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The state of the evidence on the association between state cannabis laws and opioid-related outcomes: A review

Kayla N. Tormohlen, PhD, MPH,

624 N. Broadway, Room 357, Baltimore, MD 21205

Mark C. Bicket, MD, PhD,

1500 E Medical Center Drive, Ann Arbor, MI 48109-5048

Sarah White, MSPH,

624 N. Broadway, Room 348, Baltimore, MD 21205

Colleen L. Barry, PhD, MPP,

624 N. Broadway, Room 482, Baltimore, MD 21205

Elizabeth A. Stuart, PhD,

624 N. Broadway, Room 839, Baltimore, MD 21205

Lainie Rutkow, PhD, JD, MPH,

624 N. Broadway Room 592, Baltimore, MD, 21205

Emma E. McGinty, PhD, MS

624 N. Broadway, Room 359, Baltimore, MD 21205

Abstract

Purpose of Review: This review summarizes studies examining impacts of medical and recreational cannabis laws on opioid prescribing, opioid use, opioid use disorder, opioid-related service utilization, and opioid-involved mortality. We also discuss research challenges and recommendations for future work.

Recent Findings: Twenty-one U.S. based studies published between 2014–2021 that assessed state cannabis laws' association with opioid-related outcomes were reviewed. Study results were largely inconclusive. We identified six challenges of existing work: 1) inability to directly measure cannabis/opioid substitution; 2) use of general population samples and lack of individual-level longitudinal studies; 3) challenges disentangling effects of cannabis laws from other state laws; 4) methodological challenges with staggered policy implementation; 5) limited consideration of cannabis law provisions; 6) lack of triangulation across data sources.

Summary: While existing research suggests the potential for cannabis laws to reduce high-risk opioid prescribing and other opioid-related adverse outcomes, studies should be interpreted in light of limitations.

(Corresponding Author) Kayla N. Tormohlen PhD, MPH, 624 N. Broadway, Room 357, Baltimore, MD 21205, ktormoh1@jhu.edu.
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This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

State cannabis laws; recreational cannabis laws; medical cannabis laws; opioid prescribing; opioid use; opioid overdose

Background

Unintentional drug overdose continues to be the leading cause of injury death in the United States [1]. In 2019, there were over 70,000 overdose deaths in the United States and preliminary data suggests that the number deaths due to overdose was closer to 90,000 in 2020, approximately a 29% increase from November 2019 to November 2020 [2]. The majority of overdose deaths involve an opioid; in 2019 72.9% of overdose deaths were opioid-related [3,4]. Overprescribing of opioids was and continues to play a key role in the U.S. opioid crisis. Today, approximately 30% of opioid overdose deaths involve a prescription opioid [5], and while opioid prescribing rates began to decline in 2012, today's prescribing rates continue to exceed those in the late 1990s [6]. In addition to increased opioid prescribing rates, evidence also suggests that prescribing practices including increased duration and dosage of opioid prescriptions are associated with a higher risk of opioid overdose [7,8].

Intertwined with the opioid crisis is the high prevalence of chronic non-cancer pain among U.S. adults, defined as pain occurring on at least half of days for six months or longer [9]. Twenty percent of U.S. adults at least 18 years old and 31% of those aged 65 or older have a chronic non-cancer pain condition [10]. Beginning in the late 1990s up until 2016, opioids were considered first-line treatment for chronic non-cancer pain [7], and a 2013 study found that over 50% of all adults prescribed an opioid had arthritis, a common chronic pain condition [11]. In 2016, the Centers for Disease Control and Prevention released a new guideline for the treatment of chronic non-cancer pain indicating that non-opioid treatment should be considered prior to opioid prescribing because of the risk-benefit ratio of opioid treatment for chronic pain [7].

Cannabis is a possible effective treatment for chronic non-cancer pain. In 2017, the National Academies of Science, Engineering and Medicine (NASEM) released a report supporting the effectiveness of using cannabis to treat chronic non-cancer pain among adults [12]. Some self-report data from patients also suggests that persons find pain relief by using cannabis [13]. However, according to a recent Cochrane review that examined results of clinical trials assessing efficacy, tolerability and safety of cannabis treatment for chronic neuropathic pain, the quality of evidence is low due to issues such as small sample sizes and participant exclusion criteria (i.e., history of substance use disorders and other comorbidities). This review concluded that the potential harms could outweigh the benefits of cannabis for treatment of chronic non-cancer pain [14].

The U.S. cannabis policy landscape has evolved dramatically throughout the last decade. Thirty-six states and the District of Columbia (DC) have approved medical cannabis programs; seventeen of these states and DC also have recreational cannabis laws that allow adults aged 21 years or older to use cannabis [15,16]. All states with an existing medical

cannabis law have deemed chronic non-cancer pain as an eligible condition for the use of cannabis. Among existing state medical and recreational cannabis laws, there is considerable variation in provisions and implementation. Examples of law provisions, specifically for medical cannabis laws, include qualifying conditions (e.g., non-specific chronic pain), type of cannabis allowed (e.g., dry leaf cannabis vs. tinctures), as well as requirements regarding cannabidiol (CBD) and tetrahydrocannabinol (THC) levels [17,18]. Particularly relevant to opioid treatment for chronic pain, some states have provisions that allow for the use of medical cannabis in place of an opioid prescription [19,20]. Four states (NJ, NM, NY, and PA) also include opioid use disorder as a qualifying condition for the state's medical cannabis program, despite lack of evidence for the use of cannabis for the treatment of opioid use disorder [20,21].

Implementation of cannabis laws has also shifted within and across states over time. From 2009 to 2011, the U.S. Department of Justice (DOJ) published guidance asserting that the DOJ would not enforce the federal cannabis prohibition, which makes the use, sale, and possession of cannabis illegal, if state cannabis laws incorporated regulatory schemes that achieve public health and safety goals [22,23]. This guidance led to increased "medicalization" of state medical cannabis laws, with provisions gradually becoming more aligned with medical practice standards (e.g., by imposing 30-day supply limits on medical cannabis) [24]. In addition, the 2009–2011 DOJ guidance led to proliferation of cannabis dispensaries. While only five states had operational medical cannabis dispensaries in 2010 [25], today all states with medical cannabis laws have operational dispensaries [16]. The volume of dispensaries selling cannabis for recreational use in states with recreational cannabis laws has also increased rapidly over the past decade [15]. Research shows that a higher degree of medicalization is associated with lower medical cannabis use and that higher volume of dispensaries is associated with greater cannabis access, making it important to account for variation in these factors across states and over time [17]. In addition, other specific provisions that vary considerably across states, such as whether cannabis can be grown at home, have been shown to impact the degree to which state cannabis laws influence cannabis use [17–20,25–29].

An important public health question is whether legal access to cannabis granted by state cannabis laws leads people with chronic non-cancer pain to substitute cannabis in place of opioids for pain management. This type of substitution has the potential to reduce opioid-related morbidity and mortality, but is not without potential adverse consequences. Twenty to thirty percent of people who use cannabis also have a cannabis use disorder, as indicated by a sample of adults with chronic pain treated with medical cannabis [30] and another among a national sample of adults in the US who reported past year cannabis use [31]. Heavy cannabis use can also lead to cannabis poisoning [32,33] and cannabis use may be associated with increased risk of psychosis [34]. The extant research examining the effects of state cannabis laws on opioid-related problems has shown mixed results and is subject to several important methodological limitations. The purpose of this review is to first present a brief overview of findings of existing studies exploring the association between state cannabis laws and opioid-related outcomes. We then describe research challenges in detail and consider how they might be overcome in future research.

Overview of findings from existing studies

In this section, we provide an overview of findings from existing studies examining the association between state cannabis laws and opioid-related outcomes. The section is organized by type of opioid-related measures: 1) opioid prescribing; 2) opioid use and opioid use disorder; 3) opioid-related healthcare utilization; 4) opioid-involved mortality. The studies summarized below were identified through searches conducted in April 2021, using PubMed, PsycINFO, and Embase with the following search terms: medical cannabis/marijuana; recreational cannabis/marijuana policy and/or law; dispensary AND opioids; opioid use; opioid use disorder; opioid/opiate overdose; opioid prescribing/prescriber. We also reviewed the reference lists of studies identified through the search to ensure completeness. We included quantitative studies conducted in the U.S. that estimated the effect of state cannabis laws on opioid-related outcomes by examining changes in outcomes before and after the implementation of the law of interest. We excluded non peer-reviewed publications, qualitative studies, and studies that did not explicitly examine state cannabis laws (e.g., studies examining the association between use of cannabis and opioid-related outcomes) and/or did not use methods to evaluate differences before and after law implementation. Following the summary of findings, we discuss multiple overarching limitations to the studies included in this review; findings of extant studies should be interpreted with caution.

1. Opioid prescribing

Two studies examined both medical cannabis laws (MCL) and recreational cannabis laws (RCL) and the association with opioid prescribing outcomes, six studies examined MCLs only and two studies examined the association between RCLs and these outcomes. Common outcomes included total number of opioids prescribed by a provider and/or received by a patient, days' supply of opioids, morphine milligram equivalents (MME), and costs associated with opioid prescriptions.

Medical cannabis laws.—Among studies examining medical cannabis laws, all found reductions in prescribed opioids among a general population of adults associated with MCL implementation [35–42]. Examples include reduction in daily doses of all opioids prescribed, as well as decreased dosage of opioids among states with medical cannabis laws compared to those without. Most of these studies examined laws implemented after the 2009–2011 DOJ guidance [35–40], with the exception of two studies that examined MCL implementation between 2006 and 2014 [41,42]. Although not explicitly assessed in any of the referenced studies, timing of law implementation is important to consider because of the changes in “medicalization” of laws and access to medical dispensaries following the DOJ guidance. It is possible that these changes impacted opioid prescribing outcomes.

Recreational cannabis laws.—Because all states that have recreational cannabis laws also have a medical cannabis law in place, existing studies used methods to isolate the effect of RCLs or explore the combined effect of an MCL and RCL. Results for RCLs are inconsistent, with some studies showing no significant association between RCLs and opioid prescribing outcomes [43,44], while others observed reductions in opioid prescribing

[35,38]. For example, Shi and colleagues observed no significant difference in Schedule II opioid prescribing among states with RCL+MCL compared to states with MCL only during 2010–2017 [44]. However, Wen and colleagues concluded that in states with both a MCL and RCL, the implementation of a RCL between 2011 and 2016 was associated with a reduction in Medicaid-covered opioid prescribing rates compared to states with a MCL but without a RCL [38]. McMichael et al., assessed both MCLs and RCLs among 33 states with a MCL or MCL + RCL by 2018 and found that relative to only MCL, RCLs were associated with an 11.8% reduction of number of morphine milligram equivalents prescribed in a year [35].

2. Opioid use and opioid use disorder

Four studies have examined the association between medical cannabis laws and opioid use and opioid use disorder outcomes, and no studies have examined the association between recreational cannabis laws and these outcomes. Common outcomes included ever and past year use of opioid medications, both prescribed and not prescribed by a provider, and past year opioid use disorder.

Medical cannabis laws.—All studies were repeated cross-sectional and used data from the National Survey on Drug Use and Health (NSDUH). Despite using the same data source, the studies are distinct from each other in multiple ways, including their conclusions. Powell and colleagues used NSDUH data from 2002 to 2012 to examine the association between medical cannabis laws with operational dispensaries and self-reported past-year nonmedical prescription opioid use, and found no meaningful relationship between the two [45]. In another study, Ali and colleagues compared NSDUH data from female respondents living in states without MCLs and those with MCLs but no RCL from 2002–2014. Results suggested no significant difference in opioid misuse, opioid misuse initiation or opioid use disorder among women living in states that enacted a MCL, compared to states that did not implement a MCL in this period [46]. Segura and colleagues used data from 2004 to 2014 and explored differences in self-reported nonmedical prescription opioid use and prescription opioid use disorder before and after the passage of a MCL; the researchers found a slight increase in use of prescription opioids following the passage of MCL but no difference in prescription opioid use disorder [47]. Lastly, Flexon and colleagues conducted a study using NSDUH data from 2015 and 2017 exploring the difference in prescription opioid misuse between persons living in a state with a MCL compared to those who lived in a state without a MCL. These researchers did not find a significant association between MCLs and reports of opioid misuse [48].

3. Opioid-related healthcare utilization

Two studies have examined the association between medical cannabis laws and opioid-related healthcare utilization outcomes. One study examined the association between having medical cannabis and/or recreational cannabis laws and these outcomes. Common outcomes included opioid-related hospitalizations and emergency department utilization, and treatment admissions for opioid use disorder.

Medical cannabis laws.—One study using state-level hospitalization records found that compared to states that did not implement a MCL between 1997–2014, enacting a MCL (with or without specifying operational dispensaries) was associated with a 23% reduction in the average annual hospitalization rate related to opioid use disorder and a 13% decrease in the rate of hospitalizations involving prescription opioid overdose [49]. Powell and colleagues utilized data from the Treatment Episode Data Set (TEDS) from 1999–2012 and found that MCLs, overall, were not associated with treatment admissions for prescription opioids or heroin, but that the existence of legal and active dispensaries was associated with declines in treatment admissions for both prescription opioids and heroin [45].

Lastly, comparing states with and without MCLs, another study found that MCL implementation between 2005 and 2016 was associated with reductions in opioid-related hospitalizations, but had no significant effects on opioid-related emergency department visits. This study also found that home cultivation of cannabis was associated with increased hospitalizations and emergency department encounters [50]. Additionally, the same study found that states with both a MCL and RCL had a larger number of opioid-related hospitalizations compared to states with a MCL alone [50].

4. Opioid-related mortality

Two studies have examined the association between medical cannabis laws and fatal opioid overdose outcomes and two studies have examined the association between recreational cannabis laws and this outcome. Another two examined the relationship between both medical and recreational laws and fatal opioid overdose.

Medical cannabis laws.—All studies utilized aggregated state-level data of deaths related to opioids. Two studies found that states that adopted MCLs between 1999 and 2010 had a 21% and 25% decline in opioid-related mortality rate compared to states without medical cannabis laws [45,51]. However, when subsequent studies added data beyond 2010, this association was shown to diminish [45] or reverse direction [52]. Shover and colleagues extended this analysis through 2017 and found a decrease in opioid mortality from 1999–2010 among states with a MCL compared to those without, but concluded that when extending through 2017, MCLs were associated with a 23% increase in opioid overdose mortality and a 28% increase when considering only “comprehensive” MCLs that included operational medical dispensaries [52]. However, a study using data from 1999–2013 found the combined effect of having both a MCL and active dispensaries was associated with a 25% reduction in opioid overdose deaths [45]. These differences support the idea that there are possible distinctions in impacts for different “generations” of medical cannabis laws enacted before and after the 2009–2011 DOJ memos. Another study explored county-level associations between the volume of medical and recreational cannabis dispensaries and opioid-related death between 2014 and 2018, and observed a reduction in opioid-related mortality associated with an increased number of medical cannabis dispensaries within a county [53].

Recreational cannabis laws.—Results of studies examining the relationship between recreational cannabis laws and opioid-related mortality are inconsistent. Two of the four

existing studies explored this question with Colorado's recreational cannabis law. Livingston and colleagues used data from 2000 to 2015 to compare changes in opioid-related deaths before and after the RCL implementation, defined by the start of retail sales of cannabis, and observed a reduction in opioid-related deaths in the first two years of recreational cannabis with active retail dispensaries, after accounting for comparison state (Utah and Nevada) trends in opioid-related deaths [54]. However, another study that used aggregated state-level data from 1999 to 2017 found no significant effect of the policy change on overdose death rates in Colorado compared to a synthetic control or weighted combination of comparison states designed to mirror pre-law trends in outcomes of interest in the state that changes its recreational cannabis laws. The synthetic control was created from a pool of all states with a medical cannabis law [55,56]. Using U.S. state-aggregated overdose death data, not limited to Colorado, Shover and colleagues found no significant association between state implementation of a RCL and opioid overdose mortality [52].

Research Challenges

Among existing studies that examine the relationship between state cannabis laws and opioid-related outcomes, conflicting results are apparent in several outcome areas. Even in outcome areas with consistent findings, design quality and methodological challenges stand in the way of drawing robust conclusions about the question of interest. In this section, we discuss limitations and challenges present in existing research and consider how future research can improve and/or overcome these challenges to enhance our ability to obtain robust conclusions.

1. Inability to directly measure cannabis/opioid substitution

No existing studies used data sources that allow measurement of individual-level cannabis and opioid use. Additionally, there are no existing randomized controlled trials assessing cannabis substitution for opioid prescriptions among chronic non-cancer pain patients. Unlike other prescription medications, such as opioid prescriptions, that can be measured using data sources such as insurance claims or electronic health records, there is no comparable data source that allows for the measurement of individual-level medical and/or recreational cannabis use longitudinally. To directly examine the question of potential substitution of cannabis in place of opioid treatment for pain management, we would ideally have data that links opioid prescription information, overdose data, and data capturing cannabis use among individuals over time. Even with data linkage, not all substitution is observable (e.g., a provider decides to recommend cannabis to a new patient when they would, pre-cannabis law, have recommended opioids), but nonetheless, the lack of data linking cannabis use with opioid-related outcomes at the individual level is a significant gap. There are some states that incorporate (or are considering incorporating) medical cannabis in the state prescription drug monitoring program (PDMP). For example, Ohio requires providers to check the Ohio Automated Rx Reporting System (OARRS) before recommending medical cannabis to a patient. The OARRS system includes information on cannabis formulation (e.g., oil or tincture) and maximum dose [57]. PDMPs could play a potential role in future research, although many states impose limits on using PDMP data

for research and additional challenges could limit states' ability to incorporate cannabis into their PDMPs, such as federal scheduling of cannabis [58].

2. Use of general population samples and lack of individual-level longitudinal studies

As just mentioned, the primary proposed mechanism of a potential association between cannabis access laws and reductions in opioid use is the substitution of cannabis for opioid prescriptions, particularly for chronic non-cancer pain [36–39,41,45,51]. However, no existing studies, apart from one subgroup analysis [42], have analyzed cannabis laws' effects on outcomes in a sample of persons with chronic non-cancer pain. Future research examining laws' effects on this specific population is needed.

Another related limitation is lack of individual-level longitudinal studies, as most of the prior work uses aggregate state-level data. This challenge is persistent across all opioid-related outcomes with the use of state-level aggregate data (e.g., CDC mortality data) and repeated cross-sectional panel studies (e.g., NSDUH, Medicaid prescription data). This lack of individual-level longitudinal studies leads to the inability to measure and account for individual characteristics and to observe within-individual changes in outcomes over time. The lack of individual-level longitudinal data also precludes analysis of consistent cohorts of persons over time, making it unclear whether observed effects are due to the law change of interest or the changing composition of the sample.

3. Challenges disentangling the effects of state medical cannabis laws with other state laws

Another challenge is the potential for policy endogeneity, or the idea that many states have enacted medical cannabis laws at or around the same time as laws or other initiatives designed to reduce opioid overprescribing (e.g., state prescription drug monitoring program laws, pill mill laws, and laws limiting the dose/duration of opioid prescriptions for acute pain) [59–68]; increase access to opioid use disorder treatment; and/or decrease opioid overdose (e.g., naloxone access laws) [69,70]. These types of laws have proliferated since 2010; this timing demonstrating the overlap between the implementation of these laws and cannabis laws. To isolate the effects of state medical laws on opioid-related outcomes, studies need to be carefully designed to ensure that they are isolating the effects of cannabis laws on opioid-related outcomes from other types of policies.

4. Methodological challenges with staggered law implementation

Many of the studies discussed above used a difference-in-differences design, which compares changes in outcomes pre- and post- policy implementation in the treatment group to changes over the same time frame in the control group. This is a stronger design for causal inference than studies that simply examine changes in outcomes pre/post law in a single state or do simple time-point comparisons of outcomes. However, recent work has suggested that commonly used difference-in-differences models with two-way fixed effects are problematic when variation in policy implementation timing exists and can lead to challenges with the interpretation of the overall effect because the length of the pre- and post-periods varies by state and the composition of the treatment and comparison pools differs across the study period [71]. This is salient for cannabis laws, as states have adopted

laws at different points in time. The large majority of existing studies summarized above are subject to potential biases resulting from this methodological issue. Originating from comparative effectiveness research, a stacked difference-in-differences approach or “policy emulation”[72] could be an alternative to canonical two-way fixed-effects difference-in-differences approaches and an important innovation for cannabis laws research.

5. Limited consideration of cannabis law provisions

State cannabis laws are unique because cannabis use continues to be illegal at the federal level. Because of this, the consideration of law provisions is especially important because states have had to carefully navigate how to implement these laws (e.g., level of provider involvement, allowed use of revenue from programs). Cannabis laws vary considerably across states because of specific provisions and details of implementation. Extant evidence shows that provisions and implementation factors have considerable influence on access to cannabis under medical cannabis laws (e.g., operating dispensaries, changes in perception of harm, costs) [25]. Different provisions and/or implementation factors could modify the effects of medical cannabis laws on opioid-related outcomes – in other words, some state’s medical cannabis laws might have different effects on outcomes than others because of variation in provisions and/or implementation. However, prior studies have largely not addressed this, with some exceptions. Of studies that do, the existence of dispensaries and/or the quantity of them are mostly commonly explored [35–37,40,41,45,47,49,50,52–55]. As depicted in a previous section and by other prior work [25], is it plausible that the existence of operational dispensaries impacts access to both medical and recreational cannabis and in turn impacts opioid-related outcomes, but more research is needed to rigorously evaluate this potential association.

6. Lack of triangulation with multiple sources of data collection

Quantitative policy evaluations are inadequate, on their own, to understand the effects of state medical cannabis laws on opioid-related outcomes. This is especially true given distinctions in law provisions across states, as already mentioned above. Other types of research are needed to characterize law implementation, and understand whether and how providers, patients, and persons who use recreational cannabis are changing opioid-related behaviors in response to medical cannabis access. Triangulation of quantitative policy evaluation methods with qualitative and survey-based research is necessary to assess the plausibility of effects of medical and recreational cannabis laws on opioid-related outcomes presented in the existing literature.

Conclusions

Current research examining cannabis access laws’ effects on opioid-related outcomes suggests that cannabis policies could have positive impacts on opioid prescribing practices and related adverse outcomes, but extant studies face important methodological challenges. With significant variation in medical and recreational cannabis law design and implementation across states and over time, careful study design and the use of innovative statistical methods are needed as we move forward with this area of research.

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References

1. WISQARS Data Visualization. <https://wisqars-viz.cdc.gov:8006/lcd/>
2. Products - Vital Statistics Rapid Release - Provisional Drug Overdose Data. 2021. <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>
3. National Institute on Drug Abuse. Overdose Death Rates. Natl. Inst. Drug Abuse 2021. <https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates>
4. Drug Overdose Deaths | Drug Overdose | CDC Injury Center. 2021. <https://www.cdc.gov/drugoverdose/deaths/index.html>
5. Prescription Opioid Overdose Death Maps | Drug Overdose | CDC Injury Center. 2021. <https://www.cdc.gov/drugoverdose/data/prescribing/overdose-death-maps.html>
6. Guy GP, Zhang K, Bohm MK, Losby J, Lewis B, Young R, et al. Vital Signs: Changes in Opioid Prescribing in the United States, 2006–2015. *MMWR Morb Mortal Wkly Rep.* 2017;66:697–704. [PubMed: 28683056]
7. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. *MMWR Recomm Rep.* 2016;65:1–49.
8. Alexander GC, Kruszewski SP, Webster DW. Rethinking Opioid Prescribing to Protect Patient Safety and Public Health. *JAMA.* 2012;308:1865. [PubMed: 23150006]
9. Intragency Pain Research Committee. National pain strategy: A comprehensive population health-level strategy for pain. Washington DC: Department of Health and Human Services; 2015.
10. Zelaya CE, Dahlhamer JM, Lucas JW, Connor EM. Chronic Pain and High-impact Chronic Pain Among U.S. Adults, 2019. 2020;8.
11. Hootman JM, Cisternas M, Murphy L, Losby J. Prevalence and trends in prescribed opioid use among US adults with arthritis, 2008–2013, medical expenditure panel survey. *Arthritis Rheumatol.* Hoboken, NJ USA; 2016.
12. National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Health Sciences Policy, Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse. Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. Phillips JK, Ford MA, Bonnie RJ, editors. Washington (DC): National Academies Press (US); 2017. <http://www.ncbi.nlm.nih.gov/books/NBK458660/>
13. Bachhuber M, Arnsten JH, Wurm G. Use of Cannabis to Relieve Pain and Promote Sleep by Customers at an Adult Use Dispensary. *J Psychoactive Drugs.* 2019;51:400–4. [PubMed: 31264536]
14. Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. *Cochrane Database Syst Rev.* 2018;3:CD012182. [PubMed: 29513392]
15. PDAPS - Recreational Marijuana Laws. <http://pdaps.org/datasets/recreational-marijuana-laws>
16. National Conference of State Legislatures. State Medical Marijuana Laws. <https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx>
17. Williams AR, Olfson M, Kim JH, Martins SS, Kleber HD. Older, Less Regulated Medical Marijuana Programs Have Much Greater Enrollment Rates Than Newer ‘Medicalized’ Programs. *Health Aff (Millwood).* Health Affairs; 2016;35:480–8. [PubMed: 26953303]
18. Chapman SA, Spetz J, Lin J, Chan K, Schmidt LA. Capturing Heterogeneity in Medical Marijuana Policies: A Taxonomy of Regulatory Regimes Across the United States. *Subst Use Misuse.* 2016;51:1174–84. [PubMed: 27191472]
19. Voelker R States move to substitute opioids with medical marijuana to quell epidemic. *Jama.* American Medical Association; 2018;320:2408–10. [PubMed: 30484825]
20. Humphreys K, Saitz R. Should physicians recommend replacing opioids with cannabis? *Jama.* American Medical Association; 2019;321:639–40. [PubMed: 30707218]

21. Shover CL, Vest NA, Chen D, Stueber A, Falasinnu TO, Hah JM, et al. Association of State Policies Allowing Medical Cannabis for Opioid Use Disorder With Dispensary Marketing for This Indication. *JAMA Netw Open*. 2020;3:e2010001. [PubMed: 32662844]
22. Memorandum for Selected United State Attorneys on Investigations and Prosecutions in States Authorizing the Medical Use of Marijuana. 2009. <https://www.justice.gov/archives/opa/blog/memorandum-selected-united-state-attorneys-investigations-and-prosecutions-states>
23. Cole J Guidance regarding the Ogden memo in jurisdictions seeking to authorize marijuana for medical use. Memorandum for United States Attorneys. 2011.
24. Richard EL, Althouse AD, Arnsten JH, Bulls HW, Kansagara D, Kerbag MN, et al. How medical are states' medical cannabis policies?: Proposing a standardized scale. *Int J Drug Policy*. 2021;94:103202. [PubMed: 33765514]
25. 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 Manag J Assoc Public Policy Anal Manag*. 2015;34:7–31.
26. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *PAIN*. 2015;156:569–76. [PubMed: 25785523]
27. Freisthler B, Gruenewald PJ. Examining the relationship between the physical availability of medical marijuana and marijuana use across fifty California cities. *Drug Alcohol Depend*. 2014;143:244–50. [PubMed: 25156224]
28. Shih RA, Rodriguez A, Parast L, Pedersen ER, Tucker JS, Troxel WM, et al. Associations between young adult marijuana outcomes and availability of medical marijuana dispensaries and storefront signage. *Addiction*. 2019;114:2162–70. [PubMed: 31183908]
29. Pacula RL, Smart R. Medical Marijuana and Marijuana Legalization. *Annu Rev Clin Psychol*. 2017;13:397–419. [PubMed: 28482686]
30. Feingold D, Goor-Aryeh I, Bril S, Delayahu Y, Lev-Ran S. Problematic Use of Prescription Opioids and Medicinal Cannabis Among Patients Suffering from Chronic Pain. *Pain Med*. 2017;18:294–306. [PubMed: 28204792]
31. Hasin DS, Saha TD, Kerridge BT, Goldstein RB, Chou SP, Zhang H, et al. Prevalence of Marijuana Use Disorders in the United States Between 2001–2002 and 2012–2013. *JAMA Psychiatry*. 2015;72:1235–42. [PubMed: 26502112]
32. Davis JM, Mendelson B, Berkes JJ, Suleta K, Corsi KF, Booth RE. Public Health Effects of Medical Marijuana Legalization in Colorado. *Am J Prev Med*. 2016;50:373–9. [PubMed: 26385161]
33. Wang GS, Hall K, Vigil D, Banerji S, Monte A, VanDyke M. Marijuana and acute health care contacts in Colorado. *Prev Med*. 2017;104:24–30. [PubMed: 28365373]
34. Hasan A, von Keller R, Friemel CM, Hall W, Schneider M, Koethe D, et al. Cannabis use and psychosis: a review of reviews. *Eur Arch Psychiatry Clin Neurosci*. 2020;270:403–12. [PubMed: 31563981]
35. McMichael BJ, Van Horn RL, Viscusi WK. The impact of cannabis access laws on opioid prescribing. *J Health Econ*. 2020;69:102273. [PubMed: 31865260] *This study used opioid prescription data at the provider-year level from 2011 to 2018, and found that medical and recreational cannabis laws were associated with decreases in MME prescribed each year, as well as reductions in days' supply, and number of patients prescribed an opioid. Results differed by type of provider, medical specialty and payer type.
36. Bradford AC, Bradford WD. Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D. *Health Aff (Millwood)*. 2016;35:1230–6. [PubMed: 27385238]
37. Liang D, Bao Y, Wallace M, Grant I, Shi Y. Medical cannabis legalization and opioid prescriptions: evidence on US Medicaid enrollees during 1993–2014. *Addiction*. 2018;113:2060–70. [PubMed: 29989239]
38. Wen H, Hockenberry JM. Association of Medical and Adult-Use Marijuana Laws With Opioid Prescribing for Medicaid Enrollees. *JAMA Intern Med*. 2018;178:673. [PubMed: 29610827]

39. Bradford AC, Bradford WD, Abraham A, Bagwell Adams G. Association Between US State Medical Cannabis Laws and Opioid Prescribing in the Medicare Part D Population. *JAMA Intern Med.* 2018;178:667–72. [PubMed: 29610897]
40. Lopez CD, Boddapati V, Jobin CM, Hickernell TR. State Medical Cannabis Laws Associated With Reduction in Opioid Prescriptions by Orthopaedic Surgeons in Medicare Part D Cohort. *JAAOS - J Am Acad Orthop Surg.* 2021;29:e188. [PubMed: 32404683]
41. Bradford AC, Bradford WD. Medical Marijuana Laws May Be Associated With A Decline In The Number Of Prescriptions For Medicaid Enrollees. *Health Aff (Millwood).* 2017;36:945–51. [PubMed: 28424215]
42. Shah A, Hayes CJ, Lakkad M, Martin BC. Impact of Medical Marijuana Legalization on Opioid Use, Chronic Opioid Use, and High-risk Opioid Use. *J Gen Intern Med.* 2019;34:1419–26. [PubMed: 30684198]
43. Kropp Lopez AK, Nichols SD, Chung DY, Kaufman DE, McCall KL, Piper BJ. Prescription Opioid Distribution after the Legalization of Recreational Marijuana in Colorado. *Int J Environ Res Public Health.* 2020.
44. Shi Y, Liang D, Bao Y, An R, Wallace MS, Grant I. Recreational marijuana legalization and prescription opioids received by Medicaid enrollees. *Drug Alcohol Depend.* 2019;194:13–9. [PubMed: 30390550]
45. 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]
46. Ali MM, McClellan C, West KD, Mutter R. Medical Marijuana Laws, Marijuana Use, and Opioid-Related Outcomes among Women in the United States. *Womens Health Issues.* 2021;31:24–30. [PubMed: 33069561]
47. Segura LE, Mauro CM, Levy NS, Khauli N, Philbin MM, Mauro PM, et al. Association of US medical marijuana laws with nonmedical prescription opioid use and prescription opioid use disorder. *JAMA Netw Open. American Medical Association;* 2019;2:e197216–e197216. *Using the National Survey on Drug Use and Health from 2004 to 2014, this repeated cross-sectional study explored the association between state medical cannabis laws and non-medical prescription opioid use and prescription opioid use disorder among those who reported using prescription opioids. Findings suggest small changes in prescription opioid use following implementation of a medical cannabis law, but no changes in prevalence of prescription opioid use disorder. The researchers emphasize the need for future work to investigate potential mechanisms for any possible association between medical cannabis laws and opioid use-related outcomes.
48. Flexon JL, Stolzenberg L, D'Alessio SJ. The effect of cannabis laws on opioid use. *Int J Drug Policy.* 2019;74:152–9. [PubMed: 31590091]
49. Shi Y Medical marijuana policies and hospitalizations related to marijuana and opioid pain reliever. *Drug Alcohol Depend.* 2017;173:144–50. [PubMed: 28259087]
50. Jayawardhana J, Fernandez JM. The associations of medical marijuana policies with opioid-related health care utilization. *Health Serv Res.* 2021;56:299–309. [PubMed: 33501701] *Utilizing quarterly rates of hospital discharge data from 2005 to 2012, this study explored the relationship between state medical cannabis laws and opioid-related hospitalizations and emergency department encounters. This study also explored if effects differed by laws allowing home cultivation and those only allowing access through a medical dispensary. Results varied by type of state medical cannabis policy. Laws with home cultivation were associated with increased number of opioid-related hospitalization and emergency department encounters, whereas the association between operational medical dispensaries and these outcomes was not statistically significant.
51. 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. [PubMed: 25154332]
52. Shover CL, Davis CS, Gordon SC, Humphreys K. Association between medical cannabis laws and opioid overdose mortality has reversed over time. *Proc Natl Acad Sci.* 2019;116:12624–6. [PubMed: 31182592]
53. Hsu G, Kovács B. Association between county level cannabis dispensary counts and opioid related mortality rates in the United States: panel data study. *BMJ.* 2021;372:m4957. [PubMed:

33504472] *This study explored the association between number of operational medical and recreational cannabis dispensaries and opioid-related mortality rates at the county level using data from 812 counties from 23 states from 2014–2018. This study found that an increased number of operational dispensaries were associated with a reduction in county-level opioid-related mortality rates.

54. Livingston MD, Barnett TE, Delcher C, Wagenaar AC. Recreational Cannabis Legalization and Opioid-Related Deaths in Colorado, 2000–2015. *Am J Public Health*. 2017;107:1827–9. [PubMed: 29019782]
55. Alcocer JJ. Exploring the effect of Colorado’s recreational marijuana policy on opioid overdose rates. *Public Health*. 2020;185:8–14. [PubMed: 32505041]
56. Abadie A, Gardeazabal J. The Economic Costs of Conflict: A Case Study of the Basque Country. *Am Econ Rev*. American Economic Association; 2003;93:113–32.
57. PDMP TTAC. Medical Marijuana Data and PDMPS. 2020. https://pdmpassist.org/pdf/TTAC_webinar_medical_marijuana_20200130.pdf
58. Mirigian LS, Hendrick LA, Pringle JL, Zemaitis MA. The Pennsylvania Prescription Drug Monitoring Program: Reducing the Misuse of Prescription Opioids. Commonwealth; 2018.
59. Haffajee RL, Jena AB, Weiner SG. Mandatory Use of Prescription Drug Monitoring Programs. *JAMA*. 2015;313:891–2. [PubMed: 25622279]
60. 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 Aff (Millwood)*. 2016;35:1876–83. [PubMed: 27702962]
61. Grecu AM, Dave DM, Saffer H. Mandatory Access Prescription Drug Monitoring Programs and Prescription Drug Abuse. *J Policy Anal Manage*. 2019;38:181–209. [PubMed: 30572414]
62. Schuchat A, Houry D, Guy GP. New Data on Opioid Use and Prescribing in the United States. *JAMA*. 2017;318:425. [PubMed: 28687823]
63. 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 Aff (Millwood)*. 2016;35:1045–51. [PubMed: 27269021]
64. Wen H, Schackman BR, Aden B, Bao Y. States With Prescription Drug Monitoring Mandates Saw A Reduction In Opioids Prescribed To Medicaid Enrollees. *Health Aff (Millwood)*. *Health Affairs*; 2017;36:733–41. [PubMed: 28373340]
65. Kennedy-Hendricks A, Richey M, McGinty EE, Stuart EA, Barry CL, Webster DW. Opioid Overdose Deaths and Florida’s Crackdown on Pill Mills. *Am J Public Health*. 2016;106:291–7. [PubMed: 26691121]
66. Rutkow L, Chang H-Y, Daubresse M, Webster DW, Stuart EA, Alexander GC. Effect of Florida’s Prescription Drug Monitoring Program and Pill Mill Laws on Opioid Prescribing and Use. *JAMA Intern Med*. 2015;175:1642. [PubMed: 26280092]
67. Chang H-Y, Lyapustina T, Rutkow L, Daubresse M, Richey M, Faul M, et al. Impact of prescription drug monitoring programs and pill mill laws on high-risk opioid prescribers: A comparative interrupted time series analysis. *Drug Alcohol Depend*. 2016;165:1–8. [PubMed: 27264166]
68. Lyapustina T, Rutkow L, Chang H-Y, Daubresse M, Ramji AF, Faul M, et al. Effect of a “pill mill” law on opioid prescribing and utilization: The case of Texas. *Drug Alcohol Depend*. 2016;159:190–7. [PubMed: 26778760]
69. Davis C, Carr D. State legal innovations to encourage naloxone dispensing. *J Am Pharm Assoc*. 2017;57:S180–4.
70. Green TC, Davis C, Xuan Z, Walley AY, Bratberg J. Laws Mandating Coprescription of Naloxone and Their Impact on Naloxone Prescription in Five US States, 2014–2018. *Am J Public Health*. American Public Health Association; 2020;110:881–7. [PubMed: 32298179]
71. Goodman-Bacon A Difference-in-differences with variation in treatment timing. Cambridge, MA: National Bureau of Economic Research; 2018 Sep. Report No.: Working paper 25018. https://www.nber.org/system/files/working_papers/w25018/w25018.pdf
72. Ben-Michael E, Feller A, Stuart EA. A trial emulation approach for policy evaluations with group-level longitudinal data. *ArXiv201105826 Stat*. 2020. <http://arxiv.org/abs/2011.05826>