EDITORIAL

Medical Marijuana
Is the Cart Before the Horse?

Deepak Cyril D'Souza, MBBS, MD; Mohini Ranganathan, MD

There is a pressing need to develop new medications for many debilitating conditions. Novel approaches based on marijuana or its constituent cannabinoids, if proven, could be added to the armamentarium of available treatments. In this issue of *JAMA*, reviews by Whiting et al[1] and Hill[2] provide detailed assessment of the pharmacology, indications, benefits, adverse effects, and laws related to medical marijuana and the cannabinoids, and the results and conclusions are consistent. There is some evidence to support the use of marijuana for nausea and vomiting related to chemotherapy, specific pain syndromes, and spasticity from multiple sclerosis. However, for most other indications that qualify by state law for use of medical marijuana, such as hepatitis C, Crohn disease, Parkinson disease, or Tourette syndrome, the evidence supporting its use is of poor quality. State laws vary widely regarding conditions for which marijuana is approved and the dispensable legal limit. Both reviews raise important issues worthy of further discussion.

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First, for most qualifying conditions, approval has relied on low-quality scientific evidence, anecdotal reports, individual testimonials, legislative initiatives, and public opinion. Imagine if other drugs were approved through a similar approach. The US Food and Drug Administration (FDA) requires evidence from at least 2 adequately powered randomized clinical trials before approving a drug for any specific indication. For most of the conditions that qualify for medical marijuana use, the evidence fails to meet FDA standards. It has been argued that the lack of high-quality evidence reflects the difficulty in conducting marijuana research in the United States. If so, the federal and state governments should support and encourage such research so that high-quality evidence can be generated to guide decisions about medical marijuana use for the conditions for which the existing evidence is either insufficient or of poor quality.

Second, there are inconsistencies in how medical conditions are qualified for medical marijuana use within a state and between states. For example, in Connecticut, psoriasis and sickle cell disease but not Tourette syndrome qualify, even though the supporting evidence for all 3 conditions is uniformly of very low quality. Similarly, posttraumatic stress disorder (PTSD) is approved as a qualifying condition in some but not all US states. These differences reflect inconsistencies in evaluating and applying current evidence toward decision making about qualifying indications for medical marijuana use.

Third, unlike most FDA-approved drugs that typically have 1 or 2 active constituents, marijuana is a complex of more than 400 compounds including flavonoids and terpenoids and approximately 70 cannabinoids other than Δ^9-tetrahydrocannabinol (THC)[3]. These cannabinoids have individual, interactive, and even entourage effects (effects of a compound that are only appreciable in the presence of other compounds) that are not fully understood and that contribute to the net effect of marijuana. Although clinical trials for some of the qualifying conditions and studies in animal models of those conditions have been conducted with individual cannabinoids (eg, THC or cannabidiol [CBD]), given that marijuana has so many constituents, the results of studies with individual cannabinoids (eg, THC or CBD) cannot be extrapolated to marijuana and vice versa. In addition, unlike FDA-approved medications that have a relatively uniform composition, the composition of cannabis preparations can vary substantially in its content of THC and CBD, such that precise dosing may be difficult. Given the variable composition, patients will have to experiment with different strains and doses to achieve the desired effects, without much input or oversight by physicians.

Fourth, some individual cannabinoids are already commercially available in the form of dronabinol and nabilone. These drugs are administered orally, and some published data are available to guide dosing. In contrast, there are few data on dosing smoked medical marijuana for many of the qualifying medical conditions for which it is used.

Fifth, while the acute adverse effects of marijuana are quite well known, the effects of repeated exposure, as would occur with medical marijuana, need further study. Approximately 1 in 10 adult users of marijuana develops addiction, and this number is even higher among adolescents.[4] Tolerance and dependence with accompanying down-regulation and desensitization of type 1 cannabinoid receptors occur with repeated exposure.[5] Based on this profile, marijuana dosing will have to be increased over time to achieve the same effect. A distinct withdrawal syndrome is also well recognized.

There is also a small but definite risk of psychotic disorder associated with marijuana use, as well as a significant risk of symptom exacerbations and relapse in patients with an established psychotic disorder.[6] Thus, explicit contraindications such as schizophrenia, bipolar disorder, or substance dependence need to be identified along with measures to minimize the likelihood that persons with contraindications would be able to obtain medical marijuana. Perhaps US states should establish clinical follow-up programs to monitor long-term outcomes prospectively, especially negative outcomes (eg, new cases of psychosis) in patients with contraindications.

Sixth, the interactions of marijuana with other drugs that may be concurrently prescribed for qualifying conditions need further study. There are claims that medical marijuana may allow patients to lower their opioid analgesic doses. However, the existing evidence does not support this contention.[7,8] Furthermore, there is some evidence of cross-tolerance between cannabinoids and opioids[9] that should be considered in attempting to partially or fully substitute opioids with marijuana in the treatment of pain syndromes. Perhaps medical marijuana should also be included in monitoring databases as has been done for opioids and benzodiazepines, so physicians could have a more complete understanding of the medication profile of their patients.

Seventh, emerging evidence suggests that the endocannabinoid system is critical in brain development and maturational processes, especially during adolescence and early adulthood. The endocannabinoid system is involved in axon elongation, neurogenesis, neural maturation and specification, glia formation, neuronal migration, and synaptic pruning.[10,11] Furthermore, the endocannabinoid system evolves during adolescence.[12] Unlike endocannabinoids, which have short durations of action, exposure to exocannabinoids (present in marijuana [eg, THC]) activates the endocannabinoid system in a prolonged nonphysiological manner. In preclinical studies, adolescent exposure to cannabinoids has been linked to long-lasting alterations in the endocannabinoid system, as well as other neurotransmitter systems.[13] Collectively, these changes in the endocannabinoid system have been linked to affective, behavioral, cognitive, and neurochemical consequences that last into adulthood. Data on the effects of repeated exposure to marijuana among youth must necessarily rely on epidemiological studies, which thus far support the animal data in demonstrating long-term consequences including cognitive deficits and increased risk for psychosis. Careful consideration is needed to determine at what age exposure to medical marijuana is justifiable because of the following factors: (1) brain development continues until age 25 years; (2) the endocannabinoid system is involved in brain development; and (3) cannabinoid exposure during critical periods of brain development is associated with long-lasting changes in behavior and cognition.

Eighth, it is important to understand the mechanism(s) underlying the potential beneficial effects of marijuana or its constituent cannabinoids. Specifically, it is uncertain how or why marijuana could be effective in treating epilepsy, sickle cell disease, PTSD, Crohn disease, psoriasis, or amyotrophic lateral sclerosis—conditions with no obvious common pathophysiology. Perhaps marijuana provides nonspecific subjective relief, similar to the effects of benzodiazepines.

For physicians, the legal implications of certifying patients for medical marijuana remain unclear given the differences between the views of state vs federal government. Marijuana is classified as a Schedule I substance by the FDA, meaning it has no currently accepted medical use and a high potential for abuse from a federal perspective. The prescription, supply, or sale of marijuana is illegal by federal law. Furthermore, it is not known to what extent, if any, a physician who certifies a patient for medical marijuana may be liable for negative outcomes (eg, motor vehicle crashes). It is not known if malpractice insurance will cover liability attributable to physicians certifying medical marijuana use.

In conclusion, if the states' initiative to legalize medical marijuana is merely a veiled step toward allowing access to recreational marijuana, then the medical community should be left out of the process, and instead marijuana should be decriminalized. Conversely, if the goal is to make marijuana available for medical purposes, then it is unclear why the approval process should be different from that used for other medications. Evidence justifying marijuana use for various medical conditions will require the conduct of adequately powered, double-blind, randomized, placebo/active controlled clinical trials to test its short- and long-term efficacy and safety. The federal government and states should support medical marijuana research. Since medical marijuana is not a life-saving intervention, it may be prudent to wait before widely adopting its use until high-quality evidence is available to guide the development of a rational approval process. Perhaps it is time to place the horse back in front of the cart.

ARTICLE INFORMATION

Author Affiliations: Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut (D'Souza, Ranganathan); Psychiatry Service, VA Connecticut Healthcare System, West Haven (D'Souza, Ranganathan); Abraham Ribicoff Research Facilities, Connecticut Mental Health Center, New Haven (D'Souza, Ranganathan).

Corresponding Author: Deepak Cyril D'Souza, MBBS, MD, Psychiatry Service, VA Connecticut Healthcare System, 950 Campbell Ave, West Haven, CT 06516 (deepak.dsouza@yale.edu).

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