The Use of Medical CBD Oil

In a Primary Care Setting

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x. Introduction

Cannabis has endured a storied and vibrant reputation throughout human history and has been used for recreational, medicinal, and religious purposes in many cultures. It is one of the earliest known plants to be domesticated by humans, with evidence of its cultivation of dating approximately 36 million years ago in central Asia (1). It is only in the 20th century that quality control issues, the lack of a defined chemistry, and above all else, political and ideological motivations led to the prohibition of cannabis use in the United States (2). In the 21st century, the sociopolitical climate is changing, moving toward the social acceptance and legality of cannabis use. The use of medical cannabis (MC) continues to grow throughout the world, including the United States, with 35 states and the District of Columbia having legalized cannabis for medical and/or recreational use to date[1]. This shifting climate in regards to the use of cannabis necessitates the education of the underlying effects of MC for the patients who use it and the physicians who prescribe it.

1. The Endocannabinoid System

The resurgence of appreciation for the therapeutic potential of medical cannabis over the past two decades is in part due to the significant increase of scientific understanding of the body's endocannabinoid system (3). The endocannabinoid system (ECS) is a relatively recent discovery made by Israeli chemist Raphael Mechoulam and National Institute of Mental Health researchers Dr. William Devane and Dr. Lumir Hanus the early 1990's (1). The endocannabinoid system is a naturally occurring communication network that plays a role in many physiological processes. This system has been found to be implicated in gastrointestinal function, appetite and metabolism, pain, memory, movement, immune function, and inflammation (4-5). The actions "relax, eat, sleep, protect, and forget" are a concise summary of the functions of the ECS, which are regulated by an array of receptors, ligands, and enzymes (1).

The ECS is comprised of two G-protein-coupled receptors: cannabinoid receptors 1 (CB1) and 2 (CB2) (3, 4). CB1 receptors are located in the central and peripheral nervous systems, adipocytes, leukocytes, spleen, heart, lung, gastrointestinal tract, kidney, bladder, reproductive organs, skeletal muscle, bone, joints, and skin (1-4). In the brain, CB1 receptors are found in the central nervous system structures related to pain (cerebral cortex), movement (globus pallidus, caudate/putamen, cerebellum), reward (substantia nigra), and memory (hippocampus) (3). In contrast to the nearly ubiquitous presence throughout the body, CB1 receptors are sparse to absent in the brainstem, medulla, and thalamus. The low receptor density of CB1 in the brainstem and medulla may explain the virtually absent risk of mortality from respiratory depression from cannabis overdose (1). Most CB2 receptors are found in the immune system, with receptors found in bone, liver, spleen, tonsils, gastrointestinal tract, and nerve cells(1,4). CB2 receptors primarily modulate immune function, with evidence supporting that these receptors also have analgesic effects on induced nerve damage and pain in animal models (1). Studies show that CB2 receptors may also contribute to pain relief by dopamine release modulation (5). The recent findings about the body's endocannabinoid system has provided the medical community the opportunity to utilize this new-found understanding of the ECS to help develop treatments for various maladies and conditions.

2. Therapeutic Indications of Medical Cannabis

As previously stated in this article, the use of medicinal cannabis for myriad health conditions has been described by many cultures for thousands of years. In modern times, chronic pain is the most frequently reported condition for which MC is prescribed (6). Other conditions that have been supported by medical literature to be treatable with MC include: arthritis, insomnia/sleep disorders, headaches/migraines, epilepsy, fibromyalgia, multiple

[1] DISA Global Solutions, website: "Map of Marijuana Legality by State." *Information is current as of March 2019.*

sclerosis, mental health conditions (e.g., anxiety, depression, PTSD), and gastrointestinal disorders (1, 5, 6, 7). Recent studies have shown that cannabis is effective at relieving some symptoms of HIV/AIDS and cancer, as well as stimulating poor appetite during treatment (6, 8). Medical cannabis has also been shown to be a promising option for opioid users to wean off of or substitute MC for opioid pain medications (6). This option is becoming increasingly attractive to physicians who treat pain due to the high risk of overdose and/or addiction for patients prescribed opioid pain management medications (9).

3. Medical Cannabis and the Treatment of Pain

Over the last decade, the therapeutic potential of cannabis has gained much interest in the global medical community. In November 2017, The World Health Organization announced that in humans, CBD, a major cannabinoid in MC, exhibits no evidence for abuse or dependence potential and that there is no evidence of public health related problems associated with the use of pure CBD (6). Cannabis has a superior safety profile in comparison to many other medications, with absolutely no reported deaths due to cannabis overdose, likely due to the lack of CB1 receptors in the brainstem cardiorespiratory centers (2). Cannabinoids have also been shown to have a low risk of clinically significant drug interactions (3), lessening the risk of harm for patients who are prescribed multiple medications.

The endocannabinoid system, which is distributed throughout the central and peripheral nervous system, is involved in inflammation and pain processing and plays regulatory physiological roles across nearly every organ system (6). This system is present throughout several pain pathways, with cannabinoid receptor agonists demonstrating antinociceptive effects (the action of blocking the detection of a painful or injurious stimulus by sensory neurons) in animal models of acute, inflammatory, and neuropathic pain (4). Cannabinoids have been shown to act on the active qualities of chronic pain by reducing sensory limbic functional connectivity between the amygdala and the primary somatosensory cortex (4).

It is well-known in the medical community that inflammation in the body has a significant relationship to the experience of pain. CBD, a cannabinoid found in MC, has powerful analgesic and anti-inflammatory effects. Its anti-inflammatory effect is several hundred times more potent than aspirin (6). Medical cannabis' other major cannabinoid, THC, has twenty times the anti-inflammatory properties than aspirin, twice as anti-inflammatory as hydrocortisone, and has well documented analgesic and anti-inflammatory benefits including arthritic and other inflammatory conditions (6). These findings, coupled with MC's superior safety profile have led medical providers to reconsider the option of MC treatment.

4. Medical Cannabis and Opioids

Chronic pain is among the most frequently diagnosed medical conditions, affecting more than 100 million Americans each year (9, 10). Despite the high prevalence of people diagnosed with chronic pain, the condition remains difficult to treat. Treatment for chronic pain conditions require frequent doctor visits to monitor changes, which has become increasingly difficult for many Americans in the current economic and medical climate (9). Opioids, one of the most commonly prescribed medications used for the treatment of chronic pain, provide additional challenges to a patient's health in the long-term. Opioids are ineffective for many types of pain conditions, as well as being highly addictive and associated with significant risk of morbidity and mortality (3, 9). Due to the nature of rapidly developing tolerance to opioids, 1 in 4 people treated in a primary care setting for non-cancer pain with these medications develop opioid use disorder (10).

Since the start of medical cannabis use in the United States, studies have shown that chronic pain patients using MC were able to decrease medication side effects that affected daily functioning, decrease the amount of total medications being taken, and increase self-reported quality of life while effectively managing their pain levels (5, 6,

7, 9,10). In the treatment of chronic pain, medical cannabis demonstrates an opioid-sparing effect, providing analgesia while allowing the patient to use a lower dose of opioids for overall pain control (1, 11). Studies have shown that in states that legalized medical cannabis, there was an average 24.8% reduction in opioid overdose deaths (9). Additional findings showed that chronic pain patients who received MC treatment reported a significant reduction in adverse medication side effects, which strongly correlated to a reduction in opioid use. The medications that pain patients reported to decrease included opioids, antidepressants, anti-anxiety medication, migraine medication, alcohol, and sleeping pills (3, 6). Pain patients being treated with MC were also found to report significantly lower pain levels (scale of 1-10) than their opioid-prescribed counterparts throughout their treatment (12). The opioid-sparing effect medical cannabis provides pain patients shows great potential in the battle against opioid overuse and overdose (6,9).

5. Medical Cannabis and Mental Health

In treating chronic pain, physicians treat the entire person-- including mental health. Chronic pain is associated with a significant decrease in daily activities, occupational productivity, and quality of life (12). The association between chronic pain, depression, and anxiety has gained attention in the medical field due to the strong correlation of comorbid psychiatric conditions with chronic pain. High rates of depression and anxiety have been consistently reported among patients suffering from chronic pain with up to 54% of patients reporting high rates of depressive symptoms, and up to 50% reporting clinically significant anxiety. The large number of pain patients suffering from anxiety and/or depression may be partially due to ongoing withdrawal symptoms experienced among daily opioid users, which commonly present as restlessness, irritability, anxiety, and dysphoria (4, 12). In studies comparing opioid and MC treatment of chronic pain, levels of depression and anxiety were found to be significantly lower in the MC groups than those receiving opioids (12). Patients in the MC group replied “not at all” to all PH-Q9 items more commonly than those in the opioid group. Similar reporting of anxiety symptom severity was found true for patients answering scaling questions for the GAD-7 (12). The association between MC use and depression and/or anxiety symptom relief is not yet completely understood, although researchers have suggested a connection between action at cannabinoid receptors sights may be responsible for the decrease in depression symptoms (12). It is also important to note that MC is not a “cure all” for mental health conditions, and each patient will have unique reactions to MC treatment, largely affected by the specific chemovar (i.e., “strain”) used by the patient, level of tolerance, and personal biology.

6. Administration and Dosing

It is recommended that signed informed consent and treatment agreement documents should be obtained from patients before authorizing MC. These documents will outline the specifications of MC treatment as well as an agreement to only used MC as prescribed (i.e., correct dosage/chemovar, no giving it away or selling it) and that MC will need to be dispensed from an authorized source. During this process, physicians must also discuss the risks and benefits of MC with their patients, including the necessary precautions regarding engaging in activities that require mental alertness, such as driving or operating heavy machinery (3). Patients will also need to be educated on the available modes of administration of MC and/or specific cannabinoids (e.g., CBD). The most common modes include inhalation (smoking or vaporization) and oral administration or consuming “edibles”. Oromucosal (i.e., Nabiximol spray) is used primarily for the treatment of muscle spasticity in patients with multiple sclerosis, however, studies have shown a potential use for an option in treating neuropathic pain (4).

Inhalation is the most common route of administration with the quickest onset of action and shortest duration, giving MC patients the capacity to titrate their dose by adjusting their smoking behavior. Of the two inhalation options, vaporization is more is more discreet and has fewer toxic by-products (2, 4). This makes it the method generally preferred by prescribing physicians for patients requiring rapid relief for a shorter duration of time. Oral cannabinoids can be taken as pills (e.g., nabilone), drops, or mixed with foods such as oils, butters, or teas (4). It should be noted that the longer duration and slower onset of oral cannabinoid administration provides challenges

for patients attempting to adjust their MC dose to achieve desired results (2, 4).

It is advised that physicians proceed cautiously, encouraging their patients "start low and go slow" until a dose is reached that achieves symptom management while causing minimal euphoria or cognitive impairment (2, 3). Physicians should educate their patients on certain pharmacokinetic factors such as recent meals, depth of inhalation, duration of breath holding, and temperature of vaporization. All of these factors can all affect cannabis absorption, which can vary from 20-30% orally, and up to 10-60% for inhalation (2). To ensure MC treatment expectations are met, physicians must also specify the quantity of MC to be dispensed as well as the CBD and THC content of the chemovar recommendations.

7. Risks and Vulnerable Populations

There are certain demographics for which treatment with MC may not be appropriate, including individuals under the age of 25, pregnant or breastfeeding women, those with a history of chronic lung, heart, or kidney disease, patients with a history of substance use disorder, and patients who have a personal or family history of a psychotic disorder (3,4). Potential psychiatric outcomes of long-term cannabis use, such as the increased risk of developing a psychotic disorder among those with the genetic predisposition, as well as physical effects of long-term inhalation including chronic bronchitis, should be carefully considered before prescribing (12).

8. FAQs

- What are the differences between medical cannabis patients in contrast to recreational users?
    - MC patients more frequently use CBD-predominant chemovars with a smaller amount of THC to achieve symptom control, functionality, and quality of life, with fewest adverse effects (2, 4).
- Which chemovars or "strains" are indicated for which conditions?
    - Chemovar type preference is typically unique to the individual. Research has shown, however, that indica chemovars were shown to be preferred for the treatment of sleep disorders, sativa chemovars in the treatment of mental health conditions, and hybrid chemovars for the treatment of pain and gastrointestinal disorders (6).
- What are the differences between indica and sativa chemovars?
    - Cannabis sativa chemovars are commonly described as energetic, uplifting, creative, euphoric, spacey, cerebrally focused effects, and are better for day use. Cannabis indica chemovars are described as relaxing, calming, sedative, having full body effects such as a "body buzz," and better for night use. Hybrid strains qualities are unique to their "parent" plants, and typically have qualities of both indica and sativa chemovars.
- Should I be worried about "contact highs" or failing a drug test after breathing in secondhand cannabis smoke?
    - It is very unlikely that secondhand marijuana smoke would give anyone a contact high or lead them to fail a drug test. This is because very little THC is released in the air when a person exhales (8). Unless you are in an enclosed space (e.g., car, small enclosed room/closet) breathing in lots of smoke for many hours (also known as "hotboxing"), you will be just fine.

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