.org/research/civil-and-criminal-justice/marijuana-overview.aspx (accessed 30 April 2018) (Archived at http://www.webcitation.org/6z50uMi61).
37. Scott E Marijuana decriminalization. Available at: https://www.cga.ct.gov/2010/rpt/2010-R-0204.htm (accessed 30 April 2018) (Archived at http://www.webcitation.org/6z514RgS2).
38. MPP.org. Medical Marijuana Dent Program Implementation Timelines. Marijuana Policy Project; 2017 Available at: https://www.mpp.org/issues/medical-marijuana/state-by-state-medical-marijuana-laws/medical-marijuana-program-implementation-timeline/ (accessed 30 April 2018) (Archived at http://www.webcitation.org/6z51AX6oP).
39. KFF.org. Status of State Action on the Medicaid Expansion Decision. Henry J Kaiser Family Foundation. Available at: https://www.kff.org/health-reform/state-indicator/state-activity-around-expanding-medicaid-under-the-affordable-care-act (accessed 30 April 2018) (Archived at http://www.webcitation.org/6z51cP72W:).
40. Bureau of Labor Statistics (BLS). Local Area Unemployment Statistics. Available at: https://www.bls.gov/web/laus/laumstrk.htm (accessed 30 April 2018) (Archived at http://www.webcitation.org/6z51qzpRV).

41. Census. Historical Poverty Tables: People and Families—1959 to 2016. Available at: https://www.census.gov/data/tables/time-series/demo/income-poverty/historical-poverty-people.html (accessed 30 April 2018) (Archived at http://www.webcitation.org/6z51yO3Nm).
42. KFF.org. Federal Medical Assistance Percentage (FMAP) for Medicaid and Multiplier. Henry J Kaiser Family Foundation Available at: https://www.kff.org/medicaid/state-indicator/federal-matching-rate-and-multiplier (accessed 30 April 2018) (Archived at http://www.webcitation.org/6z5267tqM:).
43. Drug Enforcement Administration (DEA). Prescriptions: Questions and Anwers. Available at: https://www.deadiversion.usdoj.gov/faq/prescriptions.htm (accessed 30 April 2018) (Archived at http://www.webcitation.org/6z52K7lXg).
44. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 2007; 68: 515–21. [PubMed: 17296917]
45. Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 2009; 34: 672–80. [PubMed: 18688212]
46. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain 2013; 14: 136–48. [PubMed: 23237736]
47. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain 2008; 9: 506–21. [PubMed: 18403272]
48. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH Efficacy of inhaled cannabis on painful diabetic neuropathy. J Pain 2015; 16: 616–27. [PubMed: 25843054]
49. MACPAC. MACStats: Medicaid and CHIP Data Book: Medicaid and CHIP Payment and Access Commission. Washington, DC: MACPAC; 2015.
50. Nam YH, Shea DG, Shi Y, Moran JR State prescription drug monitoring programs and fatal drug overdoses. Am J Manag Care 2017; 23: 297–303. [PubMed: 28738683]
51. Paulozzi LJ, Kilbourne EM, Desai HA Prescription drug monitoring programs and death rates from drug overdose. Pain Med (Malden, MA) 2011; 12: 747–54.
52. Meara E, Horwitz JR, Powell W, McClelland L, Zhou W, O'Malley AJ et al. State legal restrictions and prescription-opioid use among disabled adults. N Engl J Med 2016; 375: 44–53. [PubMed: 27332619]
53. Patrick SW, Fry CE, Jones TF, Buntin MB Implementation of prescription drug monitoring programs associated with reductions in opioid-related death rates. Health Affairs (Project Hope) 2016; 35: 1324–32. [PubMed: 27335101]
54. Bao Y, Pan Y, Taylor A, Radakrishnan S, Luo F, Pincus HA et al. Prescription drug monitoring programs are associated with sustained reductions in opioid prescribing by physicians. Health Affairs (Project Hope) 2016; 35: 1045–51. [PubMed: 27269021]
55. Buchmueller TC, Carey C The effect of prescription drug monitoring programs on opioid utilization in medicare. Cambridge, MA: National Bureau of Economic Research; 2017.
56. Dowell D, Zhang K, Noonan RK, Hockenberry JM Mandatory provider review and pain clinic laws reduce the amounts of opioids prescribed and overdose death rates. Health Affairs (Project Hope) 2016; 35: 1876–83. [PubMed: 27702962]
57. Pardo B Do more robust prescription drug monitoring programs reduce prescription opioid overdose? Addiction 2017; 112: 1773–83. [PubMed: 28009931]
58. Hall W, West R, Marsden J, Humphreys K, Neale J, Petry N It is premature to expand access to medicinal cannabis in hopes of solving the US opioid crisis. Addiction 2018; 113: 987–8. [PubMed: 29468760]
59. Olfson M, Wall MM, Liu SM, Blanco C Cannabis use and risk of prescription opioid use disorder in the United States. Am J Psychiatry 2018; 175: 47–53. [PubMed: 28946762]

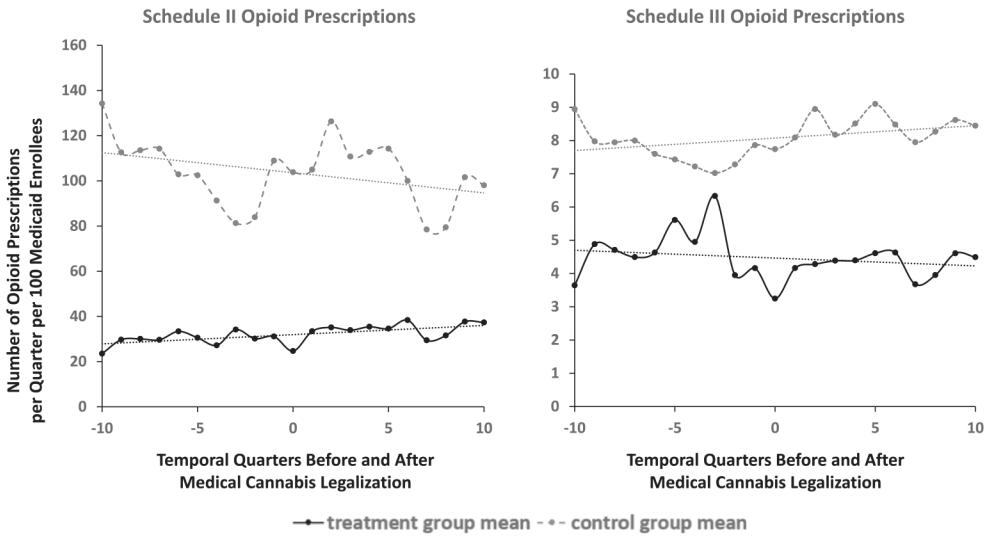

Figure 1.

Unadjusted pre- and post-legalization trends in number of opioid prescriptions per quarter per 100 Medicaid enrollees for states that did and did not legalize medical cannabis during 1993–2014. For the 23 states and Washington DC that legalized medical cannabis, quarter 0 encompasses the date that legalization occurred with trends from time −10 (10 quarter before implementation) to time +10 (10 quarters after implementation) obtained by calculating the average number of opioid prescriptions at each time-point across states. For the 27 states without medical cannabis legalization, 24 computations of before and after trends were calculated in each state using time 0 as the legalization date for each of the states and Washington DC that did legalize. These were then aggregated across states to obtain final projections

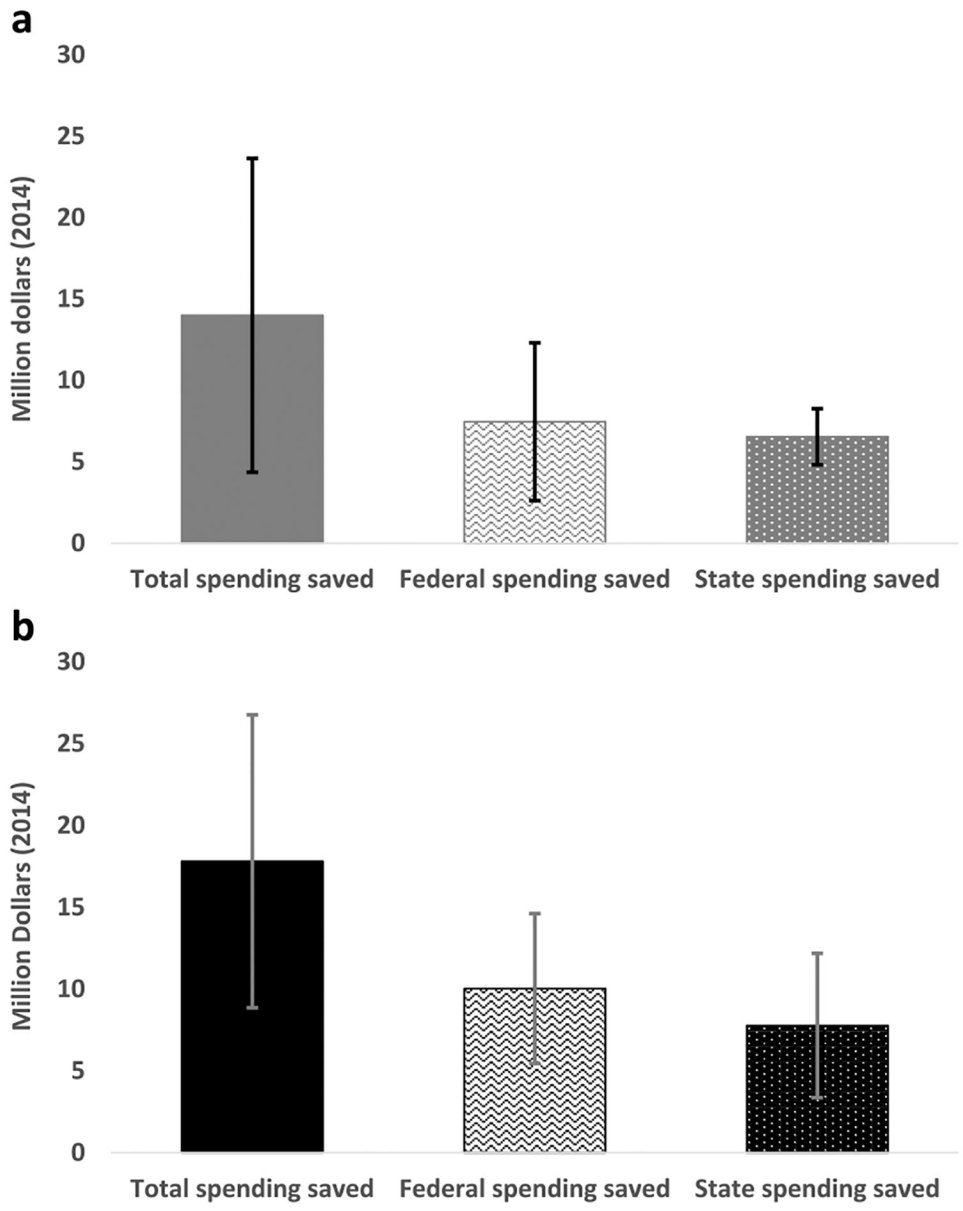

Figure 2.

Predicted annual Medicaid cost savings on Schedule III opioids received by Medicaid fee-for-service enrollees. Data shown in (a) are for states that had implemented medical cannabis legalization by 2014; data shown in (b) are for all 50 states and Washington DC, assuming they had all implemented legalization by 2014. Error bars represented the 95% confidence intervals of estimated savings. Regression results from model 1 were used to estimate savings. More detailed information is presented in Supporting information, Table S4 [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1

Descriptive statistics of pooled 1993–2014 data (mean and 95% confidence intervals).

	All states	Medical cannabis legalized during study period	
		Yes (n = 24 states)	No (n = 27 states)
Opioid prescriptions			
Schedule II			
Number of opioid prescription dispensed per quarter per 100 Medicaid enrollees	56 (48, 63)	37 (34, 41)	80 (64, 97)
Oral morphine milligram equivalents per quarter per 100 Medicaid enrollees	46 766 (43 399, 50 132)	37 466 (34 744, 40 187)	59216 (52274, 66158)
Medicaid spending on opioid prescriptions per quarter per 100 Medicaid enrollees, 2014 dollars	$3012 ($2649, $3376)	$2235 ($1980, $2490)	$ 4050 ($3276, $4824)
Schedule III			
Number of opioid prescription dispensed per quarter per 100 Medicaid enrollees	7 (7, 8)	6 (5, 7)	8 (8, 9)
Oral morphine milligram equivalents per quarter per 100 Medicaid enrollees	1254 (1154, 1353)	1177 (1027, 1326)	1357 (1237, 1477)
Medicaid spending on opioid prescriptions per quarter per 100 Medicaid enrollees, 2014 dollars	$118 ($85, $151)	$115 ($58, $172)	$122 ($111, $133)
Cannabis-related policies			
% State-quarters with medical cannabis legalization in effect	17 (16, 18)	29 (28, 31)	0
% State-quarters having active medical cannabis dispensaries	6 (6, 7)	11 (10, 12)	0
% State-quarters with cannabis decriminalization in effect	20 (19, 21)	25 (24, 27)	14 (12, 15)
% State-quarters with recreational cannabis legalization in effect	0.35 (0.18, 0.53)	0.63 (0.32, 0.93)	0
Medical care characteristics			
% State-quarters with prescription drug monitoring program in effect	46 (44, 47)	45 (43, 47)	48 (45, 50)
% State-quarters with Medicaid expansion as part of Affordable Care Act	1.7 (1.4, 2.1)	2.7 (2.1, 3.3)	0.46 (0.16, 0.77)
Population demographic characteristics			
Median household income, 2014 dollars	55 114 (54 864, 55 364)	58 174 (57 839, 58 509)	51 081 (50 791, 51 370)
Number of active physicians per 100 000 population	258 (255, 262)	290 (286, 294)	217 (212, 221)
% Families with income below the federal poverty line	13 (13, 13)	12 (12, 12)	14 (13, 14)
% Unemployed population in labor force	6 (6, 6)	6 (6, 6)	5 (5, 5)

Observations at state-quarter level over the study period (1993–2014) were pooled to calculate the statistics.

Table 2

Linear regression results for Schedule II opioid prescriptions, 1993–2014; coefficients (95% confidence intervals).

	Logged number of opioid prescription dispensed per quarter per 100 Medicaid enrollees		Logged oral morphine milligram equivalents per quarter per 100 Medicaid enrollees		Logged Medicaid spending on opioid prescriptions per quarter per 100 Medicaid enrollees	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Medical cannabis Legalization in effect	−0.15 (−0.43, 0.14) P = 0.32	−0.17 (−0.45, 0.12) P = 0.24	−0.060 (−0.33, 0.21) P = 0.66	−0.071 (−0.35, 0.20) P = 0.61	−0.10 (−0.39, 0.20) P = 0.52	−0.12 (−0.41, 0.18) P = 0.44
Having active medical cannabis dispensaries	NA	0.39 (−0.072, 0.85) P = 0.096	NA	0.23 (−0.18, 0.64) P = 0.26	NA	0.40 (−0.10, 0.91) P = 0.12
Cannabis Decriminalization in effect	0.13 (−0.34, 0.61) P = 0.57	0.084 (−0.40, 0.57) P = 0.73	0.18 (−0.34, 0.70) P = 0.48	0.15 (−0.38, 0.69) P = 0.56	0.43 (−0.33, 1.19) P = 0.26	0.38 (−0.34, 1.10) P = 0.30
Recreational cannabis Legalization in effect	0.18 (−0.26, 0.62) P = 0.43	0.32 (−0.18, 0.83) P = 0.21	0.31 (−1.18, 0.56) P = 0.48	−0.22 (−1.15, 0.71) P = 0.64	−0.11 (−0.52, 0.30) P = 0.60	0.043 (−0.37, 0.46) P = 0.83

Data were analyzed at state-quarter level. All regressions also controlled for Prescription Drug Monitoring Program in effect, Medicaid expansion as part of affordable care act, median household income, number of active physicians per 1000 population, poverty rate, unemployment rate, state indicators, year indicators, quarter indicators and state-specific time trends before and after 2006. Standard errors were clustered at state level. Please see full regression results in Supporting information, Table S2. NA = not available.

Table 3

Linear regression results for Schedule III Opioid Prescriptions, 1993–2014; coefficients (95% confidence intervals).

	Logged number of opioid prescription dispensed per quarter per 100 Medicaid enrollees		Logged oral morphine milligram equivalents per quarter per 100 Medicaid enrollees		Logged Medicaid spending on opioid prescriptions per quarter per 100 Medicaid enrollees	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Medical cannabis Legalization in effect	*−030** (−0.57, −0.024) P = 0.033	−0.30* (−0.58,−0.024) P= 0.034	−0.30* (−0.55,−0.048) P = 0.021	−0.30* (−0.56,−0.047) P = 0.021	−0.29* (−0.56,−0.014) P = 0.040	−0.30* (−0.57,−0.03) P = 0.029
Having active medical cannabis dispensaries	NA	0.11 (−0.28, 0.50) P= 0.57	NA	0.097 (−0.30, 0.49) P = 0.62	NA	0.29 (−0.20, 0.78) p = 0.24
Cannabis decriminalization in effect	0.26 (−0.22, 0.73) P= 0.29	0.24 (−0.24, 0.72) P= 0.32	0.10 (−0.45, 0.66) P = 0.71	0.092 (−0.47, 0.65) P = 0.74	0.40 (−0.34, 1.14) P= 0.29	0.36 (−0.31, 1.04) P = 0.28
Recreational cannabis Legalization in effect	0.073 (−0.22, 0.36) P = 0.61	0.11 (−0.23, 0.46) P= 0.50	−0.39 (−1.30, 0.52) P = 0.40	−0.35 (−1.34, 0.63) P = 0.48	−0.0088 (−0.36, 0.3 5) P= 0.96	0.10 (−0.27, 0.47) P = 0.59

* $P < 0.05$. Data were analyzed at state-quarter level. All regressions also controlled for Prescription Drug Monitoring Program in effect, Medicaid expansion as part of affordable care act, median household income, number of active physicians per 1000 population, poverty rate, unemployment rate, state indicators, year indicators, quarter indicators and state-specific time trends before and after 2006. Standard errors were clustered at state level. Please see full regression results in Supporting information, Table S3. NA = not available.