

VIEWPOINT

Should Physicians Recommend Replacing Opioids With Cannabis?

Keith Humphreys, PhD

Veterans Affairs Health Services Research and Development Center; and Stanford University, Palo Alto, California.

Richard Saitz, MD, MPH

Department of Community Health Sciences, Boston University School of Public Health, Boston, Massachusetts; Clinical Addiction Research and Education Unit, Section of General Internal Medicine, and Grayken Center for Addiction, Boston Medical Center, Boston, Massachusetts; and Associate Editor, *JAMA*.

Recent state regulations (eg, in New York, Illinois) allow medical cannabis as a substitute for opioids for chronic pain and for addiction. Yet the evidence regarding safety, efficacy, and comparative effectiveness is at best equivocal for the former recommendation and strongly suggests the latter—substituting cannabis for opioid addiction treatments is potentially harmful. Neither recommendation meets the standards of rigor desirable for medical treatment decisions.

Efficacy of Cannabis for Chronic Pain and for Opioid Use Disorder

Recent systematic reviews^{1,2} identified low-strength evidence that plant-based cannabis preparations alleviate neuropathic pain and insufficient evidence for other types of pain. Studies tend to be of low methodological quality, involve small samples and short-follow-up periods, and do not address the most common causes of pain (eg, back pain). This description of evidence for efficacy of cannabis for chronic pain is similar to how efficacy studies of opioids for chronic pain have been described (except that the volume of evidence is greater for opioids with 96 trials identified in a recent systematic review³).

In a sample of 84 cannabidiol extracts purchased online, 69% (n = 58) had mislabeled cannabinoid content.

The evidence that cannabis is an efficacious treatment for opioid use disorder is even weaker. To date, no prospective evidence, either from clinical trials or observational studies, has demonstrated any benefit of treating patients who have opioid addiction with cannabis.

Comparative Effectiveness: Substituting Cannabis for Opioids

Substituting cannabis for opioids is not the same as initiating opioid therapy. There are no randomized clinical trials of substituting cannabis for opioids in patients taking or misusing opioids for treatment of pain, or in patients with opioid addiction treated with methadone or buprenorphine. In addition to surveys of patients who use medical cannabis, the other types of studies prompting a move to cannabis to replace opioids are population-level reports stating that laws allowing medical cannabis use are followed by fewer opioid overdose deaths than expected. The methodological concern with such studies is that correlation is not causation. Many factors other than cannabis use may affect opioid overdose deaths, such as prescribing guidelines, opioid

rescheduling, Good Samaritan laws, incarceration practices, and availability of evidence-based opioid use disorder treatment and naloxone. Furthermore, the aggregate population associations (eg, between medical cannabis and opioid overdose) may be opposite of those seen within individuals. In the only individual-level analysis, which included 57 146 people aged 12 and older, of a nationally representative sample, medical cannabis use was positively associated with greater use and misuse of prescription opioids.⁴

The largest prospective study of cannabis as a substitute for opioids was a 4-year cohort study of 1514 patients with chronic pain who had been prescribed opioids.⁵ Cannabis use was associated with more subsequent pain, less self-efficacy for managing pain, and no reductions in prescribed opioid use. There was no substitution; rather, cannabis was simply added to the mix of addictive substances taken by patients with pain.

For opioid use disorder, there is concern that the New York State Health Commissioner has defined opioid addiction to include people being treated with US Food and Drug Administration–approved, efficacious, opioid agonist medications, as a qualifying condition for medical cannabis.⁶ Methadone and buprenorphine treatment reduces illicit opioid use, blood-borne disease transmission, criminal activity, adverse birth outcomes, and mortality. Discontinuing such medications increases the risk of return to illicit opioid use, overdose, and death. The suggestion that patients should self-substitute a drug (ie, cannabis) that has not been subjected to a single clinical trial for opioid addiction is irresponsible and should be reconsidered.

These approaches reflect the stigmatized nature of people with opioid addiction that cannabis therapy might be considered reasonable with no clinical trials when no comparable provision has been made for other chronic diseases for which claims of cannabis' benefits have been made (eg, no regulations have suggested that patients with diabetes stop taking insulin and take cannabis instead). The recommendation is consistent with a history of medical professionals arguing that a different class of addictive drug will eliminate an addiction. For instance, in the past, morphine had been promoted as a cure for alcohol use disorder; cocaine as a cure for morphine addiction and alcohol use disorder; and heroin as a cure for alcohol use disorder, morphine addiction, and cocaine addiction.

Risks of Cannabis Use

Unlike opioids, cannabis appears to have no risk of fatal overdose. However, systematic reviews find increased

Corresponding

Author: Richard Saitz, MD, MPH, Department of Community Health Sciences, Boston University School of Public Health, 801 Massachusetts Ave, Fourth Floor, Boston, MA 02118 (richard.saitz@jamanetwork.org).

risks of motor vehicle crashes, cognitive impairment, structural brain changes, and psychotic symptoms.^{1,7} The risk of cannabis addiction should be mentioned, particularly when the rationale for substitution is to prevent or treat addiction in people with or at risk for cannabis and other substance addiction. In a national population-based survey of 36 309 adults, the prevalence of cannabis use disorder was 31% among those reporting any use in the past year.⁸ Cannabis addiction means use that causes clinically significant impairment or distress, including use that is out of control (the person tries to reduce use and cannot); craving; and recurrent social, occupational, and physical consequences. Cannabis use is also prospectively associated with a greater risk for other substance use disorders. All of these risks must be considered in light of the lack of evidence that taking cannabis while using opioids will necessarily result in a tapering of opioid dose, ie, it is entirely possible that these risks associated with cannabis will be added to those of opioid use.

If Cannabis Is Recommended Medicine, It Should Be Held to Medical Standards

Clinical trials of opioids are of preparations of medications manufactured and regulated by national standards, which test specified doses, frequencies, and routes of administration. The known risks and benefits are derived from such studies. In clinical practice, clinicians prescribe the studied medications. These practices are not used for cannabis. Most clinical trials do not provide comparable evidence for medical cannabis. Medical cannabis regulations make unregulated products available to be inhaled in smoke or vapor, applied topically as oils and creams, eaten in edibles, or taken orally or sublingually. The demonstrated efficacy and safety of these

products should not be labeled as medical. "Budtenders," not pharmacists, physicians, or other clinicians, make clinical recommendations. In a sample of 84 cannabidiol extracts purchased online, 69% (n = 58) had mislabeled cannabinoid content.⁹ Ecological correlational studies and individual testimonials of benefit are not the quality of evidence typically required to recommend a medication for clinical use. Vulnerable and stigmatized patients with chronic pain and patients with addiction desperate for help are those exposed to such treatments, likely with no recourse if adverse effects occur (Food and Drug Administration-level assertions of safety and efficacy do not exist, and malpractice is likely not applicable).

Conclusions

Cannabis and cannabis-derived medications merit further research, and such scientific work will likely yield useful results. This does not mean that medical cannabis recommendations should be made without the evidence base demanded for other treatments. Evidence-based therapies are available. For chronic pain, there are numerous alternatives to opioids aside from cannabis. Nonopioid medications appear to have similar efficacy,³ and behavioral, voluntary, slow-tapering interventions can improve function and well-being while reducing pain.

For the opioid addiction crisis, clearly efficacious medications such as methadone and buprenorphine are underprescribed. Without convincing evidence of efficacy of cannabis for this indication, it would be irresponsible for medicine to exacerbate this problem by encouraging patients with opioid addiction to stop taking these medications and to rely instead on unproven cannabis treatment.

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REFERENCES

- Nugent SM, Morasco BJ, O'Neil ME, et al. The effects of cannabis among adults with chronic pain and an overview of general harms. *Ann Intern Med*. 2017;167(5):319-331. doi:10.7326/M17-0155
- Campbell G, Hall W, Degenhardt L, Dobbins T, Farrell M. Cannabis use and non-cancer chronic pain—authors' reply. *Lancet Public Health*. 2018;3(10):e469. doi:10.1016/S2468-2667(18)30182-8
- Busse JW, Wang L, Kamaleldin M, et al. Opioids for chronic noncancer pain. *JAMA*. 2018;320(23):2448-2460. doi:10.1001/jama.2018.18472

4. Caputi TL, Humphreys K. Medical marijuana users are more likely to use prescription drugs medically and non-medically. *J Addict Med*. 2018;12(4):295-299. doi:10.1097/ADM.0000000000000405

5. Campbell G, Hall WD, Peacock A, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids. *Lancet Public Health*. 2018;3(7):e341-e350. doi:10.1016/S2468-2667(18)30110-5

6. New York State Department of Health. New York State Department of Health announces opioid replacement now a qualifying condition for medical marijuana. Press release, July 12, 2018. https://www.health.ny.gov/press/releases/2018/2018-07-12_opioid_replacement.htm. Accessed January 29, 2019.

7. Nader DA, Sanchez ZM. Effects of regular cannabis use on neurocognition, brain structure, and function. *Am J Drug Alcohol Abuse*. 2018;44(1):4-18. doi:10.1080/00952990.2017.1306746

8. Hasin DS, Saha TD, Kerridge BT, et al. Prevalence of marijuana use disorders in the United States between 2001-2002 and 2012-2013. *JAMA Psychiatry*. 2015;72(12):1235-1242. doi:10.1001/jamapsychiatry.2015.1858

9. Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R. Labeling accuracy of cannabidiol extracts sold online. *JAMA*. 2017;318(17):1708-1709. doi:10.1001/jama.2017.11909