Medicinal Cannabis: History, Pharmacology, And Implications for the Acute Care Setting

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INTRODUCTION

Medicinal cannabis, or medicinal marijuana, is a therapy that has garnered much national attention in recent years. Controversies surrounding legal, ethical, and societal implications associated with use; safe administration, packaging, and dispensing; adverse health consequences and deaths attributed to marijuana intoxication; and therapeutic indications based on limited clinical data represent some of the complexities associated with this treatment. Marijuana is currently recognized by the U.S. Drug Enforcement Agency's (DEA's) Comprehensive Drug Abuse Prevention and Control Act (Controlled Substances Act) of 1970 as a Schedule I controlled substance, defined as having a high potential for abuse, no currently accepted medicinal use in treatment in the United States, and a lack of accepted safety data for use of the treatment under medical supervision.[1]

Cannabis is the most commonly cultivated, trafficked, and abused illicit drug worldwide; according to the World Health Organization (WHO), marijuana consumption has an annual prevalence rate of approximately 147 million individuals or nearly 2.5% of the global population.[2] In 2014, approximately 22.2 million Americans 12 years of age or older reported current cannabis use, with 8.4% of this population reporting use within the previous month.[3,4] General cannabis use, both for recreational and medicinal purposes, has garnered increasing acceptance across the country as evidenced by legislative actions, ballot measures, and public opinion polls; an October 2016 Gallup poll on American's views on legalizing cannabis indicated that 60% of the population surveyed believed the substance should be legalized.[5] Further, a recent Quinnipiac University poll concluded 54% of American voters surveyed would favor the legalization of cannabis without additional constraints, while 81% of respondents favored legalization of cannabis for medicinal purposes.[6] Limited data suggest that health care providers also may consider this therapy in certain circumstances.[7–9] In the United States, cannabis is approved for medicinal use in 28 states, the District of Columbia, Guam, and Puerto Rico as of January 2017.[10]

The use and acceptance of medicinal cannabis continues to evolve, as shown by the growing number of states now permitting use for specific medical indications. The Food and Drug Administration (FDA) has considered how it might support the scientific rigor of medicinal cannabis claims, and the review of public data regarding safety and abuse potential is ongoing.[11,12] The purpose of this article is to review the historical significance of the use of medicinal cannabis and to discuss its pharmacology, pharmacokinetics, and select evidence on medicinal uses, as well as to describe the implications of evolving medicinal cannabis regulations and their effects on the acute care hospital setting.

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HISTORICAL SIGNIFICANCE

Cannabis is a plant-based, or botanical, product with origins tracing back to the ancient world. Evidence suggesting its use more than 5,000 years ago in what is now Romania has been described extensively.[13] There is only one direct source of evidence (Δ^6-tetrahydrocannabinol [Δ^6-THC] in ashes) that cannabis was first used medicinally around 400 AD.[14] In the U.S., cannabis was widely utilized as a patent medicine during the 19th and early 20th centuries, described in the *United States Pharmacopoeia* for the first time in 1850. Federal restriction of cannabis use and cannabis sale first occurred in 1937 with the passage of the Marihuana Tax Act.[15,16] Subsequent to the act of 1937, cannabis was dropped from the *United States Pharmacopoeia* in 1942, with legal penalties for possession increasing in 1951 and 1956 with the enactment of the Boggs and Narcotic Control Acts, respectively, and prohibition under federal law occurring with the Controlled Substances Act of 1970.[1,17,18] Beyond criminalization, these legislative actions contributed to creating limitations on research by restricting procurement of cannabis for academic purposes.

In 1996, California became the first state to permit legal access to and use of botanical cannabis for medicinal purposes under physician supervision with the enactment of the Compassionate Use Act. As previously stated, as of January 1, 2017, 28 states as well as Washington, D.C., Guam, and Puerto Rico will have enacted legislation governing medicinal cannabis sale and distribution; 21 states and the District of Columbia will have decriminalized marijuana and eliminated prohibition for possession of small amounts, while eight states, including Alaska, California, Colorado, Maine, Massachusetts, Nevada, Oregon, and Washington, as well as the District of Columbia, will have legalized use of marijuana for adult recreation.[10,19]

THE MEDICINAL CANNABIS DEBATE

As a Schedule I controlled substance with no accepted medicinal use, high abuse potential, concerns for dependence, and lack of accepted safety for use under medical supervision—along with a national stigma surrounding the potential harms and implication of cannabis use as a gateway drug to other substances—transitioning from a vilified substance to one with therapeutic merits has been controversial. The *United States Pharmacopoeia* and the FDA have considered the complexities

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of regulating this plant-based therapy, including the numerous compounds and complex interactions between substances in this product, and how it might fit into the current regulatory framework of drugs in United States.[11,12,17]

The emergence of interest in botanical medicinal cannabis is thought by many to be a collateral effect of the opioid abuse epidemic; public perception surrounding the use of medicinal cannabis suggests that this plant-based therapy is viewed as not much different than a botanical drug product or supplement used for health or relief of symptoms if disease persists. Like some herbal preparations or supplements, however, medicinal cannabis may similarly pose health risks associated with its use, including psychoactive, intoxicating, and impairing effects, which have not been completely elucidated through clinical trials. Proponents argue that there is evidence to support botanical medicinal cannabis in the treatment of a variety of conditions, particularly when symptoms are refractory to other therapies; that beneficial cannabinoids exist, as evidenced by single-entity agents derived from cannabis containing the compounds THC and cannabidiol (CBD); that cannabis is relatively safe, with few deaths reported from use; that therapy is self-titratable by the patient; and that therapy is relatively inexpensive compared with pharmaceutical agents.[20–22] Opponents of medicinal cannabis use argue, in part, that well-designed randomized trials to confirm benefits and harms are lacking; that it has not been subject to the rigors of the FDA approval process; that standardization in potency or quantity of pharmacologically active constituents is absent; that adverse health effects relate not only to smoking cannabis but to unmasking mental health disorders, impairing coordination, and affecting judgment; that standardization does not exist for product packaging and controls to prevent inadvertent use by minors or pets; that there is a potential for dependence, addiction, and abuse; and that costs pose a potential burden.[23–25]

Regardless of personal views and perceptions, to deny or disregard the implications of use of this substance on patient health and the infrastructure of the health care system is irresponsible; clinicians must be aware of these implications and informed about how this therapy may influence practice in a variety of health care settings, including acute care.

PHARMACOLOGY

Endocannabinoids (eCBs) and their receptors are found throughout the human body: nervous system, internal organs, connective tissues, glands, and immune cells. The eCB system has a homeostatic role, having been characterized as "eat, sleep, relax, forget, and protect."[26] It is known that eCBs have a role in the pathology of many disorders while also serving a protective function in certain medical conditions.[27] It has been proposed that migraine, fibromyalgia, irritable bowel syndrome, and related conditions represent clinical eCB deficiency syndromes (CEDS). Deficiencies in eCB signaling could be also involved in the pathogenesis of depression. In human studies, eCB system deficiencies have been implicated in schizophrenia, multiple sclerosis (MS), Huntington's disease, Parkinson's disease, anorexia, chronic motion sickness, and failure to thrive in infants.[28]

The eCB system represents a microcosm of psychoneuroimmunology or "mind–body" medicine. The eCB system consists of receptors, endogenous ligands, and ligand metabolic enzymes. A variety of physiological processes occur when cannabinoid receptors are stimulated. Cannabinoid receptor type 1 (CB_1) is the most abundant G-protein–coupled receptor. It is expressed in the central nervous system, with particularly dense expression in (ranked in order): the substantia nigra, globus pallidus, hippocampus, cerebral cortex, putamen, caudate, cerebellum, and amygdala. CB_1 is also expressed in non-neuronal cells, such as adipocytes and hepatocytes, connective and musculoskeletal tissues, and the gonads. CB_2 is principally associated with cells governing immune function, although it may also be expressed in the central nervous system.

The most well-known eCB ligands are N-arachidonylethanolamide (anandamide or AEA) and sn-2-arachidonoylglycerol (2-AG). AEA and 2-AG are released upon demand from cell membrane phospholipid precursors. This "classic" eCB system has expanded with the discovery of secondary receptors, ligands, and ligand metabolic enzymes. For example, AEA, 2-AG, N-arachidonoyl glycine (NAGly), and the phytocannabinoids Δ^9-THC and CBD may also serve, to different extents, as ligands at GPR55, GPR18, GPR119, and several transient receptor potential ion channels (e.g., TRPV1, TRPV2, TRPA1, TRPM8) that have actions similar to capsaicin.[28] The effects of AEA and 2-AG can be enhanced by "entourage compounds" that inhibit their hydrolysis via substrate competition, and thereby prolong their action through synergy and augmentation. Entourage compounds include N-palmitylethanolamide (PEA), N-oleoylethanolamide (SEA), and cis-9-octadecenoamide (OEA or oleamide) and may represent a novel route for molecular regulation of endogenous cannabinoid activity.[29]

Additional noncannabinoid targets are also linked to cannabis. G-protein–coupled receptors provide noncompetitive inhibition at mu and delta opioid receptors as well as norepinephrine, dopamine, and serotonin. Ligand-gated ion channels create allosteric antagonism at serotonin and nicotinic receptors, and enhance activation of glycine receptors. Inhibition of calcium, potassium, and sodium channels by noncompetitive antagonism occurs at nonspecific ion channels and activation of PPARα and PPARγ at the peroxisome proliferator-activated receptors is influenced by AEA.[30]

THC is known to be the major psychoactive component of cannabis mediated by activation of the CB_1 receptors in the central nervous system; however, this very mechanism limits its use due to untoward adverse effects. It is now accepted that other phytocannabinoids with weak or no psychoactivity have promise as therapeutic agents in humans. The cannabinoid that has sparked the most interest as a nonpsychoactive component is CBD.[31] Unlike THC, CBD elicits its pharmacological effects without exerting any significant intrinsic activity on CB_1 and CB_2 receptors. Several activities give CBD a high potential for therapeutic use, including antiepileptic, anxiolytic, antipsychotic, anti-inflammatory, and neuroprotective effects. CBD in combination with THC has received regulatory approvals in several European countries and is under study in registered trials with the FDA. And, some states have passed legislation to allow for the use of majority CBD preparations of cannabis for certain pathological conditions, despite lack of standardization of CBD content and optimal route of administration for effect.[32] Specific applications of CBD have recently emerged in pain (chronic and neuropathic), diabetes, cancer, and neuro-

degenerative diseases, such as Huntington's disease. Animal studies indicate that a high dose of CBD inhibits the effects of lower doses of THC. Moreover, clinical studies suggest that oral or oromucosal CBD may prolong and/or intensify the effects of THC. Finally, preliminary clinical trials suggest that high-dose oral CBD (150–600 mg per day) may exert a therapeutic effect for epilepsy, insomnia, and social anxiety disorder. Nonetheless, such doses of CBD have also been shown to cause sedation.[33]

PHARMACOKINETICS AND ADMINISTRATION

The three most common methods of administration are inhalation via smoking, inhalation via vaporization, and ingestion of edible products. The method of administration can impact the onset, intensity, and duration of psychoactive effects; effects on organ systems; and the addictive potential and negative consequences associated with use.[34]

Cannabinoid pharmacokinetic research has been challenging; low analyte concentrations, rapid and extensive metabolism, and physicochemical characteristics hinder the separation of compounds of interest from biological matrices and from each other. The net effect is lower drug recovery due to adsorption of compounds of interest to multiple surfaces.[35] The primary psychoactive constituent of marijuana—Δ^9-THC—is rapidly transferred from lungs to blood during smoking. In a randomized controlled trial conducted by Huestis and colleagues, THC was detected in plasma immediately after the first inhalation of marijuana smoke, attesting to the efficient absorption of THC from the lungs. THC levels rose rapidly and peaked prior to the end of smoking.[36] Although smoking is the most common cannabis administration route, the use of vaporization is increasing rapidly. Vaporization provides effects similar to smoking while reducing exposure to the byproducts of combustion and possible carcinogens and decreasing adverse respiratory syndromes. THC is highly lipophilic, distributing rapidly to highly perfused tissues and later to fat.[37] A trial of 11 healthy subjects administered Δ^9-THC intravenously, by smoking, and by mouth demonstrated that plasma profiles of THC after smoking and intravenous injection were similar, whereas plasma levels after oral doses were low and irregular, indicating slow and erratic absorption. The time courses of plasma concentrations and clinical "high" were of the same order for intravenous injection and smoking, with prompt onset and steady decline over a four-hour period. After oral THC, the onset of clinical effects was slower and lasted longer, but effects occurred at much lower plasma concentrations than they did after the other two methods of administration.[38]

Cannabinoids are usually inhaled or taken orally; the rectal route, sublingual administration, transdermal delivery, eye drops, and aerosols have been used in only a few studies and are of little relevance in practice today. The pharmacokinetics of THC vary as a function of its route of administration. Inhalation of THC causes a maximum plasma concentration within minutes and psychotropic effects within seconds to a few minutes. These effects reach their maximum after 15 to 30 minutes and taper off within two to three hours. Following oral ingestion, psychotropic effects manifest within 30 to 90 minutes, reach their maximum effect after two to three hours, and last for about four to 12 hours, depending on the dose.[39]

Within the shifting legal landscape of medical cannabis, different methods of cannabis administration have important public health implications. A survey using data from Qualtrics and Facebook showed that individuals in states with medical cannabis laws had a significantly higher likelihood of ever having used the substance with a history of vaporizing marijuana (odds ratio [OR], 2.04; 99% confidence interval [CI], 1.62–2.58) and a history of oral administration of edible marijuana (OR, 1.78; 99% CI, 1.39–2.26) than those in states without such laws. Longer duration of medical cannabis status and higher dispensary density were also significantly associated with use of vaporized and edible forms of marijuana. Medical cannabis laws are related to state-level patterns of utilization of alternative methods of cannabis administration.[34]

DRUG INTERACTIONS

Metabolic and pharmacodynamic interactions may exist between medical cannabis and other pharmaceuticals. Quantification of the *in vitro* metabolism of exogenous cannabinoids, including THC, CBD, and cannabinol (CBN), indicates hepatic cytochrome 450 (CYP450) isoenzymes 2C9 and 3A4 play a significant role in the primary metabolism of THC and CBN, whereas 2C19 and 3A4 and may be responsible for metabolism of CBD.[40] Limited clinical trials quantifying the effect of the exogenous cannabinoids on the metabolism of other medications exist; however, drug interaction data may be gleaned from the prescribing information from cannabinoid-derived pharmaceutical products such as Sativex (GW Pharmaceuticals, United Kingdom) and dronabinol (Marinol, AbbVie [United States]).[41,42] Concomitant administration of ketoconazole with oromucosal cannabis extract containing THC and CBD resulted in an increase in the maximum serum concentration and area under the curve for both THC and CBD by 1.2-fold to 1.8-fold and twofold, respectively; coadministration of rifampin is associated with a reduction in THC and CBD levels.[40,41] In clinical trials, dronabinol use was not associated with clinically significant drug interactions, although additive pharmacodynamic effects are possible when it is coadministered with other agents having similar physiological effects (e.g., sedatives, alcohol, and antihistamines may increase sedation; tricyclic antidepressants, stimulants, and sympathomimetics may increase tachycardia).[41] Additionally, smoking cannabis may increase theophylline metabolism, as is also seen after smoking tobacco.[40,42]

ADVERSE EFFECTS

Much of what is known about the adverse effects of medicinal cannabis comes from studies of recreational users of marijuana.[43] Short-term use of cannabis has led to impaired short-term memory; impaired motor coordination; altered judgment; and paranoia or psychosis at high doses.[44] Long-term or heavy use of cannabis, especially in individuals who begin using as adolescents, has lead to addiction; altered brain development; cognitive impairment; poor educational outcomes (e.g., dropping out of school); and diminished life satisfaction.[45] Long-term or heavy use of cannabis is also associated with chronic bronchitis and an increased risk of chronic psychosis-related health disorders, including schizophrenia and variants of depression, in persons with a predisposition to

such disorders.[46–48] Vascular conditions, including myocardial infarction, stroke, and transient ischemic attack, have also been associated with cannabis use.[49–51] The use of cannabis for management of symptoms in neurodegenerative diseases, such as Parkinson's, Alzheimer's, and MS, has provided data related to impaired cognition in these individuals.[52,53]

A systematic review of published trials on the use of medical cannabinoids over a 40-year period was conducted to quantify adverse effects of this therapy.[54] A total of 31 studies evaluating the use of medicinal cannabis, including 23 randomized controlled trials and eight observational studies, was included. In the randomized trials, the median duration of cannabinoid exposure was two weeks, with a range between eight hours and 12 months. Of patients assigned to active treatment in these trials, a total of 4,779 adverse effects were reported; 96.6% (4,615) of these were not deemed by authors to be serious. The most common serious adverse effects included relapsing MS (9.1%; 15 events), vomiting (9.8%; 16 events), and urinary tract infections (9.1%; 15 events). No significant differences in the rates of serious adverse events between individuals receiving medical cannabis and controls were identified (relative risk, 1.04; 95% CI, 0.78–1.39). The most commonly reported nonserious adverse event was dizziness, with an occurrence rate of 15.5% (714 events) among people exposed to cannabinoids.[54]

Other negative adverse effects reported with acute cannabis use include hyperemesis syndrome, impaired coordination and performance, anxiety, suicidal ideations or tendencies, and psychotic symptoms, whereas chronic effects may include mood disturbances, exacerbation of psychotic disorders, cannabis use disorders, withdrawal syndrome, and neurocognitive impairments, as well as cardiovascular and respiratory conditions.[52] Long-term studies evaluating adverse effects of chronic medicinal cannabis use are needed to conclusively evaluate the risks when used for an extended period of time.

MEDICINAL USES

Cannabis and cannabinoid agents are widely used to alleviate symptoms or treat disease, but their efficacy for specific indications is not well established. For chronic pain, the analgesic effect remains unclear. A systematic review of randomized controlled trials was conducted examining cannabinoids in the treatment of chronic noncancer pain, including smoked cannabis, oromucosal extracts of cannabis-based medicine, nabilone, dronabinol, and a novel THC analogue.[55] Pain conditions included neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain. Fifteen of the 18 included trials demonstrated a significant analgesic effect of cannabinoids compared with placebo. Cannabinoid use was generally well tolerated; adverse effects most commonly reported were mild to moderate in severity. Overall, evidence suggests that cannabinoids are safe and moderately effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis.[55]

While there is not enough evidence to suggest routine use of medicinal cannabis for alleviating chemotherapy-related nausea and vomiting by national or international cancer societies, therapeutic agents based on THC (e.g., dronabinol) have been approved for use as an antiemetic in the United States for a number of years. Only recently has the efficacy and safety of cannabis-based medicines in managing nausea and vomiting due to chemotherapy been evaluated. In a review of 23 randomized, controlled trials, patients who received cannabis-based products experienced less nausea and vomiting than subjects who received placebo.[56] The proportion of people experiencing nausea and vomiting who received cannabis-based products was similar to those receiving conventional antiemetics. Subjects using cannabis-based products experienced side effects such as "feeling high," dizziness, sedation, and dysphoria and dropped out of the studies at a higher rate due to adverse effects compared with participants receiving either placebo or conventional antiemetics. In crossover trials in which patients received cannabis-based products and conventional antiemetics, patients preferred the cannabis-based medicines. Cannabis-based medications may be useful for treating chemotherapy-induced nausea and vomiting that responds poorly to conventional antiemetics. However, the trials produced low to moderate quality evidence and reflected chemotherapy agents and antiemetics that were available in the 1980s and 1990s.

With regard to the management of neurological disorders, including epilepsy and MS, a Cochrane review of four clinical trials that included 48 epileptic patients using CBD as an adjunct treatment to other antiepileptic medications concluded that there were no serious adverse effects associated with CBD use but that no reliable conclusions on the efficacy and safety of the therapy can be drawn from this limited evidence.[57] The American Academy of Neurology (AAN) has issued a Summary of Systematic Reviews for Clinicians that indicates oral cannabis extract is effective for reducing patient-reported spasticity scores and central pain or painful spasms when used for MS.[58] THC is probably effective for reducing patient-reported spasticity scores but is likely ineffective for reducing objective measures of spasticity at 15 weeks, the AAN found; there is limited evidence to support the use of cannabis extracts for treatment of Huntington's disease, levodopa-induced dyskinesias in patients with Parkinson's disease, or reducing tic severity in Tourette's.[58]

In older patients, medical cannabinoids have shown no efficacy on dyskinesia, breathlessness, and chemotherapy-induced nausea and vomiting. Some evidence has shown that THC might be useful in treatment of anorexia and behavioral symptoms in patients with dementia. The most common adverse events reported during cannabinoid treatment in older adults were sedation-like symptoms.[59]

Despite limited clinical evidence, a number of medical conditions and associated symptoms have been approved by state legislatures as qualifying conditions for medicinal cannabis use. Table 1 contains a summary of medicinal cannabis indications by state, including select disease states and qualifying debilitating medical conditions or symptoms.[10,60,61] The most common conditions accepted by states that allow medicinal cannabis relate to relief of the symptoms of cancer, glaucoma, human immunodeficiency virus/acquired immunodeficiency syndrome, and MS. A total of 28 states, the District of Columbia, Guam, and Puerto Rico now allow comprehensive public medical marijuana and cannabis programs.[10] The National Conference of State Legislatures uses the following criteria to determine if a program is comprehensive:

1. Protection from criminal penalties for using marijuana for a medical purpose;

Table 1 Medicinal Cannabis Indications for Use by State[10,60,61]

	Alaska	Arizona	Arkansas	California	Colorado	Connecticut	Delaware	District of Columbia	Florida	Hawaii	Illinois	Maine
Select Medical Conditions and Diseases												
Alzheimer's disease		✓	✓	1			✓	1	1		✓	✓
HIV/AIDS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Amyotrophic lateral sclerosis		✓	✓	1			✓	1	✓		✓	✓
Cancer	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Inflammatory bowel disease (e.g., Crohn's, ulcerative colitis)		✓	✓	1		✓		1	✓		✓	✓
Glaucoma	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
Multiple sclerosis				1		✓		1	✓		✓	
Parkinson's disease				1		✓		1	✓			
Post-traumatic stress disorder		✓	✓	1		✓	✓	1	✓	✓	✓	✓
Debilitating Medical Conditions or Associated Symptoms												
Cachexia, anorexia, or wasting syndrome	✓	✓	✓	✓	✓	✓	✓	1	1	✓	✓	✓
Severe or chronic pain	✓	✓	✓	✓	✓		✓ 3	1	1	✓		✓ 3
Severe or chronic nausea	✓	✓	✓	✓	✓		✓ 3	1	1	✓		✓
Seizure disorders (e.g., epilepsy)	✓	✓	✓	✓	✓	✓	✓ 3	1	✓	✓		✓
Skeletal muscle spasticity (e.g., multiple sclerosis)	✓	✓	✓	✓	✓	✓ 3	✓	✓	1	✓	✓	✓

1 = State law additionally covers any condition where treatment with medical cannabis would be beneficial, according to the patient's physician
2 = State law covers any severe condition refractory to other medical treatment
3 = Additional restrictions on the use for this indication exist in this state
4 = State law requires providers to certify the existence of a qualifying disease and symptom
HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome

	Maryland	Massachusetts	Michigan	Minnesota	Montana	Nevada	New Hampshire	New Jersey	New Mexico	New York	North Dakota	Ohio	Oregon	Pennsylvania	Rhode Island	Vermont	Washington
	2	1	✓				✓ 4				✓	✓			✓		
	2	✓	✓	✓	✓	✓	✓ 4	✓ 3	✓	✓ 3	✓	✓	✓	✓	✓	✓ 3	✓
	2	✓	✓		✓		✓ 4	✓	✓	✓	✓	✓		✓			
	2	✓	✓	✓ 3	✓	✓	✓ 4	✓ 3	✓	✓ 3	✓	✓	✓	✓	✓	✓ 3	✓
	2	✓	✓	✓	✓		✓ 4	✓	✓	✓	✓	✓		✓			✓ 3
	2	✓	✓	✓	✓	✓	✓ 4	✓ 3	✓		✓	✓	✓	✓	✓		✓ 3
	2	✓			✓		✓ 4	✓	✓	✓		✓		✓		✓ 3	✓
	2	✓					✓ 4		✓	✓ 3		✓		✓			
	2	1	✓	✓	✓	✓			✓		✓	✓	✓	✓	✓		✓
	✓ 2	1	✓		✓	✓	✓ 4	✓ 3	✓ 3		✓		✓		✓	✓ 3	✓ 3
	✓ 2	1	✓		✓ 3	✓	✓ 3, 4		✓ 3	✓	✓	✓	✓	✓	✓ 3	✓ 3	✓ 3
	✓ 2	1	✓		✓	✓	✓ 4		✓ 3		✓		✓		✓	✓ 3	✓ 3
	✓ 2	1	✓	✓	✓	✓	✓ 4	✓ 3	✓	✓	✓	✓	✓	✓	✓	✓ 3	✓ 3
	✓ 2	1	✓	✓	✓ 3	✓	✓ 4	✓ 3	✓	✓	✓	✓	✓	✓	✓		✓ 3

Table adapted with permission from the Marijuana Policy Project;[60] table is not all-encompassing and other medical conditions for use may exist. The reader should refer to individual state laws regarding medicinal cannabis for specific details of approved conditions for use. In addition, states may permit the addition of approved indications; list is subject to change.

2. Access to marijuana through home cultivation, dispensaries, or some other system that is likely to be implemented;
3. Allows a variety of strains, including more than those labeled as "low THC;" and
4. Allows either smoking or vaporization of some kind of marijuana products, plant material, or extract.

Some of the most common policy questions regarding medical cannabis now include how to regulate its recommendation and indications for use; dispensing, including quality and standardization of cultivars or strains, labeling, packaging, and role of the pharmacist or health care professional in education or administration; and registration of approved patients and providers.

REGULATORY IMPLICATIONS OF MEDICINAL CANNABIS

The regulation of cannabis therapy is complex and unique; possession, cultivation, and distribution of this substance, regardless of purpose, remain illegal at the federal level, while states that permit medicinal cannabis use have established individual laws and restrictions on the sale of cannabis for medical purposes. In a 2013 U.S. Department of Justice memorandum to all U.S. attorneys, Deputy Attorney General James M. Cole noted that despite the enactment of state laws authorizing marijuana production and sale having a regulatory structure that is counter to the usual joint efforts of federal authorities working together with local jurisdictions, prosecution of individuals cultivating and distributing marijuana to seriously ill individuals for medicinal purpose has not been identified as a federal priority.[62]

There are, however, other regulatory implications to consider based on the federal restriction of cannabis. Physicians cannot legally "prescribe" medicinal cannabis therapy, given its Schedule I classification, but rather in accordance with state laws may certify or recommend patients for treatment. Medical cannabis expenses are not reimbursable through government medical assistance programs or private health insurers. As previously described, the Schedule I listing of cannabis according to federal law and DEA regulations has led to difficulties in access for research purposes; nonpractitioner researchers can register with the DEA more easily to study substances in Schedules II–V compared with Schedule I substances.[63] Beyond issues related to procurement of the substance for research purposes, other limitations in cannabis research also exist. For example, the Center for Medicinal Cannabis Research at the University of California–San Diego had access to funding, marijuana at different THC levels, and approval for a number of clinical research trials, and yet failed to recruit an adequate number of patients to conduct five major trials, which were subsequently canceled.[64] Unforeseen factors, including the prohibition of driving during the clinical trials, deterred patients from trial enrollment. The limited availability of clinical research to support or refute therapeutic claims and indications for use of cannabis for medicinal purposes has frequently left both state legislative authorities and clinicians to rely on anecdotal evidence, which has not been subjected to the same rigors of peer review and scrutiny as well-conducted, randomized trials, to validate the safety and efficacy of medicinal cannabis therapy. Furthermore, although individual single-entity pharmaceutical medications, such as dronabinol, have been isolated, evaluated, and approved for use by the FDA, a plant cannot be patented and mass produced by a corporate entity.[65] Despite this limitation, some corporations, including GW Pharmaceuticals, are mass producing cannabis plants and extracting complex mixtures or single cannabinoids for clinical trials.[65] The complex pharmacology related to the numerous substances and interactions among chemicals in the cannabis plant coupled with environmental variables in cultivation further complicate regulation, standardization, purity, and potency as a botanical drug product.

RELEVANCE TO HOSPITAL PRACTITIONERS

Although the public has largely accepted medicinal cannabis therapy as having a benefit when used under a provider's supervision, the implications of the use of this substance when patients transition into the acute care setting are additionally complex and multifaceted. The Schedule I designation of cannabis causes hospitals and other care settings that receive federal funding, either through Medicare reimbursement or other federal grants or programs, to pause to consider the potential for loss of these funds should the federal government intercede and take action if patients are permitted to use this therapy on campus. Similarly, licensed practitioners registered to certify patients for state medicinal cannabis programs may have comparable concerns regarding jeopardizing their federal DEA registrations and ability to prescribe other controlled substances as well as jeopardizing Medicare reimbursements. In 2009, U.S. Attorney General Eric Holder recommended that enforcement of federal marijuana laws not be a priority in states that have enacted medicinal cannabis programs and are enforcing the rules and regulations of such a program; despite this, concerns persist.

The argument for or against the use of medicinal cannabis in the acute care setting encompasses both legal and ethical considerations, with the argument against use perhaps seeming obvious on its surface. States adopting medical cannabis laws may advise patients to utilize the therapy only in their own residence and not to transport the substances unless absolutely necessary.[66] Further, many acute care institutions have policies prohibiting smoking on facility grounds, thus restricting the smoking of cannabis, regardless of purpose or indication. Of note, several Canadian hospitals, including Montreal's Jewish General Hospital and Quebec's Centre Hospitalier Universitaire de Sherbrooke, have permitted inpatient cannabis use via vaporization; the pharmacy departments of the respective institutions control and dispense cannabis much like opioids for pain. Canada has adopted national regulations to control and standardize dried cannabis for medical use.[67,68] There are complicated logistics for self-administration of medicinal cannabis by the patient or caregiver; in particular, many hospitals have policies on self-administration of medicines that permit patients to use their own medications only after identification and labeling by pharmacy personnel. The argument can be made that an herb- or plant-based entity cannot be identified by pharmacy personnel as is commonly done for traditional medicines, although medicinal cannabis dispensed through state programs must be labeled in accordance with state laws. Dispensing and storage concerns, including an evaluation of where and how this product should be stored (e.g., within the pharmacy department and treated as a controlled substance, by security personnel, or with the patient); who should admin-

ister it, and implications or violations of federal law by those administering treatment; what pharmaceutical preparations should be permitted (e.g., smoked, vaporized, edible); and how it should be charted in the medical record represent other logistical concerns. Inpatient use of medicinal cannabis also carries implications for nursing and medical staff members. The therapy cannot be prescribed, and states may require physicians authorizing patient use to be registered with local programs. In a transition into the acute care setting from the community setting, a different clinician who is not registered could be responsible for the patient's care; that clinician would be restricted in ordering continuation of therapy.

Despite the complexities in the logistics of continuing medicinal cannabis in the acute care setting, proponents of palliative care and continuity of care argue that prohibiting medicinal cannabis use disrupts treatment of chronic and debilitating medical conditions. Patients have been denied this therapy during acute care hospitalizations for reasons stated above.[69] Permission to use medicinal cannabis in the acute care setting may be dependent on state legislation and restrictions imposed by such laws. Legislation in Minnesota, as one example, has been amended to permit hospitals as facilities that can dispense and control cannabis use; similar legislative actions protecting nurses from criminal, civil, or disciplinary action when administering medical cannabis to qualified patients have been enacted in Connecticut and Maine.[70–73] Proposed legislation to remove restrictions on the certification of patients to receive medicinal cannabis by doctors at the Department of Veterans Affairs was struck down in June; prohibitions continue on the use of this therapy even in facilities located in states permitting medicinal cannabis use.[74]

CONCLUSION

Despite lingering controversy, use of botanical cannabis for medicinal purposes represents the revival of a plant with historical significance reemerging in present day health care. Legislation governing use of medicinal cannabis continues to evolve rapidly, necessitating that pharmacists and other clinicians keep abreast of new or changing state regulations and institutional implications. Ultimately, as the medicinal cannabis landscape continues to evolve, hospitals, acute care facilities, clinics, hospices, and long-term care centers need to consider the implications, address logistical concerns, and explore the feasibility of permitting patient access to this treatment. Whether national policy—particularly with a new presidential administration—will offer some clarity or further complicate regulation of this treatment remains to be seen.

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