VIEWPOINT

Perspectives on Cannabis Research—Barriers and Recommendations

Margaret Haney, PhD
Division on Substance Use Disorders, Department of Psychiatry, Columbia University Irving Medical Center, New York, New York.

The US has undergone a substantial shift in public policy and societal attitudes toward cannabis in the past 25 years. Although illegal at the federal level, cannabis or its constituents have been legalized in Washington DC and 11 states for recreational use and 33 states for medical use. This Viewpoint provides the perspective of a researcher conducting controlled investigations of cannabis as a drug of abuse and a potential therapeutic amid these societal shifts. The goal is to describe some of the barriers to research and provide recommendations to bridge the gap between societal use of cannabis and its empirical study.

To start, there are fundamental distinctions between recreational and medical cannabis legalization:

- Recreational: most Americans favor legalizing cannabis nationwide. Ideally, this decision would be made after voters were presented with data on the risks (eg, cannabis use disorder [CUD], associations with brain development, driving safety) and benefits (eg, abolishing racial inequities in prosecutions, tax income) to society of legalizing an additional drug of abuse.
- Medical: by contrast, having voters or legislators define what constitutes a medicine is problematic, which is best exemplified by the variety (>50) of conditions, varying from state to state, that cannabis is purported to treat. Cannabis is deemed efficacious to treat glaucoma for patients in New Jersey but not in New York. Whatever the original intent, this is not a rational or ethical approach to treating illness.

What Are We Talking About?

Cannabis is a plant with more than 140 unique chemical constituents, 2 of which have been approved by the US Food and Drug Administration (FDA): synthetic (1) Δ^9-tetrahydrocannabinol (THC; dronabinol) and (2) nabilone, a THC analogue, are available to treat nausea associated with chemotherapy or AIDS. Cannabidiol (CBD) is approved to treat severe childhood epilepsy. As with all other FDA-approved medications, these compounds were demonstrated to be more efficacious than placebos in randomized clinical trials (RCTs) conducted in the population of interest.

Clearly, cannabis and its constituents are being used for more than nausea and epilepsy. Critically needed are well-powered, placebo-controlled investigations to disentangle pharmacologic efficacy from expectation. However, these studies are nearly impossible to conduct, partially because of the US Drug Enforcement Agency's schedule I labeling of the cannabis plant and its constituents.

Regulatory Hurdles

Ironically, as consumers have increasing access to a vast range of cannabis products, US scientists face more regulatory scrutiny (eg, federal and state schedule I licenses, extensive regulations on storing and dispensing schedule I drugs) and have a limited variety of cannabis and CBD to study. The FDA is appropriately cautious about what it allows scientists to test in patients and none of the products available in dispensaries or online have undergone the safety and manufacturing procedures needed for FDA approval. How then to conduct the studies so needed? One example of the regulatory workarounds required even for those with the licenses, facilities, and approvals is as follows: we are conducting an 8-week RCT to test capsules with high CBD and low THC levels for chemotherapy-induced neuropathic pain. Because, to our knowledge, no such product is approved for study in the US, we obtained a schedule I importer's license to import capsules that meet FDA requirements, a costly approach in terms of time and money.

Why Insist on Placebo Control?

The effect of expectations (particularly with compounds marketed as virtual cure-alls) can be marked and is why RCTs are used to define efficacy. Many symptoms are susceptible to the placebo effect, but pain, anxiety, and sleep are notably so and are also the primary reasons patients seek cannabis products.[1,2] The neurobiology of the placebo effect has been well demonstrated,[3] so it is not surprising that rubbing CBD lotion on a sore elbow reduces discomfort despite little to suggest that most products contain CBD at any potentially meaningful level, that CBD is sufficiently absorbed by topical administration, or that it works at all. So, that elbow might feel better, but accepting this as evidence of efficacy is flawed. If this becomes the norm, all that will be needed for medication development is effective marketing.

Suggesting that the placebo effect contributes substantially to many of the purported effects of cannabinoids does not reject their medical potential. However, it does mean that we cannot look to observational studies or surveys as evidence of efficacy.

What Do We Know?

The National Academies of Science, Engineering and Medicine has reviewed the placebo-controlled evidence of cannabis and cannabis-derived products.[4] The report, which reiterates the paucity of quality research, concludes that in addition to FDA-approved uses, oral cannabinoids are effective for improving multiple sclerosis spasticity ratings and oral cannabinoids and can-

Corresponding Author: Margaret Haney, PhD, Division on Substance Use Disorders, Department of Psychiatry, Columbia University Irving Medical Center, 1051 Riverside Dr, Unit 120, New York, NY 10032 (mh235@cumc.columbia.edu).

nabis improve chronic pain. The evidence for other indications was insufficient.

Where Does This Leave Clinicians?

With a federally illegal drug legalized in individual states, scientists constrained, and federal agencies somewhat silent, clinicians have none of the data that guide their decisions for other medications (eg, which indication, product, cannabinoid ratio, dose, or route of administration; what risks for individual patients [eg, pregnant, adolescent, psychiatric?]). In this scientific vacuum, a billion-dollar industry has swept in without evidence but with an obvious conflict of interest and with little regulation of quality control, advertising, or product labeling.[5]

What Are We Not Talking About?

The public increasingly views cannabis as harmless, which is echoed in the media.[6] Many appear unaware that CUD exists and is qualitatively similar to other substance use disorders, comprising preoccupation, withdrawal, and relapse. Cannabis withdrawal symptoms (eg, irritability and insomnia) contribute to high rates of relapse,[7] just as nicotine withdrawal contributes to tobacco use. Patients seek treatment for CUD because they are dissatisfied with the effect of cannabis use on their lives and are unable to quit. Yet with legalization, there is a powerful motive to create and maintain cannabis users, with the cannabis industry adopting similar business strategies as the tobacco industry.[8]

Conclusions

Cannabis is polarizing even within science. Studying its therapeutic potential is not procannabis; the plant has constituents that produce positive and negative effects.[9] Similarly, it is not anticannabis to emphasize placebo control. Other than those currently making money, does anyone believe that unregulated products of unknown provenance and uncertain content being sold for any medical indication is an ethical approach?

In fact, labeling cannabis as medical or recreational is a somewhat false binary given THC's abuse liability; medical cannabis patients actually appear to be at heightened risk for developing CUD.[10] Measures of abuse liability should be included in studies assessing therapeutic potential to best understand the risks/benefits for a particular patient population.

An important step to addressing many of the barriers facing cannabinoid researchers is to give scientists a schedule I exemption, which would increase the number of RCTs and thereby begin to breach the divide between the use of these products and empirical evidence. There are several congressional bills addressing this issue. Further, as with tobacco, we need policy-oriented and regulatory research to guide rules about advertising, labeling, and the effect of different formulations of cannabis products.[5] Quality science that can weigh societal risks and benefits with data and not hype could then be used to guide nationwide public policy decisions regarding cannabis.

ARTICLE INFORMATION

Published Online: June 17, 2020. doi:10.1001/jamapsychiatry.2020.1032

Conflict of Interest Disclosures: Dr Haney receives funding from the US National Institute on Drug Abuse and from the Thompson Family Foundation Initiative.

Additional Contributions: I thank Caroline Arout, PhD, Tonisha Kearney-Ramos, PhD (Columbia University Irving Medical Center), and Ziva Cooper, PhD, UCLA, for their review of an earlier draft of this Viewpoint. They were not compensated for their contributions.

REFERENCES

1. Walsh Z, Callaway R, Belle-Isle L, et al. Cannabis for therapeutic purposes: patient characteristics, access, and reasons for use. *Int J Drug Policy*. 2013;24(6):511-516. doi:10.1016/j.drugpo.2013.08.010

2. Black N, Stockings E, Campbell G, et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. *Lancet Psychiatry*. 2019;6(12):995-1010. doi:10.1016/S2215-0366(19)30401-8

3. Ashar YK, Chang LJ, Wager TD. Brain mechanisms of the placebo effect: an affective appraisal account. *Annu Rev Clin Psychol*. 2017;13:73-98. doi:10.1146/annurev-clinpsy-021815-093015

4. National Academies of Sciences, Engineering, and Medicine. *The Health Effects of Cannabis and Cannabinoids: Current State of Evidence and Recommendations for Research*. The National Academies Press; 2017. doi:10.17226/24625

5. Vandrey R. The cannabis conundrum: steering policy and medicine with insufficient data. *Int Rev Psychiatry*. 2018;30(3):181-182. doi:10.1080/09540261.2018.1491107

6. Abraham A, Zhang AJ, Ahn R, Woodbridge A, Korenstein D, Keyhani S. Media content analysis of marijuana's health effects in news coverage. *J Gen Intern Med*. 2018;33(9):1438-1440. doi:10.1007/s11606-018-4492-9

7. Haney M. The marijuana withdrawal syndrome: diagnosis and treatment. *Curr Psychiatry Rep*. 2005;7(5):360-366. doi:10.1007/s11920-005-0036-1

8. Richter KP, Levy S. Big marijuana—lessons from big tobacco. *N Engl J Med*. 2014;371(5):399-401. doi:10.1056/NEJMp1406074

9. Haney M, Evins AE. Does cannabis cause, exacerbate or ameliorate psychiatric disorders? an oversimplified debate discussed. *Neuropsychopharmacology*. 2016;41(2):393-401. doi:10.1038/npp.2015.251

10. Hasin DS, Shmulewitz D, Cerdá M, et al. U.S. adults with pain, a group increasingly vulnerable to nonmedical cannabis use and cannabis use disorder: 2001-2002 and 2012-2013. *Am J Psychiatry*. 2020;p201919030284. doi:10.1176/appi.ajp.2019.19030284