PharmaVOICE

THERAPEUTIC DIGEST

MEDICINAL CANNABIS

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Table of Contents

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Medicinal Cannabis

The Promising Potential for Healing

Medicinal cannabis, or medicinal marijuana, is a therapy that has garnered a lot of 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 Abuse Prevention and Control Act (Controlled Substances Act) of 1970 as having a high potential for abuse, not 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].

General cannabis use, both for recreational and medicinal purposes, has garnered increasing acceptance across the country.

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 2018 Gallup poll on American's views on the legalization of cannabis, indicated that 66% of the population surveyed believed the substance should be legalized[3]. Further, two-thirds of Americans support marijuana legalization, according to two recent polls. The latest poll from the Pew Research Center found that 67% of Americans now back marijuana legalization, up from 62% in 2018. Opposition to legalization dropped to 32%, down from 34% from 2017[4]. Cannabis is approved for medicinal use in 33 states, 12 of which for adult recreational use, and limited data suggest that healthcare providers in the United States also may consider this therapy in certain circumstances.

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[5,6].

HISTORICAL SIGNIFICANCE

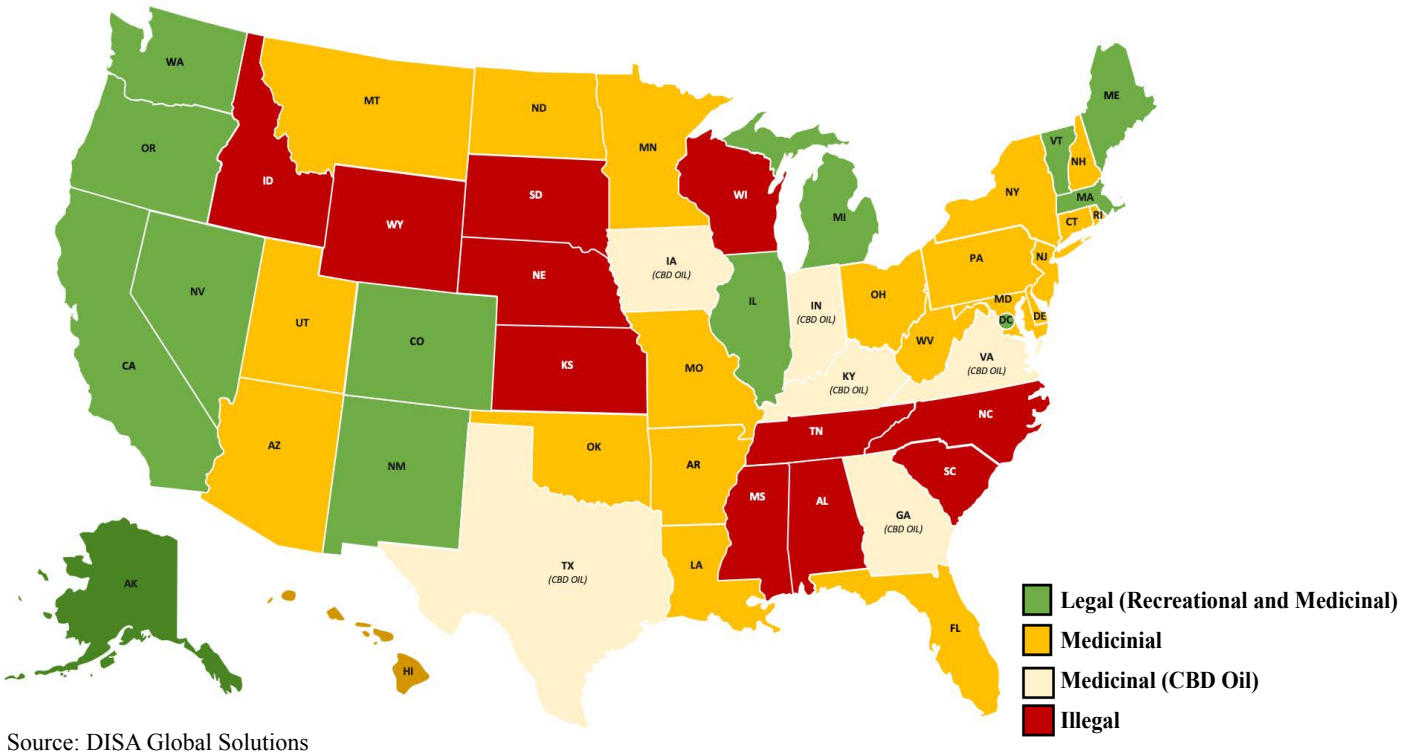
Cannabis is a plant-based, or botanical, product with origins tracing back to the ancient world. Its use more than 5,000 years ago in what is now Romania has been described extensively. Cannabis is so prevalent throughout the historical record, it's almost more surprising where we don't find references. Its use is mentioned by the Egyptians, Greeks, Romans, Chinese, and Persians as well as in multiple archaeological digs, this is a plant that meant something to the ancients.

The earliest documented use as a medicine is in ancient Egypt around 400 AD.

Earliest documentation of cannabis use as a medicine is in ancient Egypt around 400 AD. In the United States, cannabis was widely utilized as a patent medicine during the 19th and early 20th centuries and 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[7,8]. 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 Controls Acts, respectively. Prohibition under federal law occurred with the Controlled Substances Act of 1970. 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 medical purposes under physician supervision with the enactment of the Compassionate Use Act. As of today, there are 33 states, including the District of Columbia (DC) that have enacted legislation governing medicinal cannabis sale and distribution, plus six more states that have permitted use of CBD oil, which is one of more than 100 chemical compounds known as cannabinoids found in the marijuana plant. Forty-one states and DC have either legalized the use of cannibis or CBD oil for recreational or medicinal use, while 11 states, Alabama, Idaho, Kansas, Mississippi, Nebraska, North Carolina, South Carolina, South Dakota,,Tennessee, Wisconsin, and Wyoming have not legalized the use of marijuana for any use[9].

Map of Marijuana Legality by State Figure 1



Source: DISA Global Solutions

UNDERSTANDING CANNABIS TERMINOLOGY

The versatility of cannabis is perhaps matched only by the number of names used to describe it. Marijuana, perhaps the best-known name, refers to cannabis that contains enough psychoactive compounds to be used for medicine or as a recreational drug. In common usage, marijuana can refer to a cannabis plant itself; a mix of dried cannabis stems, leaves, and seeds meant to be smoked or vaporized; or even oils or extracts with psychoactive ingredients from the cannabis plant.

Hemp refers to a cannabis plant grown for industrial or food use, with tetrahydrocannabinol (THC) — the main active ingredient — content lower than 0.3% by dried weight. This is cannabis not intended — essentially unable — to produce a THC-based high. Although we cannot know the exact THC content of this type of marijuana plant if it was grown for use as a food or cloth.

Cannabis Terminology Table 1

Names for Cannabis	
Cannabis sativa, cannabis:	A species of flowering plant containing more than 480 chemical compounds that has been cultivated for over 6,000 years for use as a medicine, a food, a fiber, and a recreational drug. It is often abbreviated as "cannabis," which is technically the genus name.
Marijuana	Cannabis grown to produce a recreational high or for medicinal purposes. It usually contains a THC content of 5% or more.
Hemp	Cannabis with THC content below 0.3%, usually grown for industrial use, such as for making cloth or for food cultivation. It does not contain enough THC to produce a high.
Cannabinoid	A chemical compound that reacts with body's cannabinoid receptors. THC and CBD are cannabinoids.
Methods of Consumption	
Edible	Food infused with marijuana oil, which produces a high approximately 30 to 90 minutes after consumption. The effects generally last longer than those from smoking. The high usually lasts for 4 to 6 hours, although 20+ hour highs have been reported.
Joint, smoking	A marijuana cigarette. It produces a high in minutes.
Hash, hashish	Cannabis resin. Usually smoked, this paste-like preparation of marijuana is more common in Europe than in the US, where bud-flower, and leaf-based herbal cannabis are more popular.
Vaporizing, vaping	A method for imbibing marijuana by heating cannabis or cannabis oil to around 200°C (392°F) and inhaling it. It is believed to be less harmful than smoking, although some users claim it creates a more moderate high.
Oral, sublingual	Oral and sublingual cannabis come in a few different forms — from tinctures and sprays to strips that dissolve under your tongue. Rather than getting absorbed through the digestive system like an edible, they are absorbed through the mucosal membranes under the tongue.
Topical, transdermal	Lotions, salves, and balms that contain CBD oil. Topical CBD products work on the top 3 layers of the skin, while transdermal CBD products are absorbed and can penetrate through the skin and enter the bloodstream.
Main Chemical Compounds	
THC	Full name — tetrahydrocannabinol — a chemical compound in cannabis that can produce euphoria, anxiety, and hallucinations.
CBD	Full name — cannabidiol — a chemical compound in cannabis that has been approved by the FDA to treat two forms of childhood epilepsy. It is believed to fight anxiety and inflammation, although research has yet to confirm many claims about CBD.

Source: National Geographic

FDA APPROVED MARIJUANA-BASED MEDICINE

There are only four FDA-approved drugs derived from or closely related to marijuana.

FDA approval is the gold standard for medicine sold within the United States, but because of harsh anti-marijuana laws, many promising treatments have not been sufficiently tested and researched. As of May 2019, there were only four FDA-approved drugs derived from or closely related to marijuana. GW Pharmaceuticals' Epidiolex CBD and is approved for the treatment of seizures resulting from Lennox-Gastaut or Dravet syndromes. AbbVie's Syndros and Marinol contain synthetic THC and are approved for the treatment of nausea, vomiting, and lack of appetite. Nabilone, a product of Eli Lilly, is chemically similar to THC and is used to treat nausea and vomiting. In Canada, Nabilone is sometimes used to treat chronic pain.

These drugs only scratch the surface of marijuana's potential. Because cannabis is listed as a Schedule I drug, research has been slow, but various studies in the U.S. and abroad have begun to discover some of the many promising healing qualities of cannabis. In 2017, the National Academies of Sciences, Engineering, and Medicine released the most substantial review of studies on marijuana to date. This report, which included reviews of more than 10,000 abstracts, offered promise to marijuana advocates and also cautioned against overblowing the potential of cannabis[10]. Like any other treatment, cannabis is effective at doing certain things — but it is no cure-all.

The researchers found "conclusive evidence" that marijuana can help treat chronic pain in adults, making it an alternative to more addictive prescription painkillers. Cannabis can also treat nausea and vomiting caused by chemotherapy, and it reduces patient-reported symptoms of multiple sclerosis (MS). There is also "moderate evidence" that cannabis can improve "short-term sleep outcomes" in people suffering from chronic pain, MS, fibromyalgia, and obstructive sleep apnea. The same systemic review of studies found little to suggest marijuana is effective at treating dementia, epilepsy, Tourette's syndrome, or schizophrenia.

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 — positioning its use from a vilified substance to one with therapeutic merits has been controversial. The United States Pharmacopoeia and the FDA have considered the complexities 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].

The emergence of interest in botanical medicinal cannabis is thought by experts 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 from a botanical drug product or supplement used for health or relief of symptoms if the 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 associated with use; that therapy is self-titratable by the patient; and that therapy is relatively inexpensive compared with pharmaceutical agents[12,13]. Opponents of medicinal cannabis 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, addictions, and abuse, and that costs pose a potential burden[14,15,16].

Proponents argue there is evidence to support medicinal cannabis in the treatment of a variety of conditions.

"The federal issue is a huge issue," says Matthew Mintz, M.D., clinical associate professor at George Washington University. "While there is a body of evidence that support medical cannabis for a couple of different medical conditions, we don't have the robust research I normally rely on for treatment decisions for patients." The problem, Dr Mintz explains, is that while this type of research could be conducted by the NIH, the agency unfortunately is prohibited from doing so because it is a federal institution. And while private institutions like medical schools and/or academic health centers could technically conduct this research, a lot of the grant money and funding come from federal sources and these institutions could risk their funding getting cut. "The federal regulations make it virtually impossible to do the kind of research we need to see if and how [cannabis] really truly works," Dr. Mintz says. "This is crucial information, which we just don't have because of the federal regulation."

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

PHARMACOLOGY

There's not a single organ in the entire body that doesn't include a CB1 or CB2 receptor.

Endocannabinoids (eCBs) and their receptors are found throughout the human body, including the nervous system, internal organs, connective tissues, glands, and immune cells. The eCB system plays a homeostatic role, having been characterized as "eat, sleep, relax, forget, and protect[17]." It is known that eCBs have a role in the pathology of many disorders while also serving a protective function in certain medical conditions[18]. "The human endocannabinoid system is the most prevalent neurotransmitter system in the body; it is in everything," says John Taenzler, Ph.D., of Cannalytic Insights. "There's not a single organ in the entire body that doesn't include a CB1 or CB2 receptor." 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, Parkinson's disease, anorexia, chronic motion sickness, and failure to thrive in infants[19].

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 nervous system. 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[20].

THC is known to be the major psychoactive component of cannabis mediated by the activation of 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[21]. The cannabinoid that has sparked the most interest as a nonpsychoactive component is CBD. Unlike THC, CBD elicits its pharmacological effects without exerting any significant intrinsic activity on CB_1 ad CB_2 receptors. Several activities give CBD a high potential for therapeutic use, including antiepileptic, anxiolytic, anti-psychotic, anti-inflammatory, and neuroprotective effects.

CBD in combination with THC has received regulatory approvals in several European countries.

CBD in combination with THC has received regulatory approvals in several European countries and is being studied in registered trials by the FDA. Some states have passed legislation to allow for the use of the majority of CBD preparations of cannabis for certain pathological conditions, despite a lack of standardization of CBD content and optimal route of administration for effect[22]. Specific applications of CBD have recently emerged in pain (chronic and neuropathic), diabetes, cancer, and neurodegenerative 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 may exert a therapeutic effect for epilepsy, insomnia, and social anxiety disorder. Such doses of CBD have also been shown to cause sedation[23].

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. The effects on organ systems and the addictive potential and negative consequences are associated with use[24].

Although smoking is the most common cannabis administration route, the use of vaporization has increased rapidly.

The primary psychoactive constituent of marijuana — THC — is rapidly transferred from lungs to blood during smoking. In a randomized controlled trial conducted by Huestis and colleagues[25], THC was detected in the 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[26]. Although smoking is the most common cannabis administration route, the use of vaporization has increased rapidly. Vaporization provides effects similar to smoking while reducing exposure to 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[27]. A trial of 11 healthy subjects who were administered THC 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[28].

Cannabinoids are usually inhaled or taken orally. The rise of transdermal delivery (lotions, oils, etc), as well as rectal or sublingual administration, eye drops, and aerosols have been used in only a few studies and are of little relevance in medical practice today. The pharmacokinetics of THC vary as a function 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[29].

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 vaporizing marijuana and of consuming edible marijuana than those 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 cannabis administration[30].

DRUG INTERACTIONS

Metabolic and pharmacodynamic interactions may exist between medical cannabis and other pharmaceuticals.

Metabolic and pharmacodynamic interactions may exist between medical cannabis and other pharmaceuticals. 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)[31,32]. Concomitant administration of ketoconazole, an antifungal medication, 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. Coadministration of rifampin, an antibiotic used for the treatment of tuberculosis (TB), is associated with reduction of THC and CBD levels[33,34]. In clinical trials, dronabinol-use, the man-made form of cannabis used to treat appetite loss in patients with AIDS, as well as used to treat severe nausea and vomiting caused by cancer chemotherapy, was not associated with clinically significant drug interactions. Although, additive pharmacodynamic effects are possible when it is co-administered with other agents having similar physiological effects (e.g. sedatives, alcohol, and antihistamines may increase sedation; tricyclic antidepressants, stimulants, and sympathomimetics may increase tachycardia)[35]. Additionally, smoking cannabis may increase theophylline metabolism, as is also seen after smoking tobacco[36,37].

ADVERSE EFFECTS

Much of what is known about the adverse effects of medicinal cannabis comes from studies of recreational users of marijuana[38]. Short-term use of cannabis has led to impaired short-term memory, impaired motor coordination, altered judgement, and paranoia or psychosis at high doses[39].

Long-term or heavy use of cannabis, especially in individuals who begin using as adolescents, has led to addiction, altered brain development, cognitive impairment, poor educational outcomes (e.g. dropping out of school), and diminished life satisfaction[40]. 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 variant forms of depression in persons with a predisposition to such disorders[41,42,43]. Vascular conditions, including myocardial infarction, stroke, and transient ischemic attack, have also been associated with cannabis use[44,45,46]. The use of cannabis for the management of symptoms in neurodegenerative diseases, such as Parkinson's, Alzheimer's, and MS, has provided data related to impaired cognition in these individuals[47,48].

One ongoing concern is lack of monitoring among patients who are recommended medicinal marijuana. "The vast majority of my patients don't come in for a follow-up," Dr. Mintz says. "When patients get their certification for use, I give them some instructions, but whether or not they follow those instructions and whether it works or not, in many cases I wouldn't know until they come back a year later for re-certification." The absence of ongoing communication between HCPs, patients, and dispensaries makes it difficult to keep track of how patients are doing on a particular strain of cannabis. Charles Gibson, a patient who was certified for medicinal marijuana in Pennsylvania to treat his pain-predominant IBS, says there were no guidelines or instructions given by his doctor or the dispensary. "They are certainly not following any protocol; there's no follow-up messaging, no patient portal," Mr. Gibson explains.

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[49]. 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 those related to relapsing MS. No significant differences in the rates of serious adverse events between individuals receiving medical cannabis and controls were identified. The most commonly reported non-serious adverse event was dizziness, with an occurrence rate of 15.5% (714 events) among people exposed to cannabinoids[50].

Other negative adverse effects reported with acute cannabis use included 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[51]. 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 systemic 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[52]. Pain condition included neuropathic pain, fibromyalgia, rheumatoid arthritis (RA), 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 RA[53].

Evidence suggests that cannabinoids are safe and moderately effective in neuropathic pain.

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 (a drug preventing vomiting) 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 have received cannabis-based products experienced less nausea and vomiting than subjects who received placebo[54]. The proportion of people experiencing nausea and vomiting who received cannabis-based products was similar to those receiving 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[55]. 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 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[56].

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 the 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[57].

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[58]. The most common conditions accepted by states that allow medicinal cannabis to relieve are those that relate to symptoms of cancer, glaucoma, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), and MS. A total of 33 states now allow comprehensive public medical marijuana and cannabis programs. 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
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"
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 healthcare professional in education or administration; and registration of approved patients and providers are required.

Medicinal Cannabis Indications for Use by State Table 1

	Debilitating Medical Conditions or Associated Symptoms														
	AD	HIV/AIDS	ALS	Cancer	IBD	Glaucoma	MS	PD	PTSD	Wasting syndrome	Severe/ chronic pain	Seizure / chronic nausea	Seizure disorders	Skeletal muscle spasticity
AK														
AZ														
AR														
CA	1		1		1		1	1	1					
CO														
CT														
DE											3	3	3	
DC	1		1		1		1	1	1	1	1	1	1	
FL	1									1	1	1		1
HI														
IL														
LA														
MD	2	2	2	2	2	2	2	2	2	2	2	2	2	2
MA	1								1	1	1	1	1	1
MI														
MN				3										
MO														
MT											3			3
NV														
NH	4	4	4	4	4	4	4	4		4	3, 4	4	4	4
NJ		3		3		3				3			3	3
NM										3	3	3		
NY		3		3				3						
ND														
OH														
OK														
OR														
PA														
RI											3			
UT														
VT		3		3			3			3	3	3	3	
WA					3	3				3	3	3	3	3
WV														

Abbreviations: AD (Alzheimer's Disease), HIV/AIDS (Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome), ALS (Amyotrophic lateral sclerosis), IBD (Inflammatory Bowel Disease, e.g. Crohn's, ulcerative colitis), MS (Multiple Sclerosis), PD (Parkinson's Disease), PTSD (Post-Traumatic Stress Disorder), Wasting Syndrome

State Abbreviations: AK (Arkansas), AZ (Arizona), CA (California), CO (Colorado), CT (Connecticut), DE (Delaware), DC (District of Columbia), FL (Florida), HI (Hawaii), IL (Illinois), LA (Louisiana), MD (Maryland), MA (Massachusetts), MI (Michigan), MN (Minnesota), MO (Missouri), MT (Montana), NV (Nevada), NH (New Hampshire), NJ (New Jersey), NM (New Mexico), NY (New York), ND (North Dakota), OH (Ohio), OK (Oklahoma), OR (Oregon), PA (Pennsylvania), RI (Rhode Island), UT (Utah), VT (Vermont), WA (Washington), WV (West Virginia)

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 if not yielding 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 or symptom

Source: Marijuana Policy Project

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. States that permit medicinal cannabis have established individual laws and restrictions on the sale of cannabis for medical purposes. In a 2013 US Department of Justice memorandum to all US 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[59].

There are, however, other regulatory implications to consider based on the federal restrictions 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 for research purposes; nonpractitioner researchers can register with the DEA more easily to study substances in Schedules II-V (e.g. methadone, codeine, analgesics, etc.) compared with Schedule I substances[60].

Beyond issues related to procurement of the substance for research purposes, other limitations in cannabis research exist. For example, the University of California – San Diego had access to funding for 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 consequently canceled[61]. Unforeseen factors, including the prohibition of driving during the clinical

trials, deterred patients from trial enrollment. The limited number of clinical research programs 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.

In March 2020, the FDA submitted to Congress the report on CBD[62] that the agency was directed to prepare by the Further Consolidated Appropriations Act, 2020. This report was assembled in response to the growing concerns around CBD safety-related issues. "We are concerned that some people wrongly think that the myriad of CBD products on the market have been evaluated by the FDA and determined to be safe, or that using CBD 'can't hurt,'" according to FDA Commissioner Steve Hahn, in a press release[63]. "Aside from one prescription drug approved to treat two rare, severe pediatric epilepsy disorders, no other CBD products have been evaluated or approved by the FDA." Altogether, the documents suggest that greater clarity on the regulatory path for some categories of CBD products is not on the near horizon. At the heart of the FDA's difficulty in discerning that path is insufficient scientific data regarding the safety of CBD. The agency cites several potential risks that have come to light thus far (e.g. liver injury, drug-to-drug interactions, and possible male reproductive toxicity) and points to numerous questions that remain unanswered, particularly with respect to the potential effects of sustained use.

A plant cannot be patented, and mass produced by a corporate entity.

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[64].

Despite this limitation, some companies, 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 becomes more 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 grant or programs, to pause to consider the potential loss of these funds should the federal government intercede and take action if patients are permitted to use this therapy on campus. In 2009, US Attorney General Eric Holder recommended that the enforcement of federal marijuana law not be a priority in states that have enacted medicinal cannabis programs and enforce the rules and regulations of such a program for both hospital and private-practice practitioners to alleviate concerns.

CANNABIS AT A CROSSROADS

With medical marijuana increasingly legal and accepted around the world, new businesses are springing up. The industry is at an intriguing crossroads — the federal prohibition on cannabis is both inhibiting and protecting small business. Banking restrictions mean that small outfits operate with cash and without federal tax deductions offered to other businesses. This severely inhibits large-scale growth and investment from institutional investors who are wary of getting involved in a business that remains federally illegal. Yet, these same restrictions prevent entry from big players, allowing small businesses to survive and gain a foothold in what promises to be an extremely lucrative market.

Cannabis is a rare product for which there is a large demand and widespread product recognition but no federally legal way to purchase or invest in it within the United States. To get around the ban, major American corporations such as Altria have begun taking stakes in Canadian marijuana companies to gain a foothold in the cannabis business[66].

CONCLUSION

Cannabis is a rare product for which there is a large demand.

Despite lingering controversy, use of botanical cannabis for medicinal purposes represents the revival of a plant with historical significance reemerging in present-day healthcare. Legislation governing use of medicinal cannabis continues to evolve rapidly, necessitating that clinicians keep abreast of new or changing state regulations and institutional implications. Ultimately, as the medicinal cannabis landscape continues to evolve, practices from hospitals to clinics to hospices need to consider the implications, address logistical concerns, and explore the feasibility of permitting patient access to this treatment.

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