This Editorial discusses some of the medical and legal considerations surrounding use of medical marijuana and cannabinoid drugs.

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.
Medical Marijuana
Is the Cart Before the Horse?

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First, for most qualifying conditions, approval has relied on low-quality scientific evidence, anecdotal reports, individual testimonies, 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, panic 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 20 cannabinoids other than Δ9-tetrahydrocannabinol (THC). 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 (e.g., THC or cannabidiol [CBD]), given that marijuana has so many constituents, the results of studies with individual cannabinoids (e.g., 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 dosages 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 rimonabant. 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.8 Tolerance and dependence with accompanying down-regulation and desensitization of type 1 cannabinoid receptors occur with repeated exposure.9 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 psychiatric disorder associated with marijuana use, as well as a significant risk of symptom exacerbation and relapse in patients with an established psychiatric disorder.10 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 (e.g., new cases of psychosis) in patients with contraindications.