

Medical cannabis for the treatment of chronic pain and other disorders: misconceptions and facts

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ABSTRACT

Recently, many countries have enacted new cannabis policies, including decriminalization of cannabis possession as well as legalization of medical and recreational cannabis. In this context, patients and their physicians have had an increasing number of conversations about the risks and benefits of cannabis. While cannabis and cannabinoids continue to be evaluated as pharmacotherapy for medical conditions, the best evidence currently exists for the following medical conditions: chronic pain, neuropathic pain, and spasticity resulting from multiple sclerosis. We also reviewed the current state of evidence for cannabis and cannabinoids for several other medical conditions, while addressing the potential acute and chronic effects of cannabis use, which are issues that physicians must consider before making an official recommendation on the use of medical cannabis to a patient. As the number of patient requests for medical cannabis has been increasing, physicians must become knowledgeable on the science of medical cannabis and open to a discussion about why the patient feels that medical cannabis may be helpful.

Introduction Cannabis is one of the most commonly used substances worldwide. The cannabis plant contains over 400 chemical constituents, more than 100 of which are cannabinoids—chemicals unique to the cannabis plant. In the past 20 years, many countries have enacted new cannabis policies, including decriminalization of cannabis possession as well as legalization of medical and recreational cannabis. In this context of heightened discussion about the risks and benefits of cannabis, various countries have considered cannabis as a possible treatment for several debilitating medical conditions. While this has led to research on the medical indications for cannabis pharmacotherapy, many countries have pushed policy ahead of the science, opting not to wait for the rigorous scientific investigations to provide definitive evidence on the effectiveness of cannabis.

Legal status of medical cannabis in the United States and Poland In the United States, a growing number of states are considering laws legalizing

medical cannabis. As of September 2017, 29 states and the District of Columbia have passed medical cannabis laws, and several others will likely vote on this issue in the next 1 or 2 years. Of note, there are 2 cannabinoids, dronabinol and nabiximone, that are approved by the United States Food and Drug Administration for nausea and appetite stimulation. Poland has proceeded more cautiously in enacting medical cannabis laws. However, despite the lack of medical cannabis laws, Polish citizens are aware of the intense interest surrounding medical cannabis worldwide, and this has led many of them to ask their physicians about medical cannabis as a treatment for their own medical conditions.

Conditions with moderate- to high-quality evidence **Chronic pain and neuropathic pain** There is a small number of indications for which there is substantial evidence supporting the efficacy of medical cannabis pharmacotherapy (TABLE 1).¹ For example, there have been several studies showing that cannabis can be an effective

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TABLE 1 Indications for medical cannabis and the quality of randomized placebo-controlled studies showing its efficacy

Indication	Quality of evidence
Chronic and neuropathic pain	Moderate to high ¹⁻⁷
Spasticity associated with multiple sclerosis	Moderate to high ⁸⁻²²
Seizure disorders	Moderate to high ²³⁻³¹
Gastrointestinal disorders	Moderate ³²⁻³⁹
HIV and acquired immunodeficiency syndrome	Moderate ⁴⁰⁻⁵¹
Glaucoma	Low ⁵²⁻⁵⁶
Posttraumatic stress disorder	Low ⁵⁷⁻⁶⁵
Parkinson disease	Low ⁶⁶⁻⁷²

pharmacotherapy for both chronic pain and neuropathic pain. The effectiveness of cannabis in treating pain was initially demonstrated in preclinical studies.^{2,3} The endocannabinoid system was hypothesized to play an active role in controlling pain, and animal pain models were employed to support this hypothesis.² Delta-9-tetrahydrocannabinol (THC) was shown to produce analgesic and antihyperalgesic effects in mice.⁴ These analgesic effects have been supported anecdotally in patients with chronic pain, and many clinical studies have aimed to investigate these effects in human models.

Whiting et al⁵ conducted a systemic review and meta-analysis of randomized clinical trials of cannabis and cannabinoids. This review analyzed 28 studies assessing chronic pain in a total of 2454 participants. Overall, there was a higher reduction in pain measures with cannabinoids when compared with placebo, but most of these differences were not significant within each study. A recent report released by the National Academy of Science, Engineering, and Medicine in the United States stipulated that there was “conclusive or substantial evidence” that cannabis or cannabinoids are effective treatments for chronic pain.⁶ Finally, another review determined that there was “high quality evidence,” as demonstrated by multiple positive randomized placebo-controlled trials, to support the administration of cannabis or cannabinoid pharmacotherapy for treating chronic pain and neuropathic pain.⁷

Spasticity associated with multiple sclerosis As of October 2017, there have been at least 14 randomized clinical trials aimed at showing the efficacy of cannabis treatment for spasticity associated with multiple sclerosis. Many of these studies showed that cannabis or cannabinoids were helpful in relieving spasticity.⁸⁻²¹ The American Academy of Neurology found these results promising, leading to the release of evidence-based guidelines for physicians recommending a cannabis oral extract containing both THC and cannabidiol (CBD) for the treatment of spasticity and pain associated with multiple sclerosis.²² The symptoms most often found to be alleviated with cannabis were muscle stiffness, spasticity, and sleep disturbances.^{11,13,16,18,20}

Seizure disorders Much of the evidence in favor of cannabinoids for epilepsy in children has been based on self-reports and anecdotal evidence.²³ Studies on the perceived efficacy of the use of CBD-enriched cannabis in children with epilepsy have shown a significant reduction of both the frequency and severity of seizures in a variety of seizure disorders.^{24,25} In a study of 19 children, aged 2 to 16 years, with diagnoses of Dravet syndrome, Lennox–Gastaut syndrome, and idiopathic epilepsy, complete seizure freedom and an improvement of seizures was reported in 11% and 84% of patients, respectively.²⁴ In a survey-based study of 117 parents of children with infantile spasms and Lennox–Gastaut syndrome, 14% of patients were completely seizure-free, and 85% of parents reported a reduction in seizure frequency after cannabis pharmacotherapy.²⁵ Other beneficial effects of CBD in children with epilepsy syndromes include improved sleep, alertness, and mood, as well as an increased appetite.²⁴⁻²⁶ In the first reported double-blind placebo-controlled trial of a cannabinoid for Dravet syndrome, CBD significantly reduced the median frequency of convulsive seizures per month and significantly improved the patient’s overall condition measured on the Caregiver Global Impression of Change scale, when compared with placebo.²⁷

Studies on the effectiveness of cannabinoids in adults with epilepsy have provided mixed results. It was shown that men who used cannabis up to 90 days before hospitalization were at a significantly lower risk for a new seizure than men who did not use cannabis.²⁸ In another study of adults with epilepsy, most patients associated cannabis use with a reduction in the severity and frequency of seizures.²⁹ Meanwhile, a recent survey study of patients in a tertiary epilepsy clinic showed that cannabis did not affect the frequency or severity of seizures.³⁰ While there is much published research regarding the effects of cannabinoid use on seizures in adults, most studies have not been placebo-controlled and have been largely anecdotal, underscoring the need for randomized controlled trials.³¹

There have been only 4 placebo-controlled studies that examined the effectiveness of cannabinoids for epilepsy, but they had small sample sizes and some methodological challenges.²³ While cannabinoids were shown to improve symptoms of epilepsy, the data were insufficient to draw any firm conclusions.

Conditions with low-quality evidence **Gastrointestinal disorders** Cannabinoids affect parts of the intestine through a similar mechanism as certain opioids that are currently used in the treatment of irritable bowel syndrome (IBS). This makes cannabinoids a potentially effective treatment.³² An endocannabinoid deficiency may be an underlying factor in disorders such as IBS, further suggesting that cannabinoids may provide relief to patients with this condition.^{33,34} Cannabinoids appear to target inflammation and diarrhea associated

with IBS. Many patients report that cannabis relieves symptoms of gastrointestinal disorders, such as nausea, spasms, and low appetite.³⁵

As with many other indications, there have been very few studies looking at how patients with Crohn disease (CD) respond to cannabis. Most therapies for CD are targeted towards reducing inflammation. However, in some patients, these medications do not eliminate symptoms such as chronic diarrhea, and this is where the use of cannabinoids may provide relief. Research from the last several decades has suggested that cannabis has anti-inflammatory properties.^{36,37} CBD is also a promising medication in the treatment of inflammatory bowel diseases; it has been shown to alleviate symptoms and potentially increase the efficacy of other anti-inflammatory drugs that are typically indicated for ulcerative colitis and CD.³⁸ A small-scale placebo-controlled pilot study showed that cannabis provided significant clinical benefits in patients with CD, such as improved appetite and sleep.³⁹

HIV and acquired immunodeficiency syndrome Over the last few decades, several studies have been conducted that examined the use of medical cannabis in patients with HIV or acquired immunodeficiency syndrome. The current use of medical cannabis in this population has been investigated in numerous studies, but the results have been mixed. The rates of cannabis use among HIV-positive patients have been reported to range from 15% to 44%.⁴⁰⁻⁴⁶ The most common reasons for these patients to use cannabis were to improve appetite, gain weight, and decrease nausea.^{41,45} While cannabis use is relatively common in this population, there have been only a handful of clinical trials demonstrating significant effectiveness of medical cannabis in treating HIV-related symptoms. Among these studies, evidence was somewhat strong in favor of medical cannabis for HIV-induced neuropathic pain,⁴⁷⁻⁴⁹ and of cannabinoid medications, such as dronabinol, for an increased appetite in HIV-positive patients.⁵⁰ While there are benefits from using medical cannabis in terms of pain reduction and appetite stimulation, physicians and patients should be aware that some evidence shows that frequent cannabis use may be associated with a decrease in cognitive function in patients with a more advanced stage of HIV.⁵¹

Glaucoma The use of cannabis to help treat glaucoma has been explored since the early 1970s.⁵² Although cannabis seemed promising, mostly due to findings showing that it decreases intraocular pressure in both healthy and glaucomatous eyes, further reviews have shown limited treatment efficacy.^{52,53} The American Academy of Ophthalmology does not support the use of cannabis for glaucoma, owing to the limited duration of action of cannabis.^{54,55} Furthermore, even though cannabis decreases intraocular pressure temporarily, it also lowers blood pressure. This could lead to a decrease in blood flow to the optic nerve, increasing the risk

for loss of vision.⁵⁶ Cannabis also has a more serious side effect profile than many current glaucoma treatments; therefore, until more evidence for its efficacy becomes available, most ophthalmologists would recommend that patients continue traditional treatments instead of cannabis for glaucoma.

Posttraumatic stress disorder There is a plausible mechanism to support the possible use of cannabinoids, especially CBD, as pharmacotherapy for posttraumatic stress disorder (PTSD).⁵⁷ Many studies have examined the use of medical cannabis in patients with PTSD, but there have been no large-scale randomized controlled trials on the effectiveness of medical cannabis in the treatment of PTSD.⁵⁸ Cannabis is commonly used in patients with PTSD, often as a coping mechanism for symptoms such as hyperarousal, intrusive thoughts, and sleep problems.⁵⁹⁻⁶² However, in a longitudinal cohort of 2276 United States veterans with PTSD, cannabis use was associated with greater severity of PTSD symptoms, violent behavior, and higher rates of alcohol and drug use.⁶³ By contrast, Greer et al⁶⁴ described a 75% reduction in scores on a PTSD symptom scale for individuals who obtained a medical cannabis card to alleviate such symptoms. Individuals with more severe symptoms of PTSD generally reported greater cannabis use problems, cravings, and severity of cannabis withdrawal.⁶⁵

Parkinson disease Anecdotal evidence has led to the study of cannabis and cannabinoids as pharmacotherapy for Parkinson disease. A limited number of studies have been conducted that suggest cannabinoids may improve symptoms associated with Parkinson disease, but most of these studies were observational and did not contain a control group.⁶⁶⁻⁶⁸ In addition to these observational studies, 4 randomized controlled clinical trials studied the effects of cannabinoids on parkinsonian symptoms, but none of them showed significant improvements in motor symptoms.⁶⁹⁻⁷²

Risks associated with cannabis use Although physicians may be tempted to recommend cannabis for indications for which there is some evidence of its efficacy, there are many other issues that they must consider before making an official recommendation. Besides the question of whether a physician has the full legal ability to recommend cannabis, there are also possible adverse events associated both with short- and long-term use of cannabis that should be taken into account.⁷³ Acute cannabis intoxication leads to interference with perceptions of memory and time as well as with motor functions. Cannabis worsens existing anxiety or mood disorders, and, in some instances, it can increase the likelihood that one will develop these disorders.⁷⁴⁻⁷⁶ Cannabis has also been shown to be strongly associated with the development of psychotic disorders in those with a genetic predisposition to such conditions.⁷⁷

Cannabis use during adolescence can lead to permanent changes in developing brains. Individuals who regularly used cannabis during adolescence had lower gray matter density in both the hippocampus and corpus callosum.⁷⁸ Early and regular cannabis use was also associated with up to an 8-point decline in intelligence quotient over time in a large longitudinal study.⁷⁹ A preliminary study also showed structural brain changes in the amygdala and nucleus accumbens in occasional cannabis users.⁸⁰ Although more research needs to focus on how cannabis affects the developing brain, these preliminary results have deterred many physicians from recommending cannabis to adolescent patients.

How physicians should approach medical cannabis As medical cannabis laws continue to be passed internationally, the number of patient requests for medical cannabis will likely increase. Physicians must take the same steps with these patients as they would with prescribing any other medications to ensure that medical cannabis is recommended appropriately and as safely as possible.

First and foremost, medical cannabis recommendations should be offered to patients who have a condition that is known to be responsive to cannabis, with moderate- to high-quality evidence. Patients who have medical conditions that are known to be exacerbated by cannabis use should not be recommended medical cannabis. Due to the potentially serious adverse effect profile associated with cannabis in comparison with some other treatments, the physician must discuss the risks and benefits of medical cannabis use with the patient.

Physicians should ask their patients why they believe cannabis may be effective in helping their condition. It may be that patients are already using cannabis to help alleviate some symptoms, in which case the physician must ask how it has affected them so far. If the typical first- and second-line treatments for the condition they are attempting to treat have not yet been attempted, physicians should explain that to date these other treatments have more data supporting their efficacy than cannabis. Even if cannabis does not end being used for treatment, engaging in a conversation with patients about their hopes for cannabis treatment increases the likelihood that they will receive treatments, perhaps other than medical cannabis, for their medical conditions that might not have been treated otherwise.

Conclusion As research into cannabis and its efficacy as a medication continues, medical professionals should stay informed on these findings. Cannabis and cannabinoids are promising therapeutics in several areas of medicine. **Professionals should rely on facts and research, not public opinion, to inform medical decisions.** Cannabis is often used for recreational purposes, but this should not affect how physicians view data collected on its efficacy in treating certain medical conditions.

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