Medical Cannabis for the Primary Care Physician

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Abstract
Medical cannabis use is common in the United States and increasingly more socially acceptable. As more patients seek out and acquire medical cannabis, primary care physicians will be faced with a growing number of patients seeking information on the indications, efficacy, and safety of medical cannabis. We present a case of a patient with several chronic health conditions who asks her primary care provider whether she should try medical cannabis. We provide a review of the pharmacology of medical cannabis, the state of evidence regarding its efficacy, variations in the types of medical cannabis, and safety monitoring considerations for the primary care physician.

Keywords
medical cannabis, primary care, chronic pain, medical marijuana, adverse effects

Introduction
Cannabis use is common in the United States and increasing. Cannabis was the most commonly used illicit substance in the United States in 2016 in a national survey, with an estimated 24 million (9%) Americans who used cannabis in the past month. This trend has coincided with a growing number of states that have legalized medical cannabis. Thirty-three states in the United States and the District of Columbia have laws allowing for use of medical cannabis. Cannabis has been more widely accepted in other parts of the world, including the Netherlands and Canada more recently. Israel has been a leader in cannabis research over the years. With the growing prevalence and social acceptability of cannabis use, primary care physicians (PCPs) are faced with more patients seeking information on medical cannabis. Even if the PCP is not prescribing medical cannabis, their patients may be using it and providers should be able to discuss the pros and cons of cannabis use and help to monitor for improvements and for potential adverse outcomes.

To illustrate these points, this article will describe a case of a patient engaged in primary care who is considering whether to try medical cannabis for chronic pain. The subsequent review gives a description of key information that is important for PCPs to know when caring for patients who choose to use medical cannabis, including a brief review of the pharmacology of medical cannabis, the state of evidence regarding its efficacy, variations in the types of medical cannabis, and safety monitoring considerations for the PCP.

Clinical Example
Ms J is a 54-year-old woman with a 15-year history of chronic back pain after a car accident. She has tried pharmacologic management for her pain with duloxetine as well as physical therapy and trigger point injections. The use of opioids for her pain has been discouraged due to the chronic nature of her symptoms and she had negative side effects from gabapentin and amitriptyline. In addition, Ms J complains of insomnia and irritability due to poor sleep. Ms J tells her PCP that given her continued pain, she visited a medical cannabis provider, acquired certification for cannabis to manage her pain, and visited a dispensary where
she encountered many different options for modes of consumption and type of product. She would like an opinion from the primary care perspective on (1) whether she should start medical cannabis for management of her symptoms, (2) whether one type of medical cannabis is better than another, and (3) what side effects or complications she should be concerned about.

**Basic Pharmacology of Cannabis**

As cannabis is increasingly accepted, it is important for PCPs to understand its basic pharmacology, as well as the formulations their patients might be using. Cannabis describes a family of plants that include marijuana plants, derived mainly from *Cannabis sativa* and *Cannabis indica*, as well as hemp. The cannabis plant produces over 100 cannabinooids and terpenes, the most widely studied of which are Δ9-tetrahydrocannabinol (THC) and cannabinol (CBD). The remaining cannabinooids and terpenes contribute to the smell, taste, and possibly therapeutic effect of cannabis. Cannabinoids can be endogenous (endocannabinoid), plant-derived (phytocannabinoid), or synthetic, and they act as neurotransmitters within the human endocannabinoid system.

The human endocannabinoid system includes cannabinooids and cannabinoid receptors (CB₁ and CB₂). The 2 most well-known endocannabinoids are anandamide and 2-archidonoylglycerol (2-AG). Anandamide and 2-AG target CB₁ and CB₂ receptors, respectively. Similarly, THC acts primarily on CB₁ receptors, and CBD on CB₂.

CB₁ receptors exist primarily in areas of the brain that regulate appetite, memory, fear, and motor responses. Stimulation of CB₁ receptors in the brain leads to psychotrophic effects from cannabis. CB₂ receptors are also found outside of the brain in the gastrointestinal tract, adipocytes, liver, and skeletal muscle. CB₂ is primarily expressed in macrophages and other macrophage-derived cells that are part of the immune system.

Medical cannabis can be either plant-derived or synthetic, contains different amounts and ratios of THC and CBD, and can be delivered by several routes of administration, including smoking, vaping, oromucosal, ingestion, and topical. Route of administration affects the rate of absorption of THC and CBD, and thus influences the onset, intensity, and duration of the clinical effect of cannabis. Peak THC blood levels are reached within 30 minutes and subside within 1 to 3.5 hours when cannabis is smoked. In contrast, peak THC levels are reached within 30 minutes to 2 hours when ingested and can last 5 to 8 hours. Sublingual and oromucosal THC and CBD avoid first-pass metabolism in the liver, but peak serum THC and CBD concentrations are reached 1 to 8 hours after administration.

Some forms of medical cannabis have undergone clinical trials and are available in the United States and/or other international settings. Nabiximols, which contains plant-derived THC and CBD as an oromucosal spray, is available outside of the United States for use in treating spasticity, nausea, vomiting, and pain. In the United States, the Food and Drug Administration (FDA) approved the first plant-derived cannabinoid for medical use, Epidiolex (CBD), for treatment of seizure disorder. Synthetic therapeutic cannabinooids, including dronabinol (synthetic THC) and nabilone (synthetic THC), are FDA approved for nausea, vomiting, and cachexia.

Products at the dispensary Ms J visited include a range of options that contain THC alone, CBD alone, and several different THC/CBD ratios, and that can be administered by several different modes of consumption. The potential medical effects and side effects could thus vary by the relative amounts of THC and CBD, and the timing and duration of the effects will vary according to the mode of consumption.

**Indications and Efficacy of Medical Cannabis**

When counseling Ms J on how medical cannabis may affect her symptoms, interpreting the cannabis literature can be challenging for several reasons. First, formulations vary by state due to the patchwork of state-based legislation. Products used in the literature may not be representative of what is available to medical cannabis patients at a local level. In practice, patients self-titrate to symptom relief and are encouraged to do so. Furthermore, medical cannabis has largely been sought for the management of symptoms, rather than conditions. Recent data from the Florida Department of Health show the top indications for currently registered persons in Florida are chronic pain and posttraumatic stress disorder. In New York State, similarly, the most common condition for which patients are certified to receive medical cannabis is chronic pain.

A detailed summary of all known evidence regarding the clinical efficacy of cannabis is beyond the scope of this review, and has been summarized elsewhere including a comprehensive review of the literature published by the National Academies of Sciences, Engineering and Medicine in 2017. Here, we describe evidence for some of the more common indications that are relevant to Ms J.

**Chronic Pain**

Chronic pain, such as that seen in Ms J’s case, is the most commonly cited reason for seeking out medical cannabis. Medical cannabis is used to treat chronic pain related to neuropathy, cancer, multiple sclerosis, rheumatoid arthritis, musculoskeletal issues, drug toxicity, and HIV.

A systematic review of over 28 randomized controlled trials found that cannabinoids have greater odds of ≥30% reduction in pain scores compared with placebo. Cannabis
reduces neuropathic pain in a dose-dependent fashion in other analyses. In these analyses, oral cannabinoids were found to have a smaller beneficial effect than inhaled cannabinoids. Though these findings are promising, the sample sizes are very small, many of the studies focused on specific products, including synthetic cannabinoids, and confidence intervals span close to the level of significance. Thus, we have very limited evidence regarding the efficacy of products available to patients in states with medical cannabis, including the relative benefits of THC, CBD, or various THC/CBD ratios for pain.

The mechanism of cannabis’ analgesia is not completely understood. One potential mechanism is the interaction of cannabinoids with the human endocannabinoid system, thus leading to a reduction in pain stimuli or inflammation. Cannabis may also reduce emotional stress related to chronic pain, or shift perceptions of pain.

Patients report that medical cannabis helps them reduce or stop other pain medications such as opioids. Among patients who use cannabis to manage their pain in California, an overwhelming percentage of those who were surveyed reported that cannabis was better at treating their pain than opioids and that they have subsequently reduced their chronic opioid use. In another sample of patients in Colorado using nonmedical cannabis, the majority endorsed using cannabis to self-manage pain and reported a reduction in other analgesic use when using cannabis. These observations have been documented in other states that have legalized medical cannabis as well.

Anxiety and Posttraumatic Stress Disorder

Anxiety and posttraumatic stress disorder (PTSD) are common reasons for seeking out medical cannabis. Among individuals engaged in care there is a growing desire to reduce the use of prescription anxiolytics, such as benzodiazepines, due to medication safety concerns. There is also evidence that cannabis is used to self-manage anxiety. Patients who use cannabis report that they subsequently reduce their prescription anxiolytic use, including benzodiazepines.

The mechanism by which cannabis addresses anxiety is not completely understood. Preclinical data show a relationship between anxiety and decreased endocannabinoids. There are few studies testing the efficacy of cannabis for the treatment of anxiety. In small randomized controlled trials cannabis has been found to be effective for short-term treatment of anxiety symptoms.

Self-management of PTSD with cannabis is common and PTSD is a commonly listed indication for certification. In surveys among combat veterans who use cannabis at least once per week, cannabis use is associated with improvement in some symptoms of PTSD, such as disturbing thoughts and dreams. Preclinical studies suggest that THC can reduce signals of fear and threat as directed by the amygdala and that CBD can modulate emotional and social processes. Several small studies have been performed in people with PTSD, primarily among veterans. Unfortunately, most of these studies were poor quality, due to short follow-up, small sample size, and lack of a comparison group. In the context of these limitations, cannabinoids have been found to improve PTSD symptoms.

Insomnia

Insomnia is experienced by up to 35% of individuals in the United States. Known therapies exist that are effective in the management of insomnia, such as behavioral therapy, benzodiazepines, and hypnotics. However, available pharmacologic therapies come with risk of side effects and negative health outcomes. Though insomnia is not a commonly listed indication for certification of medical cannabis, many patients self-manage insomnia with cannabis and seek medical cannabis for insomnia. Early research on cannabis and sleep shows that cannabis improves sleep onset and reduces the occurrences of awakening during sleep. Other research has found a reduction in REM (rapid eye movement) sleep with cannabis use and has raised concern that cannabis used for sleep could lead to negative consequences. These include developing tolerance to cannabis and thus increasing the dose of THC required in order to achieve the desired effect, and sleep disturbance when stopping cannabis use, therefore encouraging continued use.

Cannabis has been tested for the management of obstructive sleep apnea as well. One randomized controlled trial found improved self-reported and observed clinical measures in patients given synthetic THC versus placebo. Despite this, though, the American Academy of Sleep Medicine has advised that further research is needed prior to recommending cannabis for the management of obstructive sleep apnea.

Other specific indications for medical cannabis in which there is some evidence of benefit include intractable nausea and vomiting, cachexia, inflammatory bowel disease, epilepsy, and spasticity. As these symptoms are seen less often in the primary care setting than the previously described indications, they are not within the scope of this article.

Follow-up and Monitoring

Ms J decides to start using medical cannabis, including 10-mg CBD tablets twice daily, and a vape pen that contains THC with 2-second inhalations as needed for pain. She experiences improvement in her chronic pain, but she also reports feeling somewhat dizzy and confused, particularly immediately after using vaped THC. Her family members
say that she is more active and sleeping better, but ask about
the risk of cannabis addiction, whether she can drink any
alcohol with cannabis, and whether she is at risk for lung
disease related to vaping.

PCPs should monitor for health consequences of medical
cannabis use, while also considering how medical cannabis
could affect other prescription medications. The response to
cannabis can vary based on route of administration and
adverse events or side effects can present as acute toxicity or
effects from long-term exposure. Since legalization of
medical cannabis, observational data have emerged describ-
ing cannabis-related adverse events.

**Psychiatric Symptoms**

Chronic cannabis use is associated with psychiatric symp-
toms, including anxiety, depression, and psychosis, and has been linked to worsening schizophrenia in those
with a preexisting genetic vulnerability. However, a
direct causal relationship is difficult to establish as a mul-
titude of confounding factors blur the relationship
between cannabis use and psychiatric illness. For exam-
ple, people with symptoms like anxiety or stress may be
more likely to use cannabis. New or worsening psychiat-
ric symptoms should be monitored for in patients who are
using medical cannabis, and termination of use encour-
aged if identified.

**Cannabis Hyperemesis Syndrome**

Gastrointestinal symptoms were the most common cause for emergency room visits related to cannabis use in a
recent study in Colorado state. The most common severe
gastrointestinal side effect of cannabis use, cannabis hyper-
emesis syndrome, presents as cyclical nausea and vomit-
ing and abdominal pain in the setting of chronic cannabis
use. Symptoms may improve with hot showers or baths and
resolve after cessation of cannabis use. Patients using
 cannabis should be screened for these symptoms during
primary care visits and termination of cannabis use should
be encouraged for those experiencing cannabis hypereme-
sis syndrome.

**Motor-Vehicle Accidents**

There is concern that cannabis use will lead to motor vehicle
accidents associated with cannabis intoxication. Cannabis
use impairs driving in a dose-response manner. However,
population level studies have not shown a relationship
between medical cannabis laws and an increase in motor
vehicle accidents or traffic fatalities. Patients should be
cautions regarding driving impairment while using can-
nabis, and advised to avoid driving if intoxicated.

**Pulmonary Effects**

Chronic cannabis use can lead to symptoms of chronic bron-
chitis, including cough, sputum production, and wheezing.
Cannabis use may result in some changes to pulmonary
function tests, but unlike tobacco, it does not result in chronic
obstructive pulmonary disease in observational studies.
The mode of consumption could be associated with specific
types of respiratory syndromes. A new lung disease associ-
ated with heavy vaping use was emerging in late 2019. To
date, it remains unclear whether the risk is limited to
specific types of vaping products or oils, or with specific
use patterns. For patients who choose to vape, providers
should recommend avoiding products purchased outside of
registered facilities (eg, from a street dealer) and should
monitor for changes in breathing.

Cannabis smoking may predispose individuals to pneu-
monia through damage of central airways and changes in
local immune response. Smoked cannabis contains car-
icogens, raising concerns about lung cancer. Observational
studies show increased risk of lung cancer in all users, only
among heavy users, and not at all. These studies
included potential confounders that may have skewed
results. Further research is needed to understand how people
using cannabis should be monitored for cancer.

**Drug-Drug Interactions**

THC and CBD are metabolized in the cytochrome P450
system. Most drug interactions with medical can-
nabis are drugs that are also metabolized by this system.
Cannabis may inhibit the metabolism of strong CYP450
inhibitors, such as warfarin, rifampicin, and omeprazole.
Cannabis has additive sedative effects with other sedating
agents.

PCPs should be aware that they may need to taper other
medications that their patients are taking for pain or anxiety,
for example. Given the potential for drug interactions, it can
be important to increase monitoring of medications that
need to be within a specific therapeutic window, at least
temporarily, if someone is starting medical cannabis for the
first time, and to monitor patients much like they would if
they were using herbal or dietary supplements. Some states
have published tables with known drug interactions that can
be accessed online.

**Risk of Cannabis Use Disorder**

All patients using medical cannabis should be screened for
cannabis use disorder (CUD). Based on the *Diagnostic and
Statistical Manual of Mental Disorders, Fifth Edition*, CUD
is defined as use leading to negative social, occupational,
psychological, and physical consequences. In patients
receiving medical cannabis or using recreational cannabis, providers should monitor for symptoms and recommend tapering off of cannabis if they develop CUD.

Few valid, succinct, and reliable screening tools are available. The Cannabis Use Disorder Identification Test (CUDIT) is a 10-item screening tool that is 73% sensitive and 95% specific.85 However, its length makes it difficult to use in a clinical setting. Modifications of the CUDIT, including the CUDIT-R86 and the CUDIT-Short Form,87 attempt to make more brief screening tools appropriate for busy clinical settings, but none of these measures have been studied in the primary care setting.

Conclusions

Ms J’s PCP recommended that she avoid other sedating substances like alcohol while using her medical cannabis. Her medical cannabis provider also recommended that she reduce her THC consumption by using a vaped pen with a lower THC/CBD ratio. With these changes, her pain control and side effects improved. Her children report that she is more at ease and seems in less pain.

No matter the laws around medical cannabis, PCPs benefit from understanding what the potential uses, adverse events, and risks are of using medical cannabis. In order to make recommendations based on high-quality evidence, more randomized controlled trials and pragmatic trials are needed. Studies using cannabis are extremely restricted in the United States. Federal government’s Schedule 1 classification of cannabis, which prohibits its use for research except for in limited settings. As providers and patient advocates, we should press for changes in these laws to allow for more substantive research that is applicable to our patients.

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