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COMMENTARY

Pharmacists and the future of cannabis medicine

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ABSTRACT

Objectives: To summarize the history and evolution of cannabis use and policies and to review current therapeutic uses, safety, and the central role pharmacists can play.

Summary: Cannabis regulation and use have evolved over the centuries and are becoming more widely accepted, with over two-thirds of states in the United States having an approved cannabis program. However, changing policy and a paucity of controlled clinical trials has led to questions on the safety and effectiveness of cannabinoid therapies. Although there are conditions for which cannabinoids may be helpful, potential contraindications, adverse effects, and drug-drug interactions should be taken into account.

Conclusion: Pharmacists are in a unique position based on their accessibility, knowledge, and skills to guide product selection, dosing, and discuss drug interactions and adverse effects to educate patients on safe cannabis use, whether it be delta-9-tetrahydrocannabinol, cannabidiol, or a combination thereof. Pharmacists and pharmacy organizations, moreover, should advocate for an integral role in the medical cannabis movement to ensure patient safety and evaluate cannabinoid pharmacology, pharmacokinetics, drug-drug interactions, safety, and efficacy through rigorous investigations.

In early 2019, the *New York Times* argued that a reasonable approach to medical cannabis was necessary. It recommended that Americans, especially pharmacists and physicians, not work under the "impression that cannabis is harmless," just like they should avoid being "irrationally exuberant about its upsides."[1]

The legalization of cannabis has expanded worldwide. In the United States, robust interest in medical cannabis has mirrored many foreign countries (including Canada, Germany, Spain), and 33 states have legalized medical marijuana. However, more information and education are required. Student pharmacists themselves recently advocated for more information and research during their degree as a means of "moving pharmacy forward."[2] The University of Maryland, seizing the moment, initiated the country's first Master's degree program in 2019, whereas materials in *Pharmacy Times* have suggested that it was time to "demystify" medical cannabis.[3,4] Overall, it only makes sense that pharmacists should more broadly be given comprehensive training in this important, emerging topic.

What public health officials, doctors, and pharmacists do not know creates suspicion and caution in equal measures. Perhaps the debate has moved too rapidly? What is the effect of cannabis on developing brains? Schizophrenia? On crime? Finding answers to important cannabis questions will require "a political climate conducive" to develop this research, according to the *British Medical Journal*.[5] The sociopolitical climate has been anything but static. With approximately two-thirds of the United States legalizing some form of cannabis (recreational or medicinal), it becomes increasingly important that pharmacists are given comprehensive training.

History of cannabis for medical uses

The use of cannabis for medical purposes is far from novel. Across multiple countries, including the United States, cannabis preparations were widely available from the 1800s to the 1900s. Cannabis was included in the U.S. Pharmacopoeia in 1850 and was used for a host of ailments, including chronic coughs, childbirth, and gonorrhea. The U.S. Dispensatory, during the Civil War, listed cannabis as a legitimate medicine. Cannabis was available via drinkable, inhalable, and edible products. By the 1880s, cannabis use in medical settings, even with the emergence of new opiate analgesics, had not diminished.

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Key Points

Background:

- Cannabis use has evolved over the centuries and is becoming more mainstream.
- Currently, approximately two-thirds of the United States has an approved medical cannabis program (11 recreational and an additional 21 medical cannabis programs), and the statutes and regulations of 7 of these states include mandated pharmacist involvement.

Findings:

- There is limited rigorous research evaluating the effectiveness and safety of cannabinoids.
- With their training, knowledge, and expertise, pharmacists are in a unique position to have an integral role in the management of cannabis therapy to ensure safe use and participate in the research to further understand the effects of various cannabinoids.

Until 1915, cannabis possession and transfer were legal in every American state, when Utah enacted the first state prohibition statute. By 1937, all 48 states had adopted laws relating to cannabis. The same year, Congress entered the field of cannabis prescription with the Marihuana Tax Act, which required persons to expose themselves to state prosecution in order to comply with federal tax law. The law was opposed by the American Medical Association and many providers across the country. In 1942, cannabis was removed from the U.S. Pharmacopoeia.

Though federal marijuana prohibition began in 1937, strict enforcement and stiffened penalties began in earnest during the 1950s. The Boggs Act and the Narcotics Control Act established mandatory sentencing guidelines for many offenses, including first-time marijuana possession. Penalties ranged from 2 to 10 years in prison with fines of up to $20,000. As young, white, middle-class offenders entered the criminal justice system, there was a loud outcry to temper the stance on marijuana.[6]

Evolution of U.S. policy

Cannabis policy in the United States, according to prominent pharmacologist Dr. Richard Miller, has mostly been directed by lawmakers and law enforcement. Scientists "have had virtually no say" in the matter, and their work has been "completely overlooked" when it "didn't happen to fit in with [the government's] political position."[7]

Although it is true scientists have been excluded from many of the conversations informing cannabis policy, this statement is not entirely accurate. As early as 1934, Dr. Walter Bromberg, senior psychiatrist at Bellevue Hospital in New York, published a series of articles about cannabis users in New York. His research was a means of offering a reasonable approach to cannabis policy. Although his analyses contained less fearful accounts of cannabis use, he still fomented ideas about how the substance "released inhibitions" and "stimulated impulsive actions." Even if cannabis did not drive one into the depths of lunacy or lead to crime, it fundamentally altered the user's psychological makeup and potentially led to psychosis.[8] The Bromberg example highlights the durability and multifaceted nature of cannabis debates in the United States. As he put it, "marihuana" occupied the "attention of police officials, narcotic officers, prosecutors, judges, and physicians," yet the science did not yet present a final solution of the problems, and further experiences and controlled experiments were necessary.[9]

Despite fluctuating evidence, the regulatory landscape in the United States is shifting. In 1996, California was the first state to legalize cannabis for medical purposes, followed by Oregon, Washington, Alaska, Maine, and Washington, DC.[10] As cannabis use increased, acceptance increased, and this paved the way for the legalization of recreational marijuana. Colorado and Washington became the first 2 states to legalize marijuana for recreational use in 2012.[10] Currently approximately two-thirds of states in the United States have approved cannabis legislation with 11 states and the District of Colombia having recreational and medicinal programs and an additional 21 states having medicinal cannabis programs (Figure 1).[10]

However, its medical use will remain controversial. There may be growing support nationally and internationally for the study of cannabis and cannabinoids, and a consensus is slowly building on their efficacy. Many investigators know they have "therapeutic potential over a wide range of non-psychiatric and psychiatric disorders such as anxiety, depression, and psychosis," but what is unknown are "the mechanisms responsible for its therapeutic potential."[13] Researchers admit there is a lot to be learned:

"Strong evidence supports the use of cannabinoids for chronic pain, but more research is needed to determine which diagnoses, pain characteristics, and clinical variables are most amenable to treatment; the long term effectiveness of these drugs; optimal drug selection and dosages; the risk-benefit ratio of combining cannabinoids with other drugs; and how adverse effects can be minimised."[5]

Therapeutic uses

Despite limited rigorous studies, medical cannabis has been state-approved for a variety of conditions including Alzheimer disease, human immunodeficiency virus/acquired immunodeficiency syndrome (AIDS), amyotrophic lateral sclerosis, cancer, inflammatory bowel disease (e.g., Crohn and ulcerative colitis), glaucoma, autoimmune disorders, Parkinson disease, posttraumatic stress disorder, Tourette syndrome, autism, cachexia, chronic pain, migraine headaches, nausea/vomiting, seizure disorders, and muscle spasticity.[14,15]

Cannabis advocates argue that there is evidence to support the use of cannabis or its components for a variety of conditions and that it is relatively safe because of the ability to self-titrate and few reported deaths.[14,16-19] Those opposed to medical cannabis argue that there is a paucity of randomized trials to evaluate safety and efficacy, a lack of standardization of product quality and potency, deleterious adverse effects, and the potential for dependence or addiction.[19-21]

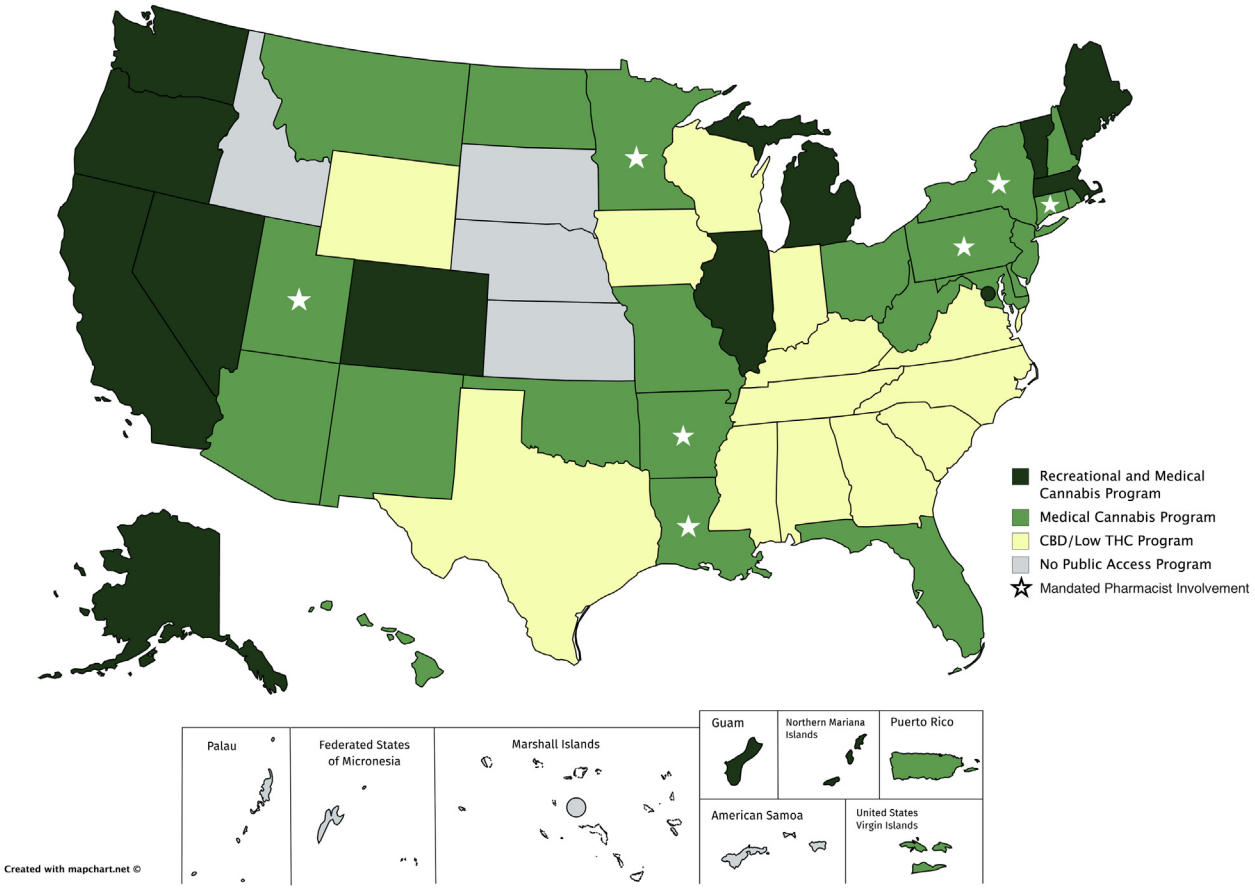

Figure 1. Cannabis regulations and pharmacist involvement by state. Abbreviations used: THC, delta-9-tetrahydrocannabinol; CBD, cannabidiol. Based on data from references 11 and 12.

Of over 100 cannabinoids in the cannabis plant, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most promising and heavily researched compounds. THC, the primary psychoactive component of the cannabis plant, produces its effects through partial agonism of the cannabinoid receptor type 1 and 2 in the endocannabinoid system.[22,23] The exact mechanism of CBD is unknown. However, it is hypothesized that some of the therapeutic effects are a result of the activation of TRPV1 and negative allosteric inhibition of cannabinoid receptor type 1, which results in the mediation of THC's psychomimetic effects.[22,23] Other possible mechanisms of CBD include agonism of 5HT1A serotonergic receptors, antagonism of G protein-coupled receptor 55, a novel receptor that has a regulatory function in the central nervous system and may play a role in anxiety and inflammation, and inhibition of fatty acid amide hydrolase, which leads to reduced hydrolysis of anandamide, an endogenous endocannabinoid.[22-27]

Several products containing synthetic or plant-derived THC, CBD, or a combination have been approved in the United States, Canada, and several European countries. Of these products or those available through state-approved programs, there are a variety of dosage forms including capsules, oral solutions, edibles, tinctures, oral spray, lozenges, and inhalation through smoking or vaporization. The different routes of administration impact the pharmacokinetics of cannabis. Inhalation results in the fastest onset of action (5-10 minutes) and the shortest duration (2-4 hours), making this route of administration most amenable to self-titration.[28-30] Oral administration has the slowest onset of action (30 minutes to 2 hours), the most prolonged duration (4-12 hours), and can be considerably impacted by first-pass metabolism and food intake.[28-30] In particular, an oral solution of CBD (Epidiolex) administered with a high fat and high-calorie meal increased maximum concentration and area under the curve by 5- and 4-fold, respectively.[31] Oromucosal administration onset of action is approximately 15 to 40 minutes, and the duration of action is 2 to 4 hours.[28-30] Drug effect and maximum concentration correspond best following inhalation, whereas maximum concentration typically precedes maximum drug effect following oral administration. However, pharmacokinetic research is challenging with these compounds because of low analyte concentration, rapid and extensive metabolism, as well as difficulty separating compounds of interest from one another and biologic matrices.[32]

Safety considerations

Many pharmacokinetic and pharmacodynamic drug interactions with cannabis may exist; however, there is a paucity of published literature. The method of consumption,

inhalation compared with oral ingestion, for example, will impact these proposed drug-drug interactions due to first-pass metabolism. Some interactions can be hypothesized based on the compounds' metabolic pathways. THC and CBD undergo hepatic metabolism via cytochrome P450 (Table 1). THC is primarily to the primary active metabolite 11-hydroxy-THC and the inactive metabolite 11-carboxy-THC, which are glucuronidated and excreted in the feces and urine.[30,33-36] CBD is primarily metabolized to 7-hydroxy-CBD.[28,35,37] Therapies that are affected by these enzymes interactions should be taken into consideration for potential drug-drug interactions. THC and CBD have been shown to increase warfarin plasma concentrations, resulting in elevated international normalized ratios.[38] Medical cannabis did not affect the plasma concentrations of irinotecan or docetaxel.[39] Coadministration of CBD and clobazam resulted in an increase clobazam concentrations that was not statistically significant and a statistically significant increase in the active metabolite, N-desmethylclobazam.[40,41] CBD also increased the plasma concentration of topiramate, rufinamide, eslicarbazepine, and zonisamide, but there was no increase in valproate, stiripentol, or levetiracetam.[41,42] In addition, there are pharmacodynamic interactions (a result of the central nervous system depressant effects of cannabis) that can be compounded when combined with alcohol, barbiturates, and benzodiazepines.[43] Few studies have been published on drug interactions caused by THC and CBD; therefore, guidelines are lacking. However, caution should be taken for users of medical cannabis on certain drugs.

Much of what is known regarding the adverse events of cannabis is derived from recreational use studies, and these are limiting because of the lack of standardization of content, potential misreporting of use, and polysubstance use. Cognitive impairment and intoxication, such as memory loss, altered thinking, paranoia, and psychosis, are the most concerning (and publicized) potential adverse effects of THC.[44-46] Other possible long-term effects are related to early adolescent use; these include altered brain development, impaired cognitive development, the triggering of psychiatric conditions, and negative educational outcomes.[45,46] Common adverse effects for CBD include somnolence, decreased appetite, diarrhea, and fatigue.[47] Although there are several potential adverse effects, cannabis is considered to have low to moderate dependence potential and a very wide therapeutic index.[48]

There are few indications for which there are sufficient clinical trials to identify an optimal dose. Dronabinol, a synthetic form of THC, is approved by the Food and Drug Administration to treat both chemotherapy-induced nausea and vomiting and anorexia related to weight loss in patients with AIDS.[49] Most patients responded to 2.5 mg twice daily with a maximum dosage of 20 mg daily. Epidiolex, a plant-derived CBD product, is indicated for the treatment of seizures associated with Lennox-Gastaut and Dravet syndrome.[31] The recommended maintenance dosage is 5 mg/kg twice daily; however, based on individual clinical response and tolerability, the dosage can be increased to a total of 20 mg/kg/d.[31] In the absence of available guidelines and literature, dosing is often an educated guess and trial-and-error process; therefore, the philosophy of "start low, go slow" should be used.[28] There may be some patients for whom cannabis therapy is not appropriate. Because of the potential adverse effects, those who are under 25 years, are pregnant or lactating, have a history of psychosis with cannabis use, a history of alcohol or substance abuse, or have a compromised cardiac status should not use THC products.[28] In addition, those with hypotension, heavy tobacco smokers, and those using drugs that have the potential for drug-drug interactions should diligently evaluate the costs and benefits of cannabis therapy.[28]

Table 1
Effect of cannabinoids on drug-metabolizing enzyme cytochrome P450

Cannabinoid	Substrate	Inhibit	Induce
THC	2C9	2B6	CYP1A2
	2C19	2C9	
	3A4	2D6	
		3A4	
CBD	2C19	1A1	
	3A4	1A2	
		1B1	
		2B6	
		2C9	
		2C19	
		2D6	

Abbreviations used: THC, delta-9-tetrahydrocannabinol; CBD, cannabidiol.

Pharmacist's role

Part of a reasonable approach the *New York Times* called for earlier this year is a base of evidence and well-defined roles for trained professionals for cannabis use. Pharmacists are uniquely qualified to ensure the safe and effective use of cannabinoids given their rigorous training in pharmacology, therapeutics, pharmacokinetics, and pharmaceutics. Several states have mandated pharmacist involvement in medical cannabis programs (Figure 1). However, the pharmacist's role varies from state to state. In Arkansas, legislation requires that each dispensary appoint a pharmacist consultant. Connecticut only awards a marijuana dispensary license to a pharmacist. Minnesota requires a pharmacist to meet with patients and develop a plan of care, including discussion of the qualifying condition and treatment goals, product selection, dosing, and final approval for all dispensing activities. New York requires a pharmacist be onsite and supervise all dispensing activities, and Pennsylvania requires a physician or pharmacist be onsite. Utah requires medical cannabis be dispensed at a medical cannabis pharmacy following a consultation with a pharmacist. Louisiana requires medical cannabis be obtained from 1 of 9 pharmacies in the state licensed to sell medical marijuana.

Conclusion

Pharmacists should leverage their skills by guiding product selection, dosing, identifying drug interactions, adverse effects, and educating patients on safe and effective cannabis use, whether it be THC, CBD, or a combination thereof. Regardless of location and regulatory climate, the pharmacist can serve as a reliable source of information to guide patients on the safety and efficacy of these products. In addition, pharmacy schools should incorporate the endocannabinoid system and cannabinol pharmacotherapy into the curriculum. Pharmacists and pharmacy organizations, moreover, should advocate for an integral role in the medical cannabis movement to ensure patient safety and positive outcomes and to evaluate cannabinoid pharmacology, pharmacokinetics,

pharmacodynamics, drug-drug interactions, safety, and efficacy through rigorous investigations.

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