**Rothman Orthopaedic Institute Foundation for Opioid Research & Education**

***RESEARCH BRIEF***

# Medical Cannabis: How do Cannabinoids Effect Pain

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*SUMMARY POINTS*

- Cannabinoids have both analgesic and anti-inflammatory properties in the nervous system and on immune cells that allow them to effectively reduce pain and inflammation within the body.

- Cannabinoids could be considered a viable option in the treatment and management of chronic pain conditions (musculoskeletal conditions specifically) and as an alternative to opioids with increasing evidence of efficacy.

- The National Center for Complementary and Integrative Health (NCCIH) has begun to recognize the benefits of cannabis in pain management through its own review of the increasing number of studies and evidence.

- Additional research is required to confirm and determine the exact role of cannabinoids in pain management and as an opioid alternative.

*ANALYSIS*

With the opioid epidemic remaining a public health crisis in the United States, health care providers and systems have sought alternative pain management methods. One such promising therapy is medical cannabis, which decreases pain perception through its primary active components, tetrahydrocannabinol (THC) and cannabidiol (CBD), both active components that bind to endogenous cannabinoid receptors in the body.[1,2] The most prominent cannabinoids receptors are the CB1and CB2 receptors; respectively, with CB1 located in the central and peripheral nervous system and CB2 located on the surface of immune cells.[1,2] As a result, activation of the CB1 receptors decreases peripheral nociceptor excitability, leading to decreased

pain signaling and perception in the spinal cord and brain.[1] On the other hand, activation of the CB2 receptor has anti-inflammatory effects by decreasing cytokine and arachidonic acid production by immune cells.[1,2] In addition, recent studies have provided potential evidence that other components of cannabis such as the minor cannabinoids and aromatic compounds known as terpenes can bind to a variety of different pain receptors and also provide a synergistic analgesic effects with THC or CBD.[3] The minor cannabinoids include cannabichromenic acid (CBCA), cannabichromene (CBC), cannabinolic acid (CBNA), and cannabinol (CBN),[4-5] The analgesic effect of minor cannabinoids and terpenes has been described as the "entourage effect," where a greater presence of minor cannabinoids and terpenes with THC or CBD has been demonstrated to significantly reduce pain or symptoms compared to cannabis extracts made up of predominantly THC or CBD.[6-8] However, the role of minor cannabinoids and terpenes in pain management is currently unclear and their exact mechanism in producing the "entourage effect" warrants further investigation.

The ability of cannabis to reduce pain and inflammation has led to multiple studies examining its effectiveness in a variety of chronic pain and inflammatory conditions such as fibromyalgia, osteoarthritis (OA), rheumatoid arthritis (RA), and other musculoskeletal problems such as back pain. Blanton et al found that relief of symptoms in chronic pain conditions from medical cannabis to be modest but statistically significant, warranting further investigation of the role of cannabinoids in treatment of chronic pain conditions.[9]

Fitzcharles et al performed a systematic review of clinical trials examining the efficacy of medical cannabis in treating chronic musculoskeletal conditions such as fibromyalgia, RA, OA, and back pain and found that its analgesic and anti-inflammatory properties improved quality of life in affected patients.[10] This included movement-related pain, rest pain, sleep, inflammation and pain intensity with no adverse effects in comparison to placebo.[10] Findings by Pascual et al also reinforced the benefits of medical cannabis in fibromyalgia patients as nearly a quarter of the patients in the study were found to have statistically significant reduction in pain.[1] However, formal recommendations and conclusions could not be made from the systemic review by Fitzcharles et al as the Cochrane Risk of Bias Tool used in their review found three of the studies to have a high risk of bias.[10]

As a result of increasing studies and evidence, the National Center for Complementary and Integrative Health (NCCIH) a branch of National Health Institute, has also begun to recognize medical cannabis as a viable option for decreasing opioid use and pain management. The NCCIH has cited multiple study reviews including two in 2018 that found greater pain relief in patients taking medical cannabis compared the placebo, and a 2015 review in which 30% of patients in 28 studies (2,454 subjects) reported a 30% pain reduction compared to the placebo.[11] This is further supported by a review conducted by the National Academies of Sciences, Engineering, and Medicine in 2017 that found substantial evidence on the benefits of cannabis or cannabinoids for chronic pain, chemotherapy-induced nausea and vomiting, and multiple sclerosis spasticity.[12] Furthermore, the NCCIH also found that administering THC with opioids may lead to greater pain control with a smaller dose of opioids.[12] In addition, supporting evidence for cannabis as an alternative to opioids in pain management and analgesia is growing as Boehnke et al found that in 244 medical cannabis patients, there was a 64% decrease in opioid use (n = 118) and an improved quality of life (45%).[13] In turn, this would decrease the opioid overdose and mortality

rates as states with cannabis laws were found to have significantly lower opioid overdose mortality rates.[14] However, more consistent data in larger, randomized clinical trials are needed to support and identify the role of cannabis in pain management and as an alternative to opioids. Findings by Nugent et al demonstrated a greater need for further investigation of the potential adverse effects as medical cannabis users had higher scores of risk for prescription opioid misuse that were statistically significant (17% in a group of 371 subjects).[15]

In conclusion, with increasing evidence of effective analgesic and anti-inflammatory properties, medical cannabis is emerging as a viable option in treatment and management of chronic pain conditions (Figure 1). However, greater evidence is required to determine the long-term adverse effects of medical cannabis and its potential as an alternative to opioids for pain management.

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| Cannabis and nabiximols supporting evidence | |
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| **Level of evidence** | **Benefits** |
| **Conclusive or substantial evidence of efficacy** | • Adult chronic pain treatment<br>• Multiple sclerosis spasticity symptoms<br>• Chemotherapy-induced nausea and vomiting<br>• Treatment of intractable seizures in Dravet and Lennox-Gastaut syndromes (CBD) |
| **Moderate evidence of efficacy** | • Improving outcomes in individuals with sleep disturbances associated with chronic pain, multiple sclerosis, fibromyalgia, obstructive sleep apnea syndrome<br>• Decreasing intraocular pressure in glaucoma |
| **Limited evidence of efficacy** | • Symptoms of dementia<br>• Symptoms of Parkinson disease<br>• Positive and negative symptoms of schizophrenia<br>• Symptoms of posttraumatic stress disorder<br>• Appetite and decreasing weight loss associated with HIV/AIDS<br>• Multiple sclerosis spasticity (clinician-measured)<br>• Traumatic brain injury/intracranial haemorrhage associated disability, mortality, and other outcomes<br>• Symptoms of anxiety in social anxiety disorders (CBD)<br>• Symptoms of Tourette syndrome |
| **Limited evidence of inefficacy** | • Depressive symptoms in chronic pain or multiple sclerosis patients |
| **Insufficient evidence of efficacy or inefficacy** | • Addiction abstinence<br>• Symptoms of irritable bowel syndrome<br>• Cancers, including glioma<br>• Cancer-associated anorexia, cachexia syndrome and anorexia nervosa<br>• Symptoms of amyotrophic lateral sclerosis<br>• Chorea and some neuropsychiatric symptoms associated with Huntington disease<br>• Dystonia |

Figure 1: Levels of evidence for cannabis-based medicines in various condition[16] (Adapted from MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. *Eur J Intern Med*. 2018;49:12-19.