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# Older, Less Regulated Medical Marijuana Programs Have Much Greater Enrollment Rates Than Newer 'Medicalized' Programs

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## **Abstract**

Twenty-three states and the District of Columbia have passed laws implementing medical marijuana programs. The nineteen programs that were in operation as of October 2014 collectively had over one million participants. All states (including D.C.) with medical marijuana laws require physicians directly or indirectly to authorize the use of marijuana at their discretion, yet little is known about how medical marijuana programs vary regarding adherence to basic principles of medical practice and associated rates of enrollment. To explore this, we analyzed marijuana programs according to seven components of traditional medical care and pharmaceutical regulation. We then examined enrollment rates, while controlling for potentially confounding state characteristics. We found that fourteen of the twenty-four programs were nonmedical and collectively enrolled 99.4 percent of participants nationwide, with enrollment rates twenty times greater than programs deemed to be "medicalized." Policy makers implementing or amending medical marijuana programs should consider the powerful relationship between less regulation and greater enrollment. Researchers should consider variations across programs when assessing programs' population-level effects.

Beginning with California in 1996, twenty-three states and the District of Columbia havelegalized possession and use of marijuana for medical purposes. As of October 2014 more than one million Americans were actively using marijuana under the aegis of such laws. Although physicians have rarely been involved in crafting medical marijuana laws or program regulations, all state programs task physicians with authorizing marijuana use, directly or indirectly, at their professional discretion. People who are eligible under state laws to participate in such programs and obtain a physician's authorization to do so are often required to register in a medical marijuana program before they can patronize dispensaries or grow a limited amount of marijuana at home.

State medical marijuana laws vary greatly in their requirements and provisions.<sup>3</sup> Early adopter states, such as California, passed laws (often via voter initiatives) that simply protected individuals who had received a physician's authorization for marijuana use from being prosecuted for possession. More recently, states have begun developing elaborate state-level agencies that oversee the manufacturing, dispensing, and labeling of cannabis-derived products within highly regulated programs.

Despite the great variation among state medical marijuana laws, published reports typically categorize states as simply having or not having medical marijuana laws. This approach overlooks policy differences across states that may affect rates of participation and population-level effects such as rates of use and heavy use, diversion of medical marijuana to adolescents, drug treatment admissions, and drugged driving. However, previous research has not assessed how medical marijuana laws vary across states with respect to their adherence to traditional standards of care in medicine.

To describe the variation among states, we analyzed medical marijuana laws and program regulations. We focused on the extent to which they incorporated basic tenets of medical practice; Current Good Manufacturing Practices, the main regulatory standard for ensuring pharmaceutical quality set by the Food and Drug Administration (FDA); and restrictions on controlled substances.<sup>2,5</sup>

Marijuana's anomalous status as a nonconventional alternative to pharmaceuticals prevents easy comparisons between the use of marijuana for medical purposes and traditional medical care. Nevertheless, the extent to which medical marijuana programs incorporate medical and pharmaceutical regulations may affect which people enroll in them (that is, people seeking treatment for verifiable medical conditions versus recreational marijuana users).

We evaluated the strength of the association between the medicalization of marijuana programs and population-based rates of enrollment. Finally, we assessed associations with other state characteristics that might contribute to program enrollment, such as the number of physicians per capita, the burden of terminal disease, medical marijuana costs, and baseline rates of recreational marijuana use.

# **Background**

Medical marijuana is frequently promoted as compassionate or palliative care for patients with severe or terminal illnesses. Such patients may use marijuana in an attempt to alleviate symptoms such as chemotherapy-induced nausea, AIDS-related cachexia (weakening or wasting of the body), or intractable pain that has not responded to conventional treatments. In addition, supporters of medical marijuana assert that the use of marijuana (both the whole plant and isolated compounds called cannabinoids) provides symptomatic relief for other debilitating medical conditions such as amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), multiple sclerosis, and posttraumatic stress disorder and that it has few adverse effects.

Unfortunately, few high-quality trials with marijuana exist for most indications.<sup>5,11</sup> This is in large measure because of marijuana's classification as a Schedule I substance. Under the

Controlled Substances Act of 1970, Schedule I substances are deemed by the FDA and the Drug Enforcement Administration as having no therapeutic value and high potential for abuse.

Despite marijuana's classification as a Schedule I substance, a 1999 Institute of Medicine (IOM) report concluded that cannabinoid drugs—primarily delta-9-tetrahydrocannabinol (THC)—had "potential therapeutic value" for pain relief, control of nausea and vomiting, and appetite stimulation. <sup>12(p3)</sup> The IOM limited its recommendations to "short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms." <sup>12(p7)</sup>

More recently, two systematic reviews of clinical trials concluded that high-quality evidence for the therapeutic efficacy of cannabinoids is limited to severe pain syndromes, neuropathic pain, and spasticity such as that due to multiple sclerosis. <sup>13,14</sup> These reviews primarily evaluated studies of existing FDA-approved medications (instead of smoked whole-plant marijuana) that are synthetic versions of THC, such as dronabinol, nabilone, or nabiximols (a sublingual spray containing THC and cannabidiol that has not yet been approved for use in the United States). <sup>15</sup>

Critics charge that medical marijuana programs are actually Trojan horses for recreational use and may cause more harm than proponents are willing to acknowledge. <sup>16</sup> Two cannabinoid-based medications (dronabinol and nabilone) have already been approved by the FDA, and alternatives to smoking whole-plant marijuana now exist, including vaporization with small portable devices. <sup>17,18</sup>

Strong evidence has also emerged for marijuana-induced psychosis that can persist for days or weeks beyond the initial period of intoxication, especially for marijuana strains with high-potency THC, <sup>19,20</sup> and earlier onset of schizophrenia among frequent marijuana users with familial and genetic vulnerabilities. <sup>16,21,22</sup> Physical dependence, withdrawal, <sup>23</sup> and clinical addiction affect as many as 9 percent of adult and 16 percent of adolescent frequent users. <sup>24,25</sup>

Of concern to policy makers, in many states people receive authorizations for medical marijuana from physicians whom they have seen for a single visit, from whom they receive no diagnosis, and with whom they do not follow up.<sup>26,27</sup> Initial studies have shown that the typical medical marijuana patient in these states is a young male with a nonspecific indication of chronic or severe pain and a history of recreational marijuana use, instead of a patient receiving ongoing medical care under a physician's supervision for a severe or terminal illness.<sup>28–30</sup>

Following the legalization of recreational marijuana use in four states and the District of Columbia, beginning in 2012, many commentators viewed medical marijuana laws as stepping-stones to inevitable legalization of marijuana for recreational purposes. Yet the great variation in medical marijuana laws complicates the politics underlying marijuana policy reform. Our study addressed these issues by analyzing the medical structure of marijuana programs, the role of physicians, and the impact of regulation on constraining versus expanding access to this controversial drug.

# **Study Data and Methods**

#### **Sources of Data and Assessment**

We analyzed legislation and program regulations from the twenty-three states and the District of Columbia with medical marijuana laws. Our analysis, including year and method of initial passage (such as voter initiative or legislative act), was based on laws and regulations publicly available through the National Conference of State Legislatures and state departments of health as of December 31, 2014, as documented in the online Appendix.<sup>31</sup> We evaluated state programs according to seven components common to medical practice and pharmaceutical regulation involving controlled substances (Exhibit 1).

Two of the components, requiring a bona fide doctor-patient relationship and using non-smoked medication, are well-accepted principles of clinical practice. A state program was considered to require a bona fide doctor-patient relationship if the statute implementing the program required the authorizing physician to complete a full medical assessment, make a diagnosis, and manage ongoing care.<sup>32</sup> Currently no medication within the pharmacopeia is smoked (because of the harms of smoking). Given alternatives to smoking (such as vaporizing liquid concentrates), there is no clinical justification for this route of administration.<sup>18</sup>

Two other components in Exhibit 1 are related to the Current Good Manufacturing Practices enforced by the FDA for pharmaceuticals.<sup>33</sup> The principles of consistent and safe production are reflected in programs' requirements for state-licensed manufacturing and dispensing and uniform testing and labeling (of the amounts and concentrations of individual cannabinoids) of marijuana products (irrespective of the place of manufacture).<sup>5,15,33</sup> Without uniform testing, consumers may receive marijuana products that are mislabeled, contaminated, or both.<sup>34</sup>

The following final three components in Exhibit 1 were derived from restrictions on the use of controlled substances by the Drug Enforcement Administration and state law enforcement agencies: a thirty-day limit on refills, linkage to prescription drug monitoring programs, and physician certification.<sup>35–37</sup> States satisfied the thirty-day refill criterion if they limited refills to thirty-day periods, which is consistent with current practice for controlled substances (such as prescription stimulants or benzodiazepines).

Prescription drug monitoring programs that track controlled substances are now operational in virtually all states.<sup>38</sup> Increasingly, physicians are required to check these online databases of patient prescription activity before prescribing controlled substances.<sup>36</sup> State programs satisfied this criterion if they required authorizing physicians to link to the state's prescription drug monitoring program.

Finally, precedent exists for requiring special training or certification for physicians who wish to prescribe certain medications such as buprenorphine (categorized as a Schedule III controlled substance, which means it has a risk of abuse that could produce physical or psychological dependence). Although there is disagreement regarding the necessity for these

restrictions on clinical practice, they reflect various current federal and state regulations related to controlled substances.

We categorized programs that met multiple medical components (thus receiving a medical orientation score greater than 1) as medicalized. We categorized the other programs as nonmedical because there was minimal or no indication that they adhered to basic tenets of medical practice or pharmaceutical regulation. We then assessed rates of enrollment in medical marijuana programs with respect to the program's category (medicalized or nonmedical), each of the seven individual components, and state-level characteristics.

Two of the authors—Arthur Robin Williams and Mark Olfson, both physicians with experience in public health and social policy—independently coded all documents containing state-level medical marijuana laws and current medical marijuana program guidelines according to the seven components listed above. There was a high level of agreement between the reviewers, yielding a kappa value of 0.95. Discordant coding was reconciled by consensus between Williams and Olfson.

#### State Characteristics

Chi-square tests and *t*-tests were used to compare the background characteristics of state programs—such as state gross domestic product<sup>39</sup> and census region<sup>40</sup>—based on their level of medicalization (Exhibit 2).

#### **Covariates of Enrollment**

Program enrollment rates were derived from publicly available collated state figures for the nineteen medical marijuana programs in operation as of October 2014. In addition to the total medical orientation score, the following independent state-level covariates were selected as factors that might influence enrollment: the number of physicians per capita, HIV prevalence, rate of people in hospice care, program registration costs, incremental or excise taxes, and rate of recreational marijuana use (for further details about the covariates, see the Appendix). <sup>31</sup>

The number of active physicians per 100,000 state residents in 2012 was derived from data from the Association of American Medical Colleges. 41 We evaluated HIV prevalence and rate of people in hospice care as proxies for the burden of severe or terminal disease by state, given that most medical marijuana laws are passed explicitly for the care of these patient populations, among others. Rates of HIV prevalence were obtained from the 2011 *HIV Surveillance Report.* 42 Rates of people in hospice care were estimated with 2008 data from the Hospice Association of America. 43

Registration costs were obtained from program websites and publicly available data that reflected the lowest cost for enrolling in a state's marijuana program.<sup>44</sup> Given variation in state and municipal sales taxes, we restricted our analysis to incremental excise taxes for medical marijuana as a proxy for the additional out-of-pocket expense for program enrollees.<sup>44</sup> True out-of-pocket expenses across states are difficult to determine and have not been well characterized.<sup>45</sup>

States' rates of recreational marijuana use (use in the previous month by individuals ages twelve and older) were estimated by aggregating 2012 and 2013 state-level public use reports from the National Survey on Drug Use and Health. <sup>46</sup> The respondents to this survey are noninstitutionalized individuals living in the community or on military bases who collectively are representative of a given state's population. Higher state-level prevalence of marijuana use has been positively associated with the passage of medical marijuana laws but has not previously been evaluated in association with program enrollment. <sup>47</sup>

#### Limitations

Our study had several limitations. First, it was limited by the number of medicalized programs with available enrollment figures, as full implementation of manufacturing and dispensing practices often requires several years.<sup>3</sup> Because of the small number of medicalized programs in full operation (five), we were unable to assess specific relationships between less common components of medical marijuana programs (such as requiring nonsmoked marijuana or linking medical marijuana program participation to prescription drug monitoring programs) and enrollment.

Second, we were also unable to assess the impact of services provided by high-volume marijuana specialty clinics on rates of enrollment in medical marijuana programs. Such specialty clinics were founded following the passage of medical marijuana laws. They solicit patients' medical records (sometimes over the Internet), conduct perfunctory patient evaluations, and claim to have enrolled hundreds of thousands of participants nationwide. They likely have a disproportionate impact in states with marijuana programs that have little regulation. For instance, one high-volume marijuana specialty clinic system that operates in seven states (all of which operate nonmedical programs) claims to have enrolled over 250,000 patients in a fifteen-year period. 27,48

Finally, although the seven components that we assessed reflect common clinical practice, it is difficult to determine which components are most relevant to the medical use of marijuana, given its federal illegality and anomalous status outside the standard purview of state and federal regulation.

# **Study Results**

## **Medical orientation**

Considerable variation existed across the twenty-three states and the District of Columbia with medical marijuana programs (for details, see the Appendix).<sup>31</sup> The mean total medicalization score was 1.96 (standard deviation: 2.15), with a range of 0 to 7 (on a scale of 0 to 7). A bona fide doctor-patient relationship (Exhibit 1) was the most common component, present in fifteen (62.5 percent) of the programs. Only two programs (those in Minnesota and New York) required nonsmoked marijuana, and only three programs required authorizing physicians to link to their state's prescription drug monitoring program (Connecticut, Massachusetts, and New York) or required physician certification through a state-based licensing or training program (Maryland, Massachusetts, and New York).

Programs in nine states and the District of Columbia were considered medicalized because they included more than one of the seven components (mean score: 4.1; SD: 1.4). Nine of these ten programs required exclusive state-licensed manufacturing and dispensing, all of which required the testing and labeling of the cannabinoid profile of products. Six of the ten programs implemented regulations reserved for controlled substances.

The other fourteen programs were considered nonmedical because they included only one or none of the components (mean score: 0.43; SD: 0.51). Eight of these fourteen did not include any of the components and thus had a score of 0. The other six included only the component of a bona fide doctor-patient relationship, giving each of them a score of 1.

Eight of the fourteen nonmedical programs had established state-licensed dispensaries as an option for participants, and another program (the one in California) allowed the use of dispensaries that were not regulated by the state.<sup>49</sup> The remaining five programs did not have dispensaries, state-licensed or otherwise. As a result, these fourteen nonmedical states allow either home cultivation of marijuana or other forms of procurement outside of state-licensed dispensaries.

Medicalized and nonmedical programs differed significantly with respect to route and year of passage (Exhibit 2). Medicalized programs were more likely than nonmedical ones to have been created by legislative act (90.0 percent versus 28.6 percent) and to have been created more recently.

#### Rate of Enrollment

Among the nineteen programs in operation as of October 2014, medicalized programs had approximately one-twentieth the rate of enrollment of nonmedical programs: 58 per 100,000 state residents (SD: 31.7) versus 1,030 (SD: 160.3), a significant difference (p = 0.002) (data not shown). See Exhibit 3 for further statistical modeling of medical orientation and enrollment rates.

As a result, 99.4 percent of all participants nationwide were in nonmedical programs. An increase in the total medical orientation score of one standard deviation was associated with a 180 percent reduction in the rate of enrollment (p < 0.01) (see Appendix C). Registration costs were also inversely and significantly related to enrollment rates, but with a smaller effect size: An increase in the cost of one standard deviation was associated with a 105 percent reduction in enrollment (p < 0.01) (see Appendix C). For further details, see the analyses in the Appendix. p < 0.01

Except for program registration costs, enrollment was not significantly related to any of the independent state-level covariates listed above—that is, the number of active physicians per capita, HIV prevalence, rate of people in hospice care, incremental or excise taxes, or rate of recreational marijuana use (for details, see the Appendix).<sup>31</sup> In post hoc analyses, we found that the strongest associations (inverse correlations) were between enrollment rates and states' requiring state-licensed manufacturing and dispensation as the only route of access to marijuana (p = 0.002) and between enrollment rates and states' requiring uniform testing and labeling of products (p = 0.002) (Exhibit 4).

# **Discussion**

There was wide variation in the extent to which the medical marijuana programs in the twenty-three states and the District of Columbia embodied principles of traditional medical practice and pharmaceutical regulation. Fourteen of the states used little regulation, and their programs can be characterized as nonmedical. The other nine states and the District of Columbia have newer and more highly regulated programs that can be characterized as medicalized.

Medicalized programs typically required state-licensed manufacturing, dispensing, testing, and labeling of marijuana products. Half of these programs also included restrictive elements for controlled substances, such as linking marijuana program activity to prescription drug monitoring programs or requiring physicians to complete a specialized training course to be eligible to authorize patient access to marijuana for medical purposes. Among the nineteen state programs in operation as of October 2014, the medicalized programs had approximately one-twentieth the rate of enrollment of the nonmedical programs.

Such stark differences in enrollment may be related to the process by which medical marijuana laws were first passed in each state. We found that early laws were mostly passed by voter initiative in western states with low population density, and the programs implemented under these laws departed from a medical model. More recent programs enacted by midwestern and northeastern legislatures since 2009 are more highly regulated and medicalized. These more recent programs typically require years of work at the state level between initial passage of a law and full implementation of a state-licensed manufacturing and dispensary system. They operate in contrast to earlier programs that simply permitted home cultivation of marijuana or provided state-level legal protections for marijuana possession, sometimes without requiring marijuana users to formally register with the state.<sup>4</sup>

The effects of dispensaries on rates of marijuana use, heavy use, use of high-potency strains, and changes in prices have received some attention in the policy literature. In general, epidemiological studies have been mixed in linking passage of medical marijuana laws with changes in marijuana use. Mixed findings may stem from variation across states with dispensaries with respect to allowing other means of marijuana procurement. For instance, early-adopter states allowed home cultivation long before any state licensed a dispensary. Such variation may confound the impact of dispensaries on marijuana use. Lower rates of medical marijuana use may occur when state-licensed dispensaries are the only means of access, which is the case in nine of the ten medicalized programs and none of the nonmedical programs. Additionally, the mere presence of dispensaries may have less influence on marijuana use, compared to regulations restricting who qualifies as dispensary patrons.

Registration costs of medical marijuana programs were also significantly (negatively) associated with enrollment rates. However, higher registration costs (typically \$50–\$100 per year, discounted for low-income state residents) may be associated with lower enrollment

rates if they are secondary to the expense of state regulatory agencies overseeing manufacturing and dispensing. For instance, registration costs of medicalized programs, which are presumably more expensive to operate, were approximately twice those of nonmedical programs.

The time lag between initial passage of a law and full implementation of a program may contribute to the great discrepancy in enrollment rates between medicalized and nonmedical programs. Yet time lags alone are unlikely to account for all of the discrepancy. Rates of enrollment were notably lower in all programs before 2009, <sup>50</sup> given the great uncertainty at the time related to the prospect of federal prosecution of program staff members and participants. <sup>49</sup> In response to these concerns, the Department of Justice released memos in 2009 and 2011 that clarified federal intentions to refrain from interfering with lawfully run programs at the state level, which facilitated the consequent expansion of enrollment. <sup>49,52</sup>

# Conclusion

With the legalization of marijuana for recreational use by adults older than twenty-one in four states and the District of Columbia, the country has entered a new era of marijuana control policy. There has been a slow decades-long reversal of marijuana prohibition—with physicians initially enlisted as gatekeepers to legal access to marijuana for medical purposes—that may have been a precursor to legalization of recreational use in some states.

Our analysis revealed that virtually all of the one million users of medical marijuana reside in states with older nonmedical programs that have minimal physician or state oversight. It is likely not a coincidence that the states that legalized recreational use of marijuana (Alaska, Colorado, Oregon, and Washington) were states with nonmedical programs first passed by voter initiative. In effect, they have simply expanded the pool of eligible users beyond the subset already using marijuana for medical purposes. In contrast, states with medicalized programs may be much less likely to legalize recreational use in the foreseeable future.

There is a need for population-level research to assess not only the presence of medical marijuana laws but also how program regulations affect enrollment rates and who participates in the programs. In particular, future research should avoid simply classifying states as having versus not having medical marijuana laws. As our findings show, there is considerable variation in the regulation of marijuana programs across states, and this variation has a significant impact on program enrollment. Additional studies are needed to determine whether regulation also affects who participates in the programs and whether nonmedical programs disproportionately attract recreational users.

In view of substantial differences in enrollmentrates between medicalized and nonmedical programs, policy makers should evaluate for associations between specific program regulations and unintended social costs—including rates of illicit marijuana use, medical marijuana diverted to adolescents, marijuana-related emergency department visits and drug treatment admissions, and drugged driving incidents—among participants in minimally regulated programs compared to participants in highly regulated ones.

# **Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

# **Acknowledgments**

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# **Notes**

- ProCon.org. Number of legal medical marijuana patients (as of Oct 27, 2014 [Internet]. Santa Monica (CA): ProCon; last updated 2015 Apr 27Available from: http:// medicalmarijuana.procon.org/view.resource.php?resourceID=005889 [cited 2016 Jan 8]
- 2. Hoffmann DE, Weber E. Medical marijuana and the law. N Engl J Med. 2010; 362(16):1453–7. [PubMed: 20410512]
- 3. Pacula RL, Sevigny EL. Marijauna liberalization policies: why we can't learn much from policy still in motion. J Policy Anal Manage. 2014; 33(1):212–21. [PubMed: 24358530]
- 4. Pacula RL, Hunt P, Boustead A. Words can be deceiving: a review of variation among legally effective medical marijuana laws in the United States. J Drug Policy Anal. 2014; 7(1):1–19. [PubMed: 25657828]
- 5. Wilkinson ST, D'Souza DC. Problems with the medicalization of marijuana. JAMA. 2014; 311(23): 2377–8. [PubMed: 24845238]
- Hazekamp A, Grotenhermen F. Review on clinical studies with cannabis and cannabinoids 2005– 2009. Cannabinoids. 2010; 5(special issue):1–21.
- Carter GT, Abood ME, Aggarwal SK, Weiss MD. Cannabis and amyotrophic lateral sclerosis: hypothetical and pratical applications, and a call for clinical trials. Am J Hosp Palliat Care. 2010; 27(5):347–56. [PubMed: 20439484]
- Koppel BS, Brust JC, Fife T, Bronstein J, Youssof S, Gronseth G, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: reports of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014; 82(17): 1556–63. [PubMed: 24778283]
- Trezza V, Campolongo P. The endocannabinoid system as a possible target to treat both the cognitive and emotional features of post-traumatic stress disorder (PTSD). Front Behav Neurosci. 2013; 7:100. [PubMed: 23950739]
- Reiman A, Aggarwal SK, Reinarman C. Medicalization of marijuana. JAMA. 2014; 312(18):1931.
   [PubMed: 25387197]
- 11. Taylor, T. Supporting research into the therapeutic role of marijuana. Philadelphia (PA): American College of Physicians; 2008. Position Paper
- 12. Institute of Medicine. Marijuana and medicine: assessing the science base. Washington (DC): National Academies Press; 1999.
- 13. Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. JAMA. 2015; 313(24):2474–83. [PubMed: 26103031]
- 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(24):2456–73. [PubMed: 26103030]
- 15. Bostwick JM. Blurred boundaries: the therapeutics and politics of medical marijuana. Mayo Clin Proc. 2012; 87(2):172–86. [PubMed: 22305029]

16. Haney M, Evins AE. Does cannabis cause, exacerbate, or ameliorate psychiatric disorders? An oversimplified debate discussed. Neuropsychopharmacology. 2016; 41(2):393–401. [PubMed: 26286840]

- 17. Kalant H. Smoked marijuana as medicine: not much future. Clin Pharmacol Ther. 2008; 83(4): 517–9. [PubMed: 18349871]
- 18. Melvin D, Markham AW. Medical marijuana. Can J Resp Ther. 2015; 51(1):11–12.
- 19. Di Forti M, Marconi A, Carra E, Fraietta S, Trotta A, Bonomo M, et al. Proportion of patients in South London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. Lancet Psychiatry. 2015; 2(3):233–8. [PubMed: 26359901]
- Castle, D.; Murray, R.; D'Souza, D., editors. Marijuana and madness. 2nd. Cambridge: Cambridge University Press; 2012.
- 21. Ogden, DW. Washington (DC): Department of Justice; 2009 Oct 19. Memorandum for selected United States attorneys: investigations and prosecutions in states authorizing the medical use of marijuana [Internet]. Available from: http://www.justice.gov/opa/blog/memorandum-selected-united-state-attorneys-investigations-and-prosecutions-states [cited 2016 Jan 8]
- 22. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet. 2007; 370(9584):319–28. [PubMed: 17662880]
- 23. Cooper ZD, Haney M. Actions of delta-9-tetrahydrocannabinol in cannabis: relation to use, abuse, dependence. Int Rev Psychiatry. 2009; 21(2):104–12. [PubMed: 19367504]
- 24. Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. Exp Clin Psychopharmacol. 1994; 2(3):244–68.
- 25. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med. 2014; 370(23):2219–27. [PubMed: 24897085]
- 26. Kleber HD, DuPont RL. Physicians and medical marijuana. Am J Psychiatry. 2012; 169(6):564–8. [PubMed: 22684592]
- Song, A. [cited 2016 Jan 8] How difficult is it to get a medical marijuana card? KATU [serial on the Internet]. 2010 May 20. Available from: http://katu.com/archive/how-difficult-is-it-to-get-amedical-marijuana-card-11-19-2015
- Reinarman C, Nunberg H, Lanthier F, Heddleston T. Who are medical marijuana patients?
   Population characteristics from nine California assessment clinics. J Psychoactive Drugs. 2011;
   43(2):128–35. [PubMed: 21858958]
- 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(10): 1668–73. [PubMed: 25154332]
- 30. Bonn-Miller MO, Boden MT, Bucossi MM, Babson KA. Self-reported cannabis use characteristics, patterns, and helpfulness among medical cannabis users. Am J Drug Alcohol Abuse. 2014; 40(1):23–30. [PubMed: 24205805]

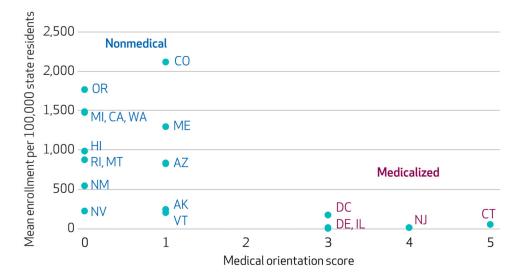
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To access the Appendix, click on the Appendix link in the box to the right of the article online.

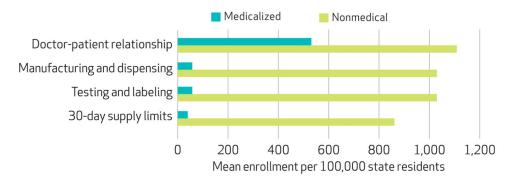
- 32. Association of American Medical Colleges. The road to becoming a doctor. Washington (DC): AAMC: 2008.
- 33. Food and Drug Administration. Silver Spring (MD): FDA; Facts about the Current Good Manufacturing Practices (CGMPs) [Internet]. last updated 2015 Jan 6Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm [cited 2015 Jan 8]
- 34. Vandrey R, Raber JC, Raber ME, Douglass B, Miller C, Bonn-Miller MO. Cannabinoid dose and label accuracy in edible medical cannabis products. JAMA. 2015; 313(24):2491–3. [PubMed: 26103034]
- Department of Justice. Pharmacist's manual: an informational outline of the Controlled Substances Act. Washington (DC): DOJ; 2010.

36. Rutkow L, Turner L, Lucas E, Hwang C, Alexander GC. Most primary care physicians are aware of prescription drug monitoring programs, but many find the data difficult to access. Health Aff (Millwood). 2015; 34(3):484–92. [PubMed: 25732500]

- Substance Abuse and Mental Health Services Administration. Buprenorphine Drug Addiction Treatment Act of 2000. Rockville (MD): SAMHSA; 2000 Oct 17.
- 38. National Alliance for Model State Drug Laws. NAMSDL. Santa Fe; NM: 2014. Compilation of state prescription monitoring program maps.
- 39. Bureau of Economic Analysis. Washington (DC): Department of Commerce; Interactive data [Internet]. Available from: https://www.bea.gov/itable/index.cfm [cited 2016 Jan 8]
- 40. Census Bureau. Population estimates: vintage 2008 national tables: annual estimates of the resident population for the United States, regions, states, and Puerto Rico: April 1, 2000 to July 1, 2008 (NSTEST2008-01) [Internet]. Washington (DC): Census Bureau; last revised 2011 Dec 8Available for download from: http://www.census.gov/popest/data/historical/2000s/vintage\_2008/ [cited 2016 Jan 15]
- 41. Association of American Medical Colleges. State physician workforce data book. Washington (DC): AAMC; 2013.
- 42. Centers for Disease Control and Prevention. Atlanta (GA): CDC; Diagnoses of HIV infection in the United States and dependent areas, 2011 [Internet]. last updated 2013 Jul 24Available from: http://www.cdc.gov/hiv/pdf/statistics\_2011\_HIV\_Surveillance\_Report\_vol\_23.pdf [cited 2016 Jan 8]
- 43. Hospice Association of America. Hospice facts & statistics. Washington (DC): The Association; 2010 Nov.
- 44. Marijuana Policy Project. State medical marijuana programs' program fees and taxes. Washington (DC): The Project; 2015 Feb.
- 45. Caulkins, JP.; Hawken, A.; Kilmer, B.; Kleiman, MAR. Marijuana legalization: what everyone needs to know. New York (NY): Oxford University Press; 2012.
- 46. Substance Abuse and Mental Health Services Administration. Rockville (MD): SAMHSA; 2014. Results from the 2013 National Survey on Drug Use and Health: summary of national findings [Internet]. Available from: http://www.samhsa.gov/data/sites/default/files/ NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.pdf [cited 2016 Jan 14]
- 47. Cerdá M, Wall M, Keyes KM, Galea S, Hasin D. Medical marijuana laws in 50 states: investigating the relationship between state legalization of medical marijuana and marijuana use, abuse, and dependence. Drug Alcohol Depend. 2012; 120(1–3):22–7. [PubMed: 22099393]
- 48. Crombie, N. [cited 2016 Jan 8] Medical marijuana: a few high-volume doctors approve most patients. Oregonian [serial on the Internet]. Updated 2012 Dec 30Available from: http://www.oregonlive.com/health/index.ssf/2012/12/medical\_marijuana\_a\_few\_high-v.html
- 49. Marijuana Policy Project. Washington (DC): MPP; State medical marijuana programs' financial information [Internet]. last updated 2013 Oct 18Available from: https://www.mpp.org/issues/medical-marijuana/state-medical-marijuana-programs-financial-information/ [cited 2016 Jan 8]
- 50. Anderson DM, Rees DI. The role of dispensaries: the devil is in the details. J Policy Anal Manage. 2014; 33(1):235–40. [PubMed: 24358532]
- 51. 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(1):7–31. [PubMed: 25558490]
- 52. Sevigny EL, Pacula RL, Heaton P. The effects of medical marijuana laws on potency. Int J Drug Policy. 2014; 25(2):308–19. [PubMed: 24502887]
- 53. Wen H, Hockenberry JM, Cummings JR. The effect of medical marijuana laws on adolescent and adult use of marijuana, alcohol, and other substances. J Health Econ. 2015; 42:64–80. [PubMed: 25863001]



**Exhibit 3. Enrollment and medical orientation scores in state medical marijuana programs Source** Authors' analysis of information on 19 state medical marijuana programs in operation as of October 27, 2014.



 $\label{lem:expression} \textbf{Exhibit 4. Enrollment in state medical marijuana programs and presence of four program components }$ 

**Source** Authors' analysis of information on 19 state medical marijuana programs in operation as of October 27, 2014. **Notes** The components are described in Exhibit 1. Each of the first three components were included in nineteen programs; thirty-day supply limits were included in sixteen programs.

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# Exhibit 1

Components of traditional medical care and pharmaceutical regulation

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Component	Description	Rationale
Doctor-patient relationship	Physician must have bona fide clinical relationship with patient, including completing full medical assessment, making diagnosis, and managing ongoing care for indicated condition.	The bedrock of clinical practice, the doctor-patient relationship obligates the physician to monitor treatment response and titrate dosing following diagnosis. These skills are taught in graduate medical training and tested in the United States Medical Licensing Examination required for physician licensure (see Note 32 in text).
Manufacturing and dispensing	State licensing required for marijuana manufacturing and dispensing, which prohibits home cultivation or procurement of marijuana outside of state-licensed dispensaries.	Licensed manufacturing and dispensation ensure that participants with valid prescriptions receive a consistent product free of contaminants and minimize the risk of diversion of marijuana to adolescents (see Note 33 in text).
Testing and labeling	Testing and labeling of marijuana cannabinoid profile required. Of the more than 60 cannabinoids in marijuana, dozens are thought to have therapeutic potential in isolation or with "entourage" (combination) effects.	Identifying active ingredients, typically isolated molecular entities, ensures patients of consistent content and suggests their intended effects.
Use of nonsmoked medication	Marijuana use limited to nonsmoked products—that is, not whole plants or home-cultivated product, but edibles or concentrates for oral use or vaporization.	No evidence to date substantiates a therapeutic need for smoked marijuana. Vaporizing and other routes of administration have made smoking obsolete within clinical practice (see Notes 17 and 26 in text).
30-day supply limits	Supply of marijuana dispensed limited to 30-day amount with no refills (unless authorized for up to 90 days, consistent with standard prescribing practices).	The Controlled Substances Act of 1970 limits refills for scheduled drugs such as methylphenidate (Schedule II), hydrocodone (Schedule III), and benzodiazepines (Schedule IV) (see Note 35 in text).
Prescription drug monitoring program	Physician required to check patient's profile in an online statewide prescription drug monitoring program that tracks prescription history.	States are increasingly implementing these programs and requirements to help prevent illicit activity such as doctor shopping and medication diversion (see Note 36 in text).
Physician training	Physician must complete training to be certified as marijuana-recommending provider.	High-risk medications such as buprenorphine, antibiotics for multidrug-resistant organisms, and expensive chemotherapies often can be prescribed only by physicians with special training (see Note 37 in text).

Source Authors' analysis. Note The manufacturing and dispensing component is a prerequisite for the following two components: testing and labeling, and the use of nonsmoked medication.

<sup>&</sup>lt;sup>a</sup>See Note 34 in text and Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypotheses. 2006;66(2):234–46.

Exhibit 2
Characteristics of state medical marijuana programs passed as of October 1, 2014

Characteristic	Medicalized programs $(n = 10)$	Nonmedical programs $(n = 14)$	p value
Created by legislative act	90.0%	28.6%	0.004
Mean years since passage of medical marijuana law (SD)	2.7 (0.50)	13 (1.18)	<0:0001
Census region (number)	West (0) Midwest (2) Northeast (5) South (3)	West (10) Midwest (1) Northeast (3) South (0)	0.13
2008 state population density $^a(SD)$	1,454.1 (939.9)	146.45 (70.1)	0.11
State GDP (millions) $^b$ (SD)	\$393,429 (\$113,390)	\$296,314 (\$142,521)	0.62
Mean enrollment per 100,000 residents $^{\mathcal{C}}$ (SD)	58 (31.7)	1,030 (160.3)	0.002

Source: Authors' analysis. Notes Most of the article's analysis deals with the 19 programs (14 nonmedical and 5 medicalized) that were in operation as of October 1, 2014. SD is standard deviation.

<sup>&</sup>lt;sup>a</sup>Population density data (people per square land mile) are derived from US Census Bureau. Population estimates (see Note 40 in text).

<sup>&</sup>lt;sup>b</sup>Gross domestic product (GDP) is expressed in 2013 seasonally adjusted millions of dollars (see Note 39 in text).

<sup>&</sup>lt;sup>C</sup>Enrollment rates are derived from publicly available data sources for the five medicalized programs and fourteen nonmedical programs that were in operation as of October 2014 (see Note 1 in text).