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STATEMENT OF FINANCIAL DISCLOSURE

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, Dr. Wise (editor) reports he is involved with sales for CNS Vital Signs and Clean Sweep. Ms. Solomon (author), Dr. Solomon (author), Dr. Elliott (peer reviewer), Ms. Coplin (executive editor), Ms. Mark (executive editor), Ms. Hatcher (editorial group manager), and Ms. Johnson (accreditations manager) report no financial relationships with companies related to the field of study covered by this CME activity.



Deciphering Medical Marijuana

Case Presentation

A 29-year-old woman is admitted to resident service with abdominal pain, nausea, and vomiting. She has had multiple admissions for abdominal pain and had relief with hot showers. She is 10 years post-heart transplant. She smokes marijuana daily to self-medicate for anxiety.

Clinical Questions: What are the potential drug interactions with other medications? Is the patient on an immunosuppressive regimen? What are the risks of smoking marijuana daily? Should we worry about withdrawal from marijuana? Is marijuana useful to treat anxiety? And if so, what is the evidence? What is cannabis hyperemesis syndrome?

Framing the Discussion

The medical utility of any pharmacologic treatment is evaluated on its composition, reproducibility, efficacy, positive and negative actions, and overall effect. This article will evaluate and assess medical marijuana, also called medical cannabis, and will cover benefits and risks, clinical considerations affecting its recommendation, and currently available evidence. Although administrators at health systems are making policy decisions regarding the medicinal use of marijuana, clinicians must take medical marijuana seriously. Patients may have tried marijuana, recreationally or medicinally, and may seek information about how it might help them.

A number of resources, especially systematic reviews and meta-analyses, serve as indices for how medical marijuana might find its niche. Clinicians need to be comfortable using these systematic reviews to extrapolate clinical utility and make comparisons as additional medical marijuana research becomes available.

In traditional pharmaceutical discovery, medicine is developed to target an already identified disease. In the case of medical marijuana, politicians and special interests, including the cannabis industry, have created a “medicine” in search of a disease. In the United States, medical marijuana laws are in place in 33 states. “Qualified conditions,” medical conditions approved by a state for medical marijuana use, do not ensure evidence of benefit for medical marijuana treatment for that condition. In fact, there is little or no clinical evidence of efficacy for treating many conditions for which medical marijuana is approved, as reported by the three major systematic reviews from the United States, Canada, and Australia.¹⁻⁴ Even when state laws are written with best practice in mind, medical marijuana legislation usually does not reference medical evidence. Medical marijuana laws often reflect the history of successful implementation in other state rollouts. In most states, few healthcare professionals have participated on legislative committees writing medical marijuana laws. Although there often is a mechanism for adding to the list of qualifying conditions, there is not always a method to remove a qualifying condition when medical marijuana has been shown to be ineffective or harmful. In medical conditions for which conventional treatment is not very effective, interested parties have promoted

EXECUTIVE SUMMARY

The expansion of the sanctioned use of marijuana for recreational and medical purposes has exploded in recent years and warrants a critical appraisal of the primary care physician's role in providing advice to and counseling patients.

- With regard to medical marijuana, politicians and special interests, including the cannabis industry, have created a "medicine" in search of a disease. Qualified conditions as approved by each state do not ensure evidence of benefit for those conditions.
- Federal laws under the Drug Enforcement Agency still categorize marijuana as Schedule I, making marijuana federally illegal even in states that have legislated its availability.
- The three main forms of cannabis are marijuana, hashish, and hash oil containing the psychoactive substance

delta-9-tetrahydrocannabinol (THC), attributing to the adverse effects as well as several beneficial actions.

- Acutely, THC causes increased dopamine release and neuronal activity, while long-term use is associated with blunting of the dopamine system. Heavy use is associated with increased risk of psychosis, addiction, depression, suicidality, cognitive impairment, and decreased motivation.
- Nine percent of marijuana users will develop cannabis use disorder, with addiction rates as high as 25% to 50% among daily long-term users.
- Although medical marijuana has been promoted for many conditions, evidence for its efficacy and safety is limited by the lack of high-quality, unbiased research. National research organizations have concluded that medical marijuana is not appropriate as a first-line treatment for any medical condition.

substituting medical marijuana publicly, even when evidence of effectiveness with medical marijuana does not exist.

Federal laws covering the general use of marijuana, under the Drug Enforcement Agency (DEA) Controlled Substances Act, still categorize it as Schedule I, making marijuana federally illegal even where states have legislated its availability. Healthcare professionals must determine the value of medical marijuana treatment based on which formulations, genetic strains, and potencies are legal in each state. Clinical risks must be weighed against possible benefits. Challenges include decades of research that are difficult to decipher, in part because of unpredictable product composition, differing potencies (or ratios) of the major components, and various formulations.

Marijuana vs. Medical Marijuana

The National Institute on Drug Abuse (NIDA) defines marijuana as dried leaves, flowers, stems, and seeds from the *Cannabis sativa* (or less often, the *Cannabis indica*, the source of hemp) plant. The three main forms of cannabis are marijuana, hashish, and hash oil.⁵ The plant contains delta-9-tetrahydrocannabinol (THC), which is a psychoactive substance⁶ that often is directly related to marijuana's adverse effects, as well as to several beneficial actions. For comparison of different strains, the general potency of marijuana is defined by its THC content. Today, recreational marijuana potency varies from 12% to 19%,⁷ to as much as 50% or more,^{8,9}

dramatically higher than what was available several decades ago. Recreational users may seek higher percentages of THC as dependency develops⁸ because of its ability to provide euphoria and other psychoactive effects.

The term medical marijuana refers to using the whole unprocessed plant or its basic extracts to treat symptoms of illness and other conditions. The marijuana plant consists of more than 421 components, including at least 60 cannabinoid compounds.^{8,10-12} Cannabidiol (CBD), another ingredient of major significance, is responsible for many of the anti-inflammatory and immunomodulatory effects. The multitude of cannabinoids in marijuana create complex, often unpredictable actions, depending on the genetics and plant parts incorporated into the mix. The THC content is used to compare potency of different marijuana strains. For medical purposes, experts often recommend a 1:1 ratio of THC to CBD. Higher THC content is sought for certain effects, while higher CBD content is predictive of other effects.

Each state law specifies the potency of marijuana to be marketed as medical marijuana. In Ohio, for example, three tiers of strengths of medical marijuana are available: 23% THC or less, 23-35% THC, and a strength of 70%, including oils, transdermal applications, and other products.¹³ These tiers allow for equivalent amounts of THC by weight to be dispensed for up to 90 days of treatment in various forms.¹³

Since marijuana is a Schedule I illegal substance, it cannot be prescribed. Instead, physicians are "certified to recommend"

medical marijuana by exhibiting basic proficiency in its lawful medical use. In Ohio, two hours of focused continuing medical education are required to achieve certification.¹³ Also, patients are required to register for a license to use medical marijuana and purchase it from state-approved dispensaries.

Since state legislation clarifies the potency and route of administration allowed, clinicians need to know and understand the differences between the distinct strains of commercially available product specifically available for patient use. Although recreational marijuana often has contaminants, some states have strict growing rules for medical marijuana to avoid contamination with pesticides and fungus. Some states offer higher percentages of THC content than other states. Higher strength THC will not be appropriate for some medical conditions. Healthcare providers need to take this into consideration, as it pertains to patient welfare regarding benefits and risks. Remembering that high THC usually means low CBD content and vice versa allows clinicians to recommend formulations that may have more optimum effects for certain conditions where efficacy has been shown.

Adverse Effects of Marijuana Use

It is important to recognize the psychoactive properties of THC, which often are responsible for adverse health effects.¹⁴ Some patients' expectations of medical marijuana's actions may include

a powerful euphoric feeling or high, usually considered a side effect when THC is in greater amounts. The high can differ from the intended effect of pain reduction, reduced spasticity, or other symptomatic relief associated with measured outcomes for efficacy. Acutely, THC causes increased dopamine release and neuron activity.⁶ Long-term use is associated with blunting of the dopamine system. Heavy use of cannabis is associated with an increased risk of psychosis, addiction, depression, suicidality, cognitive impairment, and decreased motivation.⁶ A recent study suggests that daily or frequent use of higher THC content (> 10%) marijuana is associated with a more than two-fold increase in psychoses.¹⁵ Clinicians need to be mindful that patients may use medical marijuana containing a high percentage of THC, daily and chronically, adding to the potential for adverse effects, including dependence, tolerance, overuse, and abuse.⁸

Volkow et al documented the addictive qualities of marijuana and noted that long-term marijuana use can lead to addiction. Generally, 9% of users will develop cannabis use disorder. If users begin as teenagers and continue into adulthood, addiction numbers go up to approximately 16%. Addiction rates among daily long-term users can be as high as 25% to 50%.¹⁶ In frequent users, cannabis withdrawal syndrome can cause symptoms of irritability, sleeping difficulties, dysphoria, craving, and anxiety, which contribute to challenges in cessation and relapse.¹⁷

Prior to recommending medical marijuana use, clinicians should talk with patients about the issue of driving under the influence. No adequate roadside test currently exists to detect marijuana in drivers suspected of driving under the influence. Quick measurement of marijuana is difficult, in part because of the need to obtain multiple extractions to get results.⁸ Researchers from the University of Iowa National Advanced Simulator found that drivers using alcohol and cannabis together weave more on virtual roadways than those who use either substance alone. The combination does not double the effect and does not create synergy, but instead delivers a potent addictive effect.¹⁸⁻²⁰ Drug-positive driving has increased in weekend nighttime drivers over the past decade. Patients also should be prepared for employers to stipulate standards for

operating machinery and performing duties on the job while under the influence of medical marijuana.

Based on results from 11 systematic reviews and 32 primary studies of patients, harms from marijuana include increased risk for psychotic symptoms, short-term cognitive impairment, and an increase in motor vehicle accidents. Although adverse pulmonary effects were not seen in younger populations, other long-term physical harms in heavy or long-term cannabis users, or in older populations, remain unclear.²¹ The effect of long-term marijuana smoking on the risk of lung cancer also remains unclear. Data collection in these areas often has not been included in research efforts. One joint-year of marijuana use equals one cigarette (joint) of marijuana smoked per day for one year. The use of marijuana for the equivalent of 30 or more joint-years is associated with an increased incidence of lung cancer and several other cancers.¹⁴ Marijuana smoking is associated with inflammation of the large airways with increased airway resistance, causing regular users to report symptoms of chronic bronchitis.^{14,21}

Cannabis can alter brain structure, interfere with executive function, manipulate the brain's reward system, and create complicated effects on emotional processing.²² Researchers believe a large number of neuro-pharmaceutical systems, including the endocannabinoid, dopamine, glutamate, and GABA systems, are affected.²²

Like alcohol and nicotine, marijuana primes the brain for a heightened response to other drugs,^{23,24} characterizing it as one of the gateway substances. With excessive use, marijuana may cause significant cognitive impairment.²⁵ Heavy marijuana use is associated with lower incomes, higher need for socioeconomic support, unemployment, criminal behavior, and lower levels of satisfaction with one's life.^{26,27}

There is consistent evidence for cognitive impairment from cannabis use during adolescence.²⁸⁻³⁰ Orr et al reinforced concerns about marijuana's effects on teen brains.³¹ They found that a low level of marijuana use suggests an increase in gray matter volume especially in the amygdala (emotions, including fear) and hippocampus (emotion, memory, autonomic nervous system) of the adolescent brain.^{31,32} Since important brain changes occur at this time of life, heavy cannabis

use during the teen years may reflect significant hippocampal hypertrophy (mean exposure two years, mean age 17 years).³³ A relationship between prefrontal brain volume and executive dysfunction in adolescent cannabis users has been found.³⁴ Prenatal or adolescent exposure to THC can recalibrate the sensitivity of the reward system to other drugs,³⁵ and prenatal exposure interferes with the establishment of axonal connections between neurons.³⁶ Placebo-controlled studies into the effects of cannabis in adolescents would be helpful.^{37,38} Questions arise when attempting to compare dosages, potencies, participant populations and how the product is actually being administered.²³

The unique composition of each cannabis plant, including the potency of marijuana, as measured by the percentage THC,²³ significantly affects the individual patient response. This extends to pharmacologic actions, pharmacodynamics, and pharmacokinetic effects.³⁹ Even factors such as the patient's frequency of use can affect the acute response, as chronic users may have a reduced effect vs. marijuana-naïve patients given similar doses.^{40,41} Tolerance can become an issue with real-time daily users of medical marijuana for chronic conditions. Challenges in comparing patients from different studies include frequency of use, quantity used, cannabis history, and history of other drugs (including illicit use, age of cannabis use onset, amount of time that subjects abstained from cannabis use, rates of tobacco smoking, and alcohol consumption).^{42,43}

Because of the "entourage" or additive actions²⁰ created by the various cannabinoids mixed with other constituents found in marijuana, drug-drug and disease-drug interactions can be problematic. Cytochrome P450 (CYP) enzymes, which are responsible for most drug metabolism, dramatically affect the clinical picture. The CYP1A2, CYP3A4, CYP2C9, and CYP2C19 are known to be affected by marijuana.^{44,45} THC can add to sedative, psychomotor, respiratory, and other CNS depressant effects, including additive actions when the patient is consuming alcohol.⁴⁶⁻⁴⁸ Cannabinoids can cause tachycardia and at times hypertension, particularly with anticholinergics, cocaine, or sympathomimetics.⁴⁹⁻⁵¹ Disulfiram and fluoxetine can present specific additive effects.⁵²⁻⁵⁴ The package inserts of two

FDA-approved THC-derived drugs, nabixone (Cesamet) and dronabinol (Marinol), refer to possible hypomania symptoms.^{51,55} Patients who take warfarin and also use marijuana should have close INR monitoring, especially with intermittent use or varying doses.⁵⁶ CBD is associated with significant inhibition of CYP3A4, CYP3A5, CYP2C6, and CYP2C19, similar to that of grapefruit juice, and it competes for elimination with numerous drugs in the liver. This includes many of the antiepileptic drugs, specifically topiramate, rufinamide, and clobazam; CBD can elevate serum levels of these medications.⁵⁷ CBD has been shown to affect liver function tests, especially when patients are taking concomitant medications; patients should be monitored closely for changes in their liver profiles while taking any CBD-containing product, whether medical marijuana, Epidiolex, or other CBD-containing products.⁵⁸

State regulations specify drug delivery systems considered legal for medical marijuana use in each state. Some states allow patients to purchase the product for smoking, but others do not. It is important to note that currently no FDA-approved drugs are administered by smoking. Medical marijuana formulations include vaporized product for inhalation, oils, tinctures, topical creams/sprays, and edible products. Absorption viability of eye drops and transdermal gels has been questionable and is not well understood, with some formulations currently under investigation.⁵⁹

Transdermal application has not been evaluated thoroughly for absorption characteristics. Several medical marijuana products, including nabiximols (a 1:1 ratio THC:CBD oromucosal spray currently available in Europe and Canada), offer buccal absorption. Koehler et al reported adverse mucosal effects associated with oral discomfort leading to discontinuation among some multiple sclerosis (MS) patients being treated for MS-related spasticity.⁶⁰ Topical adverse effects have slowed pharmaceutical approval of this formulation in some countries, including the United States.⁶¹ When the clinician and patient decide on therapy, in whatever form, it is important for patients to be counseled about proper use and appropriate dosing for the specific condition and formulation being recommended.

Table 1. Commonly Used Terminology Regarding Medical Marijuana

- The most common route of administration is via inhalation (smoking or vaping).
- It is smoked in cigarettes called joints, cigars, pipes, water pipes or bongs, or blunts, or vaporized in cartridges similar to those found with electronic cigarettes. The propellants used in vaporizer cartridges may contain chemicals also found in antifreeze, such as propylene glycol or glycerin.
- Bongs filter smoke through the liquid in the water pipe.
- A blunt is marijuana rolled in the tobacco-leaf wrapper from a hollowed out cigar.
- Greenish-gray shredded leaves and flowers, along with seeds and stems, of the *Cannabis sativa* plant are smoked.
- Hashish is a related product created from the resin of marijuana flowers, smoked by itself, or in a tobacco mixture, and can be ingested orally.
- When ingested, marijuana usually is heated and made into butters, oils, or tinctures. An oil-based extract of marijuana can be mixed into food products and heated.
- Marijuana can be brewed as a tea.
- Common terms for marijuana include pot, weed, grass, 420, ganga, dope, reefer, Mary Jane, stickweed, and buds.

Smoking marijuana in the form of blunts, joints, pipes, or bongs⁶² requires inhaling a high heat product containing combustible substances, including polycyclic aromatic hydrocarbons that are more potent than tobacco byproducts.^{63,64} (See Table 1.) Using medical marijuana by inhalation via a cartridge vaporizer, with a more controlled heat,³ has become increasingly popular.⁶⁵⁻⁶⁷ Vaporizers aerosolize cannabis liquid via transfer of active ingredients from liquid to vapor. In comparison, electronic cigarettes also use the cartridge technology, in which propellants, such as propylene glycol or glycerin,⁶⁸ turn liquids into vapor. These propellants, known as antifreeze ingredients, are inherently harmful when heated and inhaled. The process creates formaldehyde-related compounds that build up in the lungs.⁶⁹ The majority of liquid cannabis formulations for vaping contain the same or similar propellants, and in certain cases, may comprise flavorings used in electronic cigarette/nicotine formulations. The flavorings, generally recognized as safe when used in small quantities in food, have inherent risks when heated, including irreversible lung damage such as that seen in bronchiolitis obliterans.⁷⁰ Examples of this damage have been associated with diacetyl, the well-known buttery popcorn flavor used in some e-cigarettes.⁷¹ These concerns merit researchers clarifying and

further substantiating the effects of additives in inhalation constituents. Although marijuana vaping via cartridge theoretically may avoid the inhalation of toxins, irrespective of the propellants discussed herein, rigorous clinical studies are sorely needed.⁷²

For medical marijuana to be administered orally, extracted oils from the cannabis plant are derived by baking the cannabis flowers, mixing them with a lipophilic solution, applying further heat or using solvent extraction, and then straining the ground flowers. This can be administered directly as “hash oil,” in capsules, or baked in food. However, first-pass metabolism in the liver significantly reduces the bioavailability of oral marijuana products. When smoked or vaped, THC is absorbed rapidly, producing physical effects within minutes. Oral doses, however, delay the onset of effects by 30 to 120 minutes, producing lower and irregular peak plasma levels compared to smoked THC, and prolonging the duration of effect.³ This differs dramatically from the onset and duration of other marijuana products. Oral ingestion of marijuana (edibles) can be associated with unpredictable outcomes, creating the opportunity for overdose and overuse of marijuana due to the delay of onset. Monte et al recently found that in patients ingesting marijuana, it is much harder to estimate the dose for its desired

effect, increasing the risk of an overdose as well as delayed elimination.⁷³ The inhaled route allows for real-time dose titration, whereas delayed onset with oral consumption means that the individual cannot reduce the dose once effects, including negative ones, emerge. Hence, individuals who are not familiar with the effects of THC or other cannabinoids may become overwhelmed by the effects of oral consumption. Healthcare professionals must be alert to the dramatic differences in onset of action and duration of effect of the various delivery systems for medical marijuana. Product variability, as identified by the content ratio THC:CBD, even within the same route of administration, is significant, often presenting problems for patients.

To protect children and pets from unintended ingestion, patients and caregivers should store their medical marijuana products safely. Many states have reported significantly greater numbers of emergency department visits due to edible marijuana products, with pets, children, or others in the household sometimes consuming the formulations. Proper dispensing and labeling can help, but without patient education, accidental poisonings will continue to be a real outcome of marijuana's availability.

Unfortunately, most states have chosen to have non-medical personnel dispensing medical marijuana in state-authorized dispensaries. In Ohio, it was deemed too costly to require medical marijuana dispensaries to hire registered pharmacists to oversee the dispensing operation. Only three states currently require registered pharmacists on site in medical marijuana dispensaries. Also, conventional pharmacies are not approved as legal dispensaries for medical marijuana because of its Schedule I status. Having non-medical personnel in the roles of dispenser and patient educator presents unique challenges for patients seeking accurate medical information.

Dissemination of misinformation from non-medical dispensary personnel can be harmful. Many dispensary employees answer questions using their own opinions without knowing specific factual details. Increased efforts to formalize education for dispensary personnel could improve the number of safe patient encounters. Authors of a study in Oregon concluded

that dispensary personnel advise patients on marijuana's effects, use, and product selection, usually with no medical training.⁷⁴ Providing written "scripting" for employees answering questions and reviewing written or pictorial education sheets with patients might reduce this troubling level of misinformation.

Cannabis Use Disorder

While states currently vary in how they offer medical marijuana, mixtures containing higher percentages of THC are associated with a greater number of cannabis inpatient admissions with greater harm to users. If given daily for chronic medical conditions, medical marijuana has the potential for creating long-term harm. A long-term study from the Netherlands found that changes in the THC concentration in cannabis sold in national retail establishments were associated with increased numbers of people entering treatment for cannabis problems.⁷⁵ In Europe, marijuana has overtaken opiates as the primary reason for first-time drug treatment.²²

Daily long-term use of marijuana can cause nausea, vomiting, and abdominal pain, known as cannabinoid hyperemesis syndrome.⁷⁶ Often, vomiting is intense and overwhelming. Many sufferers will take frequent hot showers because it eases their nausea. They may be unable to eat because of slowed gastric emptying and will require intravenous fluid replacement along with proton pump inhibitors, pain medications, and perhaps medications like haloperidol. Clinicians should be careful when treating these patients with multiple medications, as there is significant opportunity for drug interactions, particularly with opioids and benzodiazepines, requiring a tapering of one before adding the other.

Pregnancy presents a major concern with marijuana use. Dickson et al concluded that the majority (70%) of Colorado cannabis dispensaries contacted recommend cannabis to treat first trimester nausea in pregnant women,⁷⁷ even though prenatal cannabis exposure appears to be related to fetal growth restriction during pregnancy and increased frontal cortical thickness among school-age children.^{78,79} Prenatal or adolescent exposure to THC can recalibrate the sensitivity of the reward system to other drugs.⁸⁰ Prenatal exposure interferes with cytoskeletal

dynamics, critical to axonal connections between neurons.³⁶ Inappropriate advice given by non-medical personnel in dispensaries may contribute to a generation of babies with long-term problems.

Medical Marijuana: Its Clinical Efficacy

Although medical marijuana has been promoted for many medical conditions, the evidence for its efficacy and safety is limited by a lack of high-quality, unbiased research. Because of the many variables in composition, drug delivery forms, and other parameters, specific conclusions about safety, efficacy, and medical usefulness confound researchers and clinicians. Critics believe lack of standardization, differing populations of chronic vs. naïve users, and varying pharmacodynamics related to delivery systems are significant.

Researchers at the National Academy of Sciences in the United States, the Department of Health of Australia, and The University of Alberta in Canada have conducted systematic reviews that all reached the same conclusions: Medical marijuana is not appropriate as first-line treatment for any medical condition.¹⁻³ However, there is adequate evidence to suggest modest clinical benefit for chronic neuropathic pain, nausea and vomiting after chemotherapy, and spasticity in MS.¹⁻⁴

Chronic Noncancer Pain

Chronic noncancer pain (CNCP) is the most commonly cited reason for use of medical marijuana in the United States, Canada, and the Netherlands.²⁻⁴ The definition of CNCP varies widely across studies, with pain duration from three to six months and types of pain that include neuropathic, arthritis, and fibromyalgia. Generalizing the use of medical marijuana to all CNCP conditions is not supported by existing evidence. The most common cause of CNCP is musculoskeletal pain and not neuropathic pain. Researchers have found no benefit to using medical marijuana for musculoskeletal pain.^{2-4,81} Clinicians should exercise caution when prescribing medical marijuana for patients, especially for those with non-neuropathic CNCP.⁸²

Neuropathic Pain

Neuropathic pain is defined as pain caused by a lesion or disease of the

somatosensory nervous system.³ Authors of systematic reviews from Australia, Canada, and the United States concluded that patients who used medical marijuana for neuropathic pain were more likely to experience a reduction in pain scores compared with placebo.²⁻⁴ Pain reduction is considered meaningful (clinically relevant) when there is at least a 30% reduction in pain.³ Twenty-nine percent of patients reported a meaningful reduction in pain with medical marijuana use compared to 26% with placebo use. This means that 24 patients need to be treated with medical marijuana for one patient to have benefit greater than placebo (number needed to treat [NNT] = 24; odds ratio [OR], 1.46). The improvements in pain scores were meaningful (30% reduction in pain) in about half of the studies of neuropathic pain.⁸³ Adverse effects were common among patients using medical marijuana for pain. Of patients using medical marijuana, 81% noted adverse effects, compared with 66% using placebo. This means that six patients were required to be treated with medical marijuana for one patient to have adverse effects greater than placebo (number needed to harm [NNH] = 6; OR, 2.33). Sixteen percent of patients withdrew from studies because of adverse effects from medical marijuana compared with 4.6% with placebo. This means that 40 patients were treated with medical marijuana for one patient to have significant adverse effects greater than placebo (NNH = 40; OR, 3.47).¹ Although patients reported pain reduction, those who used medical marijuana for neuropathic pain reported no change in physical functioning, emotional functioning, or quality of life.³

The efficacy of medical marijuana for neuropathic pain can be compared with other therapies.² Meaningful pain improvement with medical marijuana treatment was reported in 9% of patients, improvement with placebo or no treatment was reported in 25% of patients, and no improvement was noted in 66% of patients. Contrast this with amitriptyline treatment, for which meaningful pain improvement was reported in 25% of patients, improvement with placebo or no treatment was reported in 25% of patients, and no improvement was noted in 50% of patients. With high-dose opioid treatment (oral morphine 60 to 110 mg per

day), meaningful pain improvement was reported in 18% of patients, improvement with placebo or no treatment was reported in 25% of patients, and no improvement was noted in 57% of patients. With gabapentin treatment, meaningful pain improvement was reported in 15% of patients, improvement with placebo or no treatment was reported in 25% of patients, and no improvement was noted in 60% of patients. Efficacy like gabapentin and superior to marijuana was reported for venlafaxine, pregabalin, and duloxetine. This suggests that although medical marijuana is superior to placebo for neuropathic pain, it is less effective than other drug therapies. The systematic reviews suggest medical marijuana might be considered a second- or third-line treatment.²⁻⁴

Although the use of medical marijuana for the treatment of neuropathic pain is supported by well-controlled clinical trials, very little is known about efficacy, dose, routes of administration, or side effects of commonly used, commercially available marijuana products in the United States.⁴

Medical marijuana use is common in people with CNCP who have been prescribed opioids. Researchers found no evidence that marijuana use improved patient outcomes.⁸² Those who used medical marijuana had greater pain and lower self-efficacy in managing pain. The researchers found no evidence that the use of medical marijuana reduced pain interference or exerted an opioid-sparing effect. There is evidence for the use of low-dose medical marijuana in refractory neuropathic pain in conjunction with traditional analgesics. However, trials were limited by short duration, variability in dosing and strength of THC, and lack of functional outcomes. Although well-tolerated in the short term, the long-term outcomes of psychoactive and neurocognitive effects of medical marijuana remain unknown. Drug interactions with marijuana also must be considered. Generalizing the use of medical marijuana to all CNCP conditions does not appear to be supported by existing evidence. Clinicians should exercise caution when prescribing medical marijuana, especially in patients with non-neuropathic CNCP.

Chemotherapy-Induced Nausea and Vomiting

Nausea and vomiting were among the first indications for which cannabinoids

were approved for use. Dronabinol (Schedule III), a synthetic version of delta-9-THC, and nabilone (an oral THC analog, Cesamet, Schedule II) are FDA-approved, synthetically derived pharmaceuticals for the treatment of chemotherapy-induced nausea and vomiting when a patient has failed to respond adequately to conventional antiemetic treatment.^{84,85} These medicines are not considered the same as medical marijuana, as they are single-agent, synthetically derived THC products. Package inserts for both products document side effects with synthetic THC and THC analogs. Dronabinol has an onset of action of approximately 30 minutes to one hour, with a peak effect at two to four hours and psychoactive effects lasting four to six hours. Both dronabinol and nabilone may be administered one to three hours prior to chemotherapy and may be used in combination with other antiemetics. Side effects include alterations in mental state, as is seen with marijuana, including changes in mood, such as euphoria, detachment, depression, anxiety, panic, and paranoia.⁵⁶ Australian Government Department of Health Guidelines note that medical marijuana should not be recommended for chemotherapy-induced nausea and vomiting unless standard approved treatments have failed.^{3,86}

Multiple Sclerosis

MS is a potentially disabling disease of the central nervous system in which the immune system attacks the protective myelin sheath that covers nerve fibers, causing the nerves to deteriorate or become permanently damaged.

MS affects millions of people and although some countries have approved medical marijuana for the treatment of MS symptoms, evidence for the efficacy of cannabinoids for MS symptoms is limited. Authors of a meta-analysis evaluated four different medicinal cannabinoids for MS-associated symptoms of spasticity, pain, and bladder spasms.⁸⁷⁻⁸⁹ They identified 17 studies involving 3,161 patients satisfying the eligibility criteria (randomized, placebo-controlled, double-blind, and parallel, crossover designed trials, with a minimum treatment length of two weeks). Small but statistically significant differences were found in favor of cannabinoids for all three symptoms. Although

Table 2. Conditions for Use of Medical Marijuana

Common qualifying conditions for approved use of medical marijuana (but does not ensure efficacy):

- Pain
- HIV/AIDS
- Cancer
- Glaucoma
- Epilepsy/seizures
- Nausea/vomiting
- Agitation in Alzheimer's disease
- Post-traumatic stress disorder

Conditions with evidence for efficacy for medical marijuana

- Spasticity/multiple sclerosis
- Chemotherapy-induced nausea and vomiting
- Neuropathic pain

cannabinoids were associated with more adverse effects and more withdrawals caused by those adverse effects, no statistically significant differences occurred in placebo or medical marijuana.⁸⁷ The authors concluded that cannabinoids provide a mild reduction in subjective outcome assessment of uncertain clinical significance and that they were safe.

Epilepsy

Epilepsy is a disorder of the brain defined by two or more unprovoked seizures occurring at least 24 hours apart, the diagnosis of an epilepsy syndrome, or one unprovoked seizure with a high probability of further seizures.⁹⁰ Preclinical studies suggest that naturally occurring cannabinoids (phytocannabinoids) have anticonvulsant effects that are mediated by the endocannabinoid system. CBD and cannabidivarin have shown anti-seizure effects. In contrast to THC, CBD does not produce euphoric or intrusive psychoactive side effects when given to treat seizures.⁹¹ Evidence is unavailable for first-line or sole use of cannabinoids for epilepsy. There is limited high-quality evidence for the use of medical marijuana products in epilepsy. When looking at epilepsy studies incorporating medical marijuana therapy, it is critical to evaluate the content of the marijuana strain being investigated. Is it high THC or high CBD? The THC:CBD content ratio is

important in evaluating the measures for epilepsy. CBD has shown some efficacy when used as adjuvant therapy with other antiepileptic drugs; however, comparative data with current best therapies are unavailable. As medical marijuana likely will be used with other antiepileptic medications in epilepsy, drug-drug interactions are common. Most published clinical and preclinical data on efficacy in epilepsy is with CBD.

CBD as a single agent pharmaceutical containing less than 0.1% THC is the FDA-approved drug, Epidiolex. Approved in 2018 in the United States, Epidiolex is an oral solution, classified as Schedule V, per the DEA. It is not considered medical marijuana. Epidiolex is approved for two pediatric orphan epileptic syndromes, Dravet syndrome and Lennox-Gastaut syndrome. It is used as an add-on to current therapies in drug-resistant epilepsy when four or five other antiepileptic drugs have not controlled the epilepsy.^{83,91} The cost of Epidiolex treatment is more than \$30,000 per year.

Epidiolex has an adverse effect profile that clinicians need to recognize, including somnolence, diarrhea, and decreased appetite.^{92,93} Significant elevations of liver aminotransferase concentrations more than three times the upper limit of normal occurred in 9% of patients and among patients receiving valproate concomitantly.^{94,95} Cannabidiol inhibits the catalytic activity of CYP2C19 and increases a clobazam metabolite with biologic activity.⁹⁶

Other Legally Approved Qualifying Conditions

The list of qualifying conditions for which medical marijuana is approved on the state level can differ dramatically from one state to another. (See Table 2.) Common conditions include pain, HIV/AIDS, cancer, glaucoma, epilepsy/seizures, nausea/vomiting, spasticity/MS, agitation in Alzheimer's disease, and post-traumatic stress disorder. To date, medical marijuana has not been shown to be curative for any disease.² Its medical use has been directed toward the improvement of certain symptoms associated with specific diseases. It is important for the clinician to match the patient's symptoms with proven clinical efficacy for that particular symptom, recognizing that qualifying conditions for medical marijuana use do not ensure

clinical effectiveness. Where little or no efficacy has been shown, it is incumbent on the physician to honestly address how medical marijuana may or may not fit into the treatment algorithm for the patient's long-term benefit.

Medical Marijuana: Considerations Today and in the Future

In the medical context of "first, do no harm," one must view medical marijuana with a wary eye. Although often touted as less risky, medical marijuana treatment is not yet fully vetted and may deliver unexpected consequences. One recent example is the "safe" replacement of medical marijuana for opiates. The question of whether opioids should be replaced with marijuana has become an effort perpetuated by states, without waiting for experts to weigh available evidence. There are no randomized clinical trials on substituting marijuana for opioids in patients taking or misusing opioids for treatment of pain, nor are there any studies of medical marijuana in patients with opioid addiction treated with methadone or buprenorphine.⁹⁷ There is real concern for the drug-drug interactions associated between opioids and marijuana, as well. The American Society of Addiction Medicine recently published an editorial suggesting that recent state legislative approvals of using cannabis for treatment of opioid use disorder (OUD) is "a disturbing trend." In 16 citations commonly quoted in defense of marijuana as opioid replacement, Haning found no citation with more than speculation associated with using cannabis in management of OUD or addiction.⁹⁸ Currently, several state legislatures are considering OUD as a qualifying condition to add to their states' list, without any justification to suggest viability or efficacy. According to a recent statement by Nora Volkow, director of the National Institute of Drug Abuse (NIDA), "There is no evidence that marijuana weans people from opioid addiction — and promoting such treatment might deny people a chance at recovery. ... there's not any evidence that marijuana works for opioid addiction."⁹⁹

Despite little evidence for efficacy of medical marijuana in non-neuropathic pain conditions, claims for marijuana to replace opioids are being promoted without adequate evidence. These include

suggestions of marijuana treatment lowering the opioid overdose mortality rate and reducing the overall number of Medicare prescriptions for opioids, possibly reducing opioid prescribing in the Medicare Part D population, thus saving millions of dollars.¹⁰⁰⁻¹⁰⁴ Researchers evaluating patients in a double-blind trial commented on their study by stating, “researchers themselves cannot say if people (actually) switched from opioid prescriptions to using a medical marijuana product.”¹⁰⁴ The authors of another report comparing opioids and cannabis for treating pain raised the question of when the treatment of chronic, daily, severe pain might begin to look like prescribed cannabis use disorder.¹⁰⁵

When Marijuana Users Are Hospitalized

Practitioners may recommend treatment with medical marijuana without ever considering that the patient may require a hospital admission at some point, or may go to an emergency department for treatment. What happens when a marijuana user is hospitalized? If use of marijuana is discontinued unexpectedly, the patient may suffer from withdrawal symptoms. Abrupt cessation of marijuana intake is not associated with a rapid decline in plasma concentration. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, cannabis withdrawal syndrome is diagnosed when three of the following six symptoms are present: irritability, nervousness/anxiety, sleep difficulty, decreased appetite or weight loss, depressed mood, and one of the following physical symptoms, such as abdominal pain, shakiness/tremors, sweating, fever, chills, or headache.^{30,106} Nausea and cramping can be more common in women than men. These symptoms generally are milder than the withdrawal associated with opiates or benzodiazepines, and the symptoms usually resolve after a few days.

When admitted, the patient may be treated by a hospitalist or other specialist unfamiliar with the patient’s outpatient marijuana use. The inpatient physician may not be “certified to recommend” medical marijuana or may not be comfortable treating the patient on medical marijuana. This likely will lead

to the discontinuation of marijuana during the hospitalization, potentially interfering with the patient’s therapy. Substitution with prescription forms of FDA-approved THC analogues, such as dronabinol or perhaps the new costly cannabidiol pharmaceutical product, may be considered, but both differ therapeutically from combination mixtures of THC:CBD in plant-based medical marijuana strains.

If the patient and physician believe medical marijuana should be continued in the hospital, hospital policies need to be followed. Hospitals must maintain compliance with federal drug laws while respecting the patient’s right to use medical marijuana following state law. As recipients of Medicare and Medicaid funding, under federal law, hospitals cannot purchase or store marijuana, nor can nursing personnel within the hospital administer it to patients, according to various state regulations. Most hospitals have policies on self-administration of medicines that permit patients to use their own medications only after identification and labeling by pharmacy personnel. Most healthcare facilities are smoke-free, eliminating the ability of patients to smoke or vape their marijuana dose. Even if a hospital were to allow marijuana use in the facility, marijuana formulations (varied leaves, flowers, edibles, tinctures) may not be identified easily by pharmacy personnel. Labeled product may be difficult to verify by potency, composition, and specific dosing.

Navigating the maze of issues, regulations, laws, and policies will create major challenges for the primary care provider. Healthcare facilities need to develop workable policies and procedures to deal with patients who are being treated with medical marijuana.

Educating Patients About Medical Marijuana

Regardless of a physician’s “certification to recommend” status to treat patients with medical marijuana, primary care providers need to be prepared for questions from patients. Questions about medical marijuana laws and specifics of medical marijuana usefulness or harm may be on patients’ minds. If clinicians recommend medical marijuana, they must be able to address individualized issues such

as safety concerns and drug interactions. Physicians should not assume someone else will be counseling their patients or the patients’ caregivers. Common questions patients frequently have involve what to expect, how best to use the treatment, how to handle adverse effects, and how to choose the optimum marijuana product at the dispensary. Most patients will not be able to rely on medical personnel at dispensaries. Most states require minimal training for dispensary workers, creating opportunity for misinformation and personal opinions to be disseminated. Because states are not providing informational scripts for dispensary personnel or requiring significant continuing education for dispensary employees, patients can receive bad advice. For example, pregnant women often are being advised to use marijuana to prevent morning sickness, a practice not based on evidence of safety and effectiveness.¹⁰⁷

Pets and children are vulnerable to unintentional marijuana poisonings. When discussing marijuana with patients, clinicians should provide tips on proper storage of medical marijuana products to avoid unnecessary exposures to those in the household for whom it is not being recommended.

Physicians have a role in assisting patients and caregivers to register as medical marijuana purchasers. It is the physician’s responsibility to provide information to the state’s patient registry initially and as treatment proceeds. It is the prescribing physician’s responsibility to verify that the patient is not abusing his or her access to medical marijuana. Certified physicians (those with active certificates to recommend) submit recommendations for their patients directly to the Patient Registry. The risks of crossing state lines with medical marijuana should be stressed to the patient and caregiver, as each state has specific rules. If a patient is found to be in a state that does not allow medical marijuana use, it is still a federal offense.¹⁰⁸

Generally, a clinician needs to know what substances the patient is using to understand the potential for adverse effects and potential interactions. The same is true for all clinicians who may see patients using recreational or medical marijuana recommended by another provider. Primary care providers must factor in the effects and consequences

Table 3. Key Clinical Questions When Considering Recommending Medical Marijuana

- What is the patient's diagnosis?
- What treatments have been tried? Were the trials appropriate in duration and dosage?
- Does the patient have concomitant medical or psychiatric conditions?
- Is there a history of psychiatric disease and/or substance abuse? Are there recreational substances used in the past or currently? If so, what, and how frequently?
- Does the patient take other medications or dietary supplements daily or intermittently?
- Has the patient used marijuana previously, either recreationally or medically? If so, how often, which mode of administration or formulation was used? Is the patient using currently, either daily or intermittently?
- Is the condition one for which medical marijuana would be approved in your specific state? Is there available information regarding efficacy of medical marijuana for this condition?

of marijuana use by individual patients. The patient's condition also must be reviewed at various intervals. An open dialogue with a nonjudgmental approach is complementary to successful communication with each patient. If a patient is using marijuana for symptoms that can be treated better with something else, or if the patient is suffering from the adverse social or physical effect of marijuana, intercession must occur.

State Board Recommendations

The Federation of State Medical Boards (FSMB) recently issued recommendations about marijuana use in patient care and warned physicians about personal use of marijuana while practicing medicine. The FSMB Model Guideline Position Statement offers a best practice guide directed at professionalism from most state medical regulators regarding medical marijuana. All clinicians practicing where medical marijuana currently is approved should read and understand this document.¹⁰⁹

Patient-physician relationships must be intact prior to and during the time period for which marijuana is recommended. Physicians should not recommend use for their family members or for themselves. The medical record should contain full documentation during patient use of medical marijuana. The clinician should fully disclose the risks and benefits to each patient. Clinicians also should advise patients of the variability and lack

of standardization among marijuana products. Where patient decision-making is unclear, both caregivers and patients should be informed of the treatment plan with full documentation, including other treatments attempted, with full disclosure of measures chosen to ease a patient's symptoms other than with marijuana. Duration of therapy recommendations regarding medical marijuana should be clarified, with authorization not to exceed 12 months.¹⁰⁹

Recommending medical marijuana for state-qualifying conditions is at the professional discretion of the physician. (See Table 3.) He or she should monitor the patient's response, including the efficacy of the treatment, the goals of the treatment, and the patient's progress. Prescription drug monitoring programs in each state should be used, both prior to and during medical marijuana treatment. If a state has specific marijuana registry procedures, clinicians should provide updates on patient information to such agencies. If the clinician has cause to believe the patient has a substance use disorder or specific mental health disorders, consultations and collaboration with other specialists should be made as necessary.¹⁰⁹

Physicians recommending marijuana should not have financial conflicts of interest with state medical marijuana entities, which includes having an office associated with a dispensary or receiving compensation from a marijuana cultivator. FSMBs posit that physicians should

abstain from personal use of marijuana for any purpose while practicing medicine. Practicing medicine under the influence may be cause for incompetence or unprofessional conduct judgments.¹⁰⁹

Notes for the Future

The legalization of medical marijuana provides challenges for how healthcare professionals practice by asking them to recommend to their patients a Schedule I controlled substance that is illegal under federal law; for which there is little evidence of clinical efficacy, with no reproducible dosing and little quality control; and that is distributed through dispensaries, often without medical personnel overseeing and properly educating patients.

Only with an understanding of the properties of medical marijuana, including the evidence or lack of evidence associated with each qualifying condition, can one begin to determine the overall efficacy, including side effects and interactions with drugs, diseases, or herbs/foods. Medical marijuana is not one entity, but instead, is a compilation of several hundred different constituents that vary depending on factors like genetics and growing conditions.

The clinical picture surrounding the use of medical marijuana is constantly being scrutinized. More high-quality studies with single-agent, reproducible products derived from cannabinoids for FDA approval may channel the clinical uses more fully. The public view, and that of health professionals, will continue to differ regarding where clinical use for medical marijuana falls in the armamentarium. Although having many qualifying conditions allows for recommendations by physicians, there is a disparity in the evidence that exists for effectiveness vs. harm.

Treating patients requires clinicians to focus on what is best for their patients, and within the law, assist their patients by providing them choices based on best practice and optimum efficacy for a positive outcome. Being familiar with the facts of medical marijuana, as it is understood today, will help assist decision-making within the clinician-patient partnership.

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CME Questions

1. The onset of delta-9-tetrahydrocannabinol effects after oral administration is:
 - a. less than five minutes.
 - b. 10 to 15 minutes.
 - c. 30 minutes to two hours.
 - d. three to four hours.
2. The strongest evidence for efficacy of medical marijuana in chronic noncancer pain is for which of the following conditions?
 - a. Fibromyalgia
 - b. Neuropathic pain
 - c. Rheumatoid arthritis
 - d. Migraine
3. Major systematic reviews support the use of medical marijuana for which of the following conditions?
 - a. Spasticity in multiple sclerosis
 - b. Post-traumatic stress disorder
 - c. Alzheimer's disease
 - d. Myotonic dystrophy

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