If the reader finds the content of this month’s Proceedings article about medical marijuana’s legal status in the United States confusing, illogical, even somewhat incoherent, don’t blame the messengers. As some Americans turn to marijuana for treatment of a variety of symptoms, with or without their doctors’ advice, health care institutions struggle with how to respond. Perlman and colleagues have accurately captured the essence of a national scene in which (1) the federal and state laws are in conflict, (2) the scientific method is rejected, and (3) the Food and Drug Administration (FDA) process by which the United States guarantees pharmaceutical purity and safety is ignored. I address these 3 points in turn.

First, the rule of law. Since 1970, the year Congress enacted the Controlled Substances Act (CSA), marijuana in any guise has kept company on Schedule I with purported bad actors like LSD, heroin, Ecstasy, and peyote. Such a designation marks a drug as having high abuse potential and no accepted medical use. American prisons are filled with individuals found guilty of trafficking substances on Schedule I. The CSA is the law of the land—or is it? With respect to marijuana, many states do not see it that way.

Since California became the first state to legalize medical marijuana in 1996, 35 additional states and several territories have followed suit, passing bespoke statutes allowing marijuana use medically, recreationally, or both. Based on the premise that they have the authority to do so, states defy federal jurisdiction over marijuana legislation. Moreover, each state has its own idiosyncratic approach to what constitutes medical marijuana, who can have it for which conditions, and how and where it can be acquired.

Congress has failed to take definitive action either for or against the states. During the Obama administration, a series of Department of Justice memoranda declared that federal agencies would remain hands-off with the states, provided they guaranteed the public safety and kept their marijuana-related commercial activities within their borders. In addition, the Rohrabacher-Farr Amendment, first passed by Congress in 2014 and renewed each year since, enjoins the Department of Justice from using federal funds to enforce national marijuana laws.

If the federal government were to follow its own policies, the implication for physicians could be stark. Whereas individual states grant licenses to practice medicine, the federal Drug Enforcement Administration issues licenses to prescribe controlled substances. Even if marijuana were not on Schedule I, the states would still not have the prerogative to do what they’re doing. Furthermore, it is only through a loophole adjudicated in Conant v Walters, a 2002 Ninth Circuit Court of Appeals case, that physicians can “recommend” medical marijuana under their First Amendment free speech rights. Doctors insisting on prescribing medical cannabis, in other words, risk losing their Drug Enforcement Administration licenses.

To protect physicians, many states have adopted an irregular workaround. In Minnesota, for example, would-be medical marijuana patients visit their doctors merely to garner certification that a state-mandated medical condition afflicts them. They then head to a medical marijuana pharmacy and hand their documentation over to a state-licensed pharmacist who decides what marijuana product to dispense and instructs the customer how to take it. In this way, pharmacists assume the prescribing prerogative that normally belongs to physicians.

Next, the scientific method. When marijuana was placed on Schedule I, next to...
nothing was known about cannabinoid pharmacology. Mechoulam in Israel had only puzzled out the structure of tetrahydrocannabinol (THC) in 1964; the CB1 receptor would not be cloned until 1992; and the existence of a widely distributed, neurotransmitter-driven endocannabinoid system in the body had only begun to be postulated.2 Meanwhile, since the 1930s, marihuana had been demonized in films like Reefer Madness. National and local campaigns against the evil weed were laced with xenophobia and racism directed against African Americans and Mexican migrant communities in which marijuana use was then popular. Even so, the public did not take heed of marijuana’s supposed dangers. By 1970, recreational use was endemic in majority communities, particularly college and university campuses.2 Yet CSA scheduling barreled ahead anyway, in the absence of science.

Fast forward to the present. Because marijuana’s Schedule I designation hinders clinical research, the evidence base supporting its use remains anemic. A pair of 2015 JAMA reviews found high-quality evidence based on multiple randomized controlled trials lacking except for chronic pain and spasticity. Use for any other indication had equivocal or poor-quality support.5,6 Yet as the public has clamored for access to marijuana (medical or recreational), state legislatures have proceeded with legalization driven as scheduling was—by politics in the absence of science.

Finally, the FDA process. Since 1938, American prescription pharmaceuticals have gained approval through an FDA paradigm standardized in an Investigational New Drug Application. Would-be marketers must demonstrate an indication for which a proposed drug is effective and a specific patient group it targets. The Investigational New Drug Application must delineate a favorable risk to benefit ratio, potential adverse effects, the form in which the drug will be delivered, and a recommended dose range. Manufacturing specifications must divulge active and inert ingredients and guarantee lot-to-lot consistency, reliable and predictable potency, and the absence of contamination. Only with these conditions met will the FDA grant permission for phased safety and efficacy trials in humans.7

Getting a new drug from laboratory bench to pharmacy shelf typically takes a decade or more and hundreds of millions of dollars. During that translational research journey, much may be learned about a novel pharmaceutical that benefits potential users. Why should it be any different for medical marijuana?8

Ironically, lost in the marijuana legalization hue and cry is the reality that FDA-vetted cannabinoids have been available on American Formularies since 1985, when dronabinol (Marinol) and nabilone (Cesamet) were approved for oral use. Both dronabinol (laboratory-synthesized THC) and nabilone (a THC-like synthetic cannabinoid) hold indications for chemotherapy-related nausea and vomiting, with nabilone gaining an additional indication in 1992 for appetite stimulation in AIDS-related anorexia. Neither dronabinol nor nabilone is actually extracted from cannabis plants. Among the FDA-approved cannabinoids, epidiolex, nearly 100%-pure cannabidiol, holds that singular distinction. After 3 double-blind randomized controlled trials showed that it reduced seizure frequency in 2 rare intractable seizure disorders of childhood, the FDA approved it for that purpose in 2018 through an alternative pathway for botanical derivatives.7 The FDA has approved only 2 other botanicals since it launched this pathway in 2004: a green tea extract (sinecatechins) for genital warts (2008) and a croton sap extract (crofelemer) for AIDS-related diarrhea (2012).9

By now, it should be evident that medical marijuana in the form of leaves and buds smoked in bowls or baked into brownies stands no chance of gaining FDA approval under current rules. With raw plant material containing dozens of cannabinoids, most uncharacterized, as well as hundreds of other compounds in varying concentrations depending on the strain and the growing conditions, it could never meet FDA standards. No pharmaceutical is administered by
smoking with instructions to toke to effect. And why would any drug company invest a fortune in research and development when the product it hopes to market is easily grown in backyards, readily available on the streets, or handily procured in stores in states with legalized use?

Although Perlman and colleagues valiantly endeavor to bring order to the “complexity of the legal and policy landscape” vis-à-vis medical marijuana, it falls to me to editorialize about the ongoing charade in which (1) states bypass federal laws that are neither enforced nor revamped, (2) the public clamors for access to a substance that is still listed as a Schedule I drug, and (3) products that state dispensaries provide wouldn’t—couldn’t—most assuredly don’t—pass FDA muster for purity and safety. As Witek put it in a recent commentary, “recreational use of marijuana is not at debate here, nor is the right of an individual patient to explore cannabis therapeutically; however, allowing broad unsubstantiated claims around medicinal cannabis to infiltrate the general public is a disservice.” At present, more than 20 states have legalized recreational marijuana. As more states go that route, the conflicting laws and regulations surrounding medical marijuana may become increasingly less relevant because the product will be available to consumers outside of the medical system. However, the issue of the public taking a physiologically active substance to relieve medical ailments in the absence of compelling scientific evidence remains relevant, if not more so.

In short, in the current medical marijuana political climate, it is impossible to make sense of nonsense, no matter how hard we try.

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