MAYO CLINIC

Medical Cannabis

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Learning Objectives: On completion of this article, you should be able to (1) recognize the role that clinicians are able play in patient use of medical cannabis, (2) identify the key pharmacological differences between Δ9-tetrahydrocannabinol and cannabidiol, and (3) apply knowledge about medical cannabis risk and benefits to conversations with patients.

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Abstract

Medicolegal realities surrounding "medical marijuana" or "medical cannabis" are rapidly evolving in the United States. Clinicians are increasingly being asked by patients to share information about or certify them for medical cannabis. In order to engage in informed discussions with patients or be comfortable certifying them in states with medical cannabis laws, clinicians may benefit from an understanding of the current state of medical knowledge about medical cannabis. Intended for the generalist and subspecialist, this review provides an overview of the legal status, pharmacology, benefits, risks, and abuse liability of medical cannabis along with a general framework for counseling patients.

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Cannabis can be classified for the intention of use (ie, recreational or medical). "Medical marijuana" or "medical cannabis" should be conceptualized as a group of pharmacological agents derived from the subspecies of the flowering plant genus *Cannabis* delivered to consumers with the intent of alleviating a symptom or condition. "Medical cannabis" can be delivered in a variety of ways (inhaled, swallowed, or topical application to skin or buccal mucosa) and does not refer to a specific variety, mode of delivery, or dosage.

Public opinion and policy changes are rapidly transforming the landscape of US cannabis consumption, frequently in the

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absence of scientific evidence for indications for which it is being promulgated. The purpose of this concise review is to provide clinicians with information facilitating discussions with patients about medical cannabis.

LEGAL STATUS

The US Comprehensive Drug Abuse Prevention and Control Act of 1970 prohibits the use of cannabis for any purpose, listing it as a Drug Enforcement Agency schedule I drug (ie, "no currently accepted medical use and a high potential for abuse").[1] US states are the first governmental bodies in the world to legalize cannabis. Presently, 30 US states and the District of Columbia have programs authorizing cannabis use for specific medical conditions.

States generally restrict indications for medical cannabis to specific qualifying conditions. Some states allow physicians to determine additional qualifying conditions. States have variable statutory approaches for patient legal protections addressing legal arrest, housing, and employment.[2]

Because cannabis is illegal under federal law, clinicians cannot prescribe it and pharmacies cannot dispense it. States require willing health care professionals to be registered in order to certify patients for cannabis use. Clinicians who certify are protected against federal legal repercussions because states limit their role to documentation of qualifying medical conditions under state law. Some states require that patients have an ongoing relationship with the certifying clinician, generally defined as an interaction including a complete examination and medical history with ongoing care involvement. Clinician certification must be reviewed periodically in most states.

Cannabis is supplied to patients through state-licensed medical cannabis dispensaries. Dispensaries are predominantly for-profit centers selling any preparation or product in compliance with state regulations; however, no "good manufacturing practices" exist since they are not regulated by the US Food and Drug Administration. Routes of medical cannabis self-administration vary by state, with many providing capsules, oil, and vaporizing liquid. Most medical cannabis states allow patient access to dried flowers or whole-plant cannabis.[2] Many states have possession limits; in Minnesota, for example, state law limits patients to a 30-day supply of cannabinoids. Patients generally pay a fee to participate in the cannabis program, and cannabis obtained through state dispensaries is not covered by insurance. As a result, cost can be prohibitive. Currently, federal legislation restricts the Department of Justice from using federal funds to prevent states from implementing state cannabis laws.

ENDOCANNABINOID SYSTEM

Cannabis interacts with the endocannabinoid system. The endocannabinoid system is a distributed network of receptors, signaling molecules, and synthetic and degrading enzymes. The type 1 cannabinoid receptor (CB_1) is highly expressed in the central nervous system on neurons concentrated in the prefrontal cortex, basal ganglia, hippocampus, amygdala, hypothalamus, and cerebellum. Retrosynaptic γ-aminobutyric acid signaling generates the neuropsychiatric effects of cannabis.[3,4] The CB_1 receptors are also found in smooth muscle, myocardium, adipocytes, and preganglionic sympathetic neurons integrated with the autonomic and endocrine systems. The type 2 cannabinoid receptor (CB_2) is expressed in peripheral blood mononuclear cells, most strongly on macrophages, B cells, and natural killer cells.[5] The CB_2 receptor has been described in mesenchymal-derived central nervous system microglia, where they are hypothesized to regulate neuroinflammatory response.[6,7] The CB_2 receptor is also well described in myocardium, vascular endothelium, and smooth muscle. Our body synthesizes endocannabinoid molecules, and the primary endogenous signaling molecules are *N*-arachidonoylethanolamine (also known as AEA or anandamide) and 2-arachidonoylglycerol.[8] Both anandamide and 2-arachidonoylglycerol are agonists at CB_1 and CB_2 receptors.

PHYTOCANNABINOIDS

Phytocannabinoids are naturally occurring molecules with affinity for mammalian cannabinoid receptors. Over 100 distinct phytocannabinoids have been isolated from cannabis.[8] Concentrations of cannabinoids in

cannabis vary considerably depending on the cannabis strain and horticultural techniques.

Δ9-Tetrahydrocannabinol

Δ9-Tetrahydrocannabinol (THC) is the primary psychoactive constituent of cannabis and acts as an agonist at both CB_1 and CB_2 receptors. It activates presynaptic CB_1 receptors, decreasing cyclic adenosine monophosphate synthesis with downstream functional effects resulting in reduced neurotransmission.[9] Effects are observed clinically as impairments of learning, memory, spatial orientation, and attention during acute cannabis intoxication. Δ9-Tetrahydrocannabinol can cause self-limited tachycardia, hypotension, orthostasis, xerostomia, and xerophthalmia. Its use does not result in the respiratory depression observed with benzodiazepine or opioid administration because CB_1 receptors are not found in medullary respiratory centers. Δ9-Tetrahydrocannabinol exhibits both analgesic and anti-inflammatory properties.

Cannabidiol

Cannabidiol (CBD) lacks the THC-induced intoxicating properties that one traditionally thinks of as the "high" from cannabis use. It demonstrates weak affinity for CB_1 and CB_2 receptors. Cannabidiol may have indirect effects at CB_1 receptors[10] and does not directly interact with the CB_2 receptor. Multiple possible pharmacological targets exist for CBD, but few have been verified. Cannabidiol has observed anticonvulsant, anxiolytic, anti-inflammatory, and neuroprotective properties.[11] The presence of CBD in a cannabis product is believed to moderate and counteract psychosis-inducing effects of THC.[12]

Minor Phytocannabinoids

Other cannabinoids present in cannabis have a variety of biological activities. For example, cannabigerol has antibacterial activity, cannabinol has sedative properties, and tetrahydrocannabivarin has antiepileptic effects.[13]

SYNTHETIC CANNABINOIDS

Synthetic cannabinoids currently marketed are dronabinol, a biochemically identical form of THC, and nabilone, a THC analogue. Both have been and can be prescribed clinically for nausea and/or vomiting, appetite stimulation, pain, and spasticity.

A library of synthetic cannabinoid ligands exists for research and development. Recreational use of illegally synthesized cannabinoid receptor agonists with unpredictable pharmacological properties are marketed as "incense" and sold over-the-counter labeled as "K-2," "Black Mamba," "Crazy Clown," or "Spice." These agents of abuse have been associated with multiple adverse effects such as psychosis, agitation, autonomic dysregulation, vomiting, and death. These substances have no role in any type of clinical therapy.

EFFICACY

The list of conditions for which medical cannabis has been allowed varies at the state level. Most states allow its use for Alzheimer disease, amyotrophic lateral sclerosis, cachexia/wasting syndrome, cancer, Crohn disease, epilepsy and seizures, glaucoma, hepatitis C infection, AIDS, multiple sclerosis (MS) with muscle spasticity, severe and chronic pain, severe nausea, and posttraumatic stress disorder.[14]

The National Academies of Sciences, Engineering, and Medicine (NASEM) conducted and published a comprehensive literature review on the health effects of cannabis and cannabinoids.[11] Evidence of associations with health effects and efficacy for health end points were assessed and graded. The NASEM concluded that there is *conclusive or substantial evidence* that cannabis or cannabinoids are effective (1) for the treatment of chronic pain in adults, (2) as antiemetics in the treatment of chemotherapy-induced nausea and vomiting, and (3) for improving muscle spasticity syndromes in MS.

Chronic Pain

Chronic pain is the most commonly cited reason patients use and request medical cannabis. Data suggest that recreational or medical cannabis use may be associated with increased risk for nonmedical prescription opioid use or opioid use disorder[15]; however, medical cannabis laws have been observed to be associated with significantly lower state-level opioid overdose mortality rates.[16] Based heavily on data from 2 systematic reviews, the NASEM concluded that

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substantial evidence exists suggesting that cannabis is an effective treatment for chronic pain in adults. However, US clinical trial data evaluated the smoked flower form of cannabis, which is not available in some state programs. Thus, although the use of cannabis for pain is supported by clinical data, very little is known about the efficacy, dose, routes of administration, or adverse effects of commonly used and available cannabis products in the United States. Some data have suggested that blended THC-CBD products have improved benefit for pain compared with CBD alone.[17]

Nausea and/or Vomiting

Treatment of nausea and/or vomiting with cannabinoids has been available in the United States for 3 decades in the form of dronabinol and nabilone. No high-quality evidence exists for the benefits of inhaled or ingested CBD-exclusive or CBD-enriched products for this indication.

Muscle Spasms

Two systematic reviews have assessed cannabinoids for treating muscle spasticity in patients with spinal cord injury or MS.[11] Based on these data, oral cannabis extract, nabiximols (combination THC-CBD), and orally administered THC are probably modestly effective for reducing patient-reported spasticity scores in patients with MS. Not enough evidence suggests that these medications are effective for spasticity in patients with spinal cord injury.

Seizures/Epilepsy

Anecdotal evidence of the anticonvulsant properties of cannabis propelled the clinical development of CBD as an adjunctive treatment for medically refractory epilepsy. On June 25, 2018, the US Food and Drug Administration approved CBD oil solution for the treatment of Lennox-Gastaut syndrome[18] and Dravet syndrome,[19] severe forms of childhood epilepsy.

Other Conditions

One of the most common state-designated indications for medical cannabis is glaucoma. Data for this indication is extremely weak, suggesting that any positive effect of cannabinoids administered orally, ophthalmically, or intravenously is short term.

When discussing the efficacy of medical cannabis with patients, clinicians should consider a few issues. First, clinical evidence supporting the efficacy of medical cannabis for pain, nausea and/or vomiting, and spasticity in MS is derived from trials evaluating different preparations such as smoked or vaporized plant flower, plant-derived oral THC and THC-CBD combinations, and synthetic THC. Strong inferences about clinical efficacy can only be made about these preparations. Second, conclusive or substantial evidence suggesting that cannabis is effective for the treatment of any medical condition does not presently exist and instead suggests that it may be effective for symptom control only. Finally, a substantial proportion of the medical conditions for which states allow certified patients to consume cannabis are not supported by high-level clinical evidence of efficacy.

HEALTH RISKS

The NASEM concluded that there is *substantial evidence* for an association between cannabis smoking and respiratory disease, motor vehicle collisions (MVCs), lower birth weight offspring, and schizophrenia or other psychoses.[11]

Respiratory Disease

Although some data suggest that short-term exposure to cannabis smoking is associated with bronchodilation, benefits may be offset by long-term cannabis effects including lower forced expiratory volume. Smoked cannabis is associated with chronic cough, phlegm production, and chronic bronchitis. Limited evidence exists that smoked cannabis is associated with the development of chronic obstructive pulmonary disease. Available evidence suggests that cannabis does not increase the risk for lung cancer. As this data relates almost exclusively to inhaled smoked organic cannabis plant material, little is known about the impact of cannabis oil vaporization on lung function, lung health, or cancer risk. Studies have suggested that vaporization of cannabis is associated with fewer respiratory symptoms.[20]

Motor Vehicle Collisions

Available data suggest that driving under the influence of cannabis indicated by self-report or the presence of THC in bodily fluid is associated with significantly higher odds of an MVC.[21] Uncertainty remains about the level of THC associated with impaired driving ability and may relate to chronicity of individual use. Cannabidiol is not known to have psychoactive activity and is likely not associated with increased risk for MVCs.

Lower Birth Weight Offspring

Endocannabinoids are involved with critical steps in neurodevelopment. Δ9-Tetrahydrocannabinol crosses the placenta and is secreted in breast milk. Cannabis use during pregnancy is linked to lower birth weight infants. Earlier in utero exposures to cannabis may affect organogenesis, and later in utero exposures may affect fetal growth. Most of the data for cannabis use during pregnancy is related to smoked organic material potentially confounded with concomitant tobacco and alcohol consumption; very little data exist for this association with other forms of cannabis use.

Psychosis

The relationship between cannabis use and psychosis-related outcomes (eg, schizophrenia, schizoaffective, schizophreniform, and psychotic disorders) appears to be moderate to large and dose dependent. Studies have evaluated cannabis use as a class of a drug across multiple different populations and have not focused on limited phytocannabinoid preparations (ie, THC only, THC-CBD, or CBD only). Available evidence suggests that the prevalence of cannabis use among people with schizophrenia is higher than that in the general population. Δ9-Tetrahydrocannabinol has psychoactive effects, whereas CBD has antipsychotic effects.[22] Preparations with lower levels of THC and higher levels of CBD may be anticipated to have lower psychosis-inducing liabilities than that observed in the population-based studies. Cannabidiol has been evaluated for the treatment of psychotic disorders; presently, however, insufficient data exist supporting the use of CBD for this indication.

ABUSE LIABILITY

Cannabis use may be associated with dependence.[23] Δ9-Tetrahydrocannabinol has a psychoactive effect of producing a "high" and has abuse liability. However, the extent to which this occurs with medical cannabis is unknown and requires further study.

COUNSELING PATIENTS

Clinicians who are comfortable with the idea of having their patients explore medical cannabis as an option for symptom management should invite patients into a discussion when they inquire about it or whenever clinical progress is difficult to achieve. Clinicians should feel comfortable disclosing to their patients the gaps in knowledge that exist about the efficacy and safety of medical cannabis. Clinicians whose patients ask about medical cannabis should be prepared to discuss (1) known risks and benefit, specifically its benefits for pain, nausea and/or vomiting, and spasticity and the risks of respiratory disease, MVCs, low birth weight offspring, and psychotic symptoms and (2) that medical cannabis remains illegal under federal law, which should be considered when flying or driving across state lines.

Caution should be exercised when considering medical cannabis for individuals under the age of 25 years because the brain continues to develop until this age, and the potential for cannabis to have a lasting impact on cognitive performance is unknown.[11] Clinicians should manage patient expectations by relating that it is difficult to extrapolate currently available evidence on medical cannabis to patient-experienced benefits or harms from medical cannabis products obtained from state programs because horticultural techniques, drug extraction techniques, and drug delivery modalities are rapidly evolving.

Certifying clinicians should additionally discuss with patients (1) that clinicians do not prescribe medical cannabis but only certify for the condition that qualifies patients under state programs, (2) recommendations for discontinuing medical cannabis if it is not beneficial or if they are experiencing adverse effects, (3) the importance of continuing other therapies because medical cannabis needs to be part of a comprehensive symptom

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management strategy rather than a singular solution, (4) how to taper off other medications such as opioids or pain-modifying agents if desired, (5) how their progress with medical cannabis should be/will be monitored, and (6) how frequently they need to be certified because states require different time lengths for recertification.

CONCLUSION

Medical cannabis laws provide clinicians with the opportunity to provide selected patients with an additional tool to help them manage disabling or troubling symptoms. Clinician awareness of potential benefits and adverse effects will help patients make informed choices about using medical cannabis to improve their quality of life. Clinicians have a unique opportunity to guide selected patients to this emerging treatment strategy.

Abbreviations and Acronyms: **CB_1** = type 1 cannabinoid receptor; **CB_2** = type 2 cannabinoid receptor; **CBD** = cannabidiol; **MS** = multiple sclerosis; **MVC** = motor vehicle collision; **NASEM** = National Academies of Sciences, Engineering, and Medicine; **THC** = Δ9-tetrahydrocannabinol

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