

Cannabidiol's Promising Role in Muscle and Visceral Pain

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The endocannabinoid system within our bodies regulates many aspects of health, including pain control. This system is comprised of endocannabinoids produced within the body, including anandamide (arachi-donylethanolamide) and 2-arachidonylglycerol (2-AG), which are able to activate receptors in the endocannabinoid system. The presence of this system was an intriguing discovery, as it indicated our bodies produce substances similar to cannabis that are able to switch endocannabinoid receptors on and off.

Two important receptors in this system that are involved in pain management are cannabinoid 1 (CB₁) and cannabinoid 2 (CB₂).¹ Activation of CB₂ receptors suppresses the pain response to thermal and mechanical stimuli,^{2,3} thermal and tactile hypersensitivity produced by peripheral inflammation,³⁻⁵ and neuropathic pain.⁶ As with endocannabinoids produced in the body, phytocannabinoids such as Δ⁹-tetrahydrocannabinol (THC), the psychoactive component of *Cannabis sativa* plant, and cannabidiol (CBD), a non-psychoactive component, are able to activate endocannabinoid receptors.

Endocannabinoids can indirectly work through the same receptors as opioid drugs to control pain. CB₂ receptors indirectly stimulate opioid receptors found in primary afferent pathways.⁷ Furthermore, CB₁ expression is weak in the areas of the brain stem that regulate respiration. This suggests that respiratory depression, a

potentially fatal adverse effect of opioid drugs, would not occur when using phytocannabinoids as painkillers.¹

An extensive amount of evidence points to the endocannabinoid system's role in the management of pain caused by a wide spectrum of conditions. This article will focus exclusively on endocannabinoid and phytocannabinoid regulation of two common types of pain: muscle and visceral pain.

Musculoskeletal Pain, Fibromyalgia, and Temporomandibular Disorders

Chronic widespread musculoskeletal pain is a common disorder, occurring in approximately 10% of the population.⁸ A subgroup of patients with this type of pain have fibromyalgia, which occurs in 3% to 5% of the population.⁸ In women with musculoskeletal pain, levels of the endocannabinoids oleoylethanolamide and stearoylethanolamide were altered compared with healthy controls.⁹

Endocannabinoid alterations are thought to play a role in fibromyalgia and its frequent comorbidities such as migraines and irritable bowel syndrome.¹⁰ A hallmark of fibromyalgia is sore muscles. The pain usually occurs in similar locations in different patients suffering from this disorder. Studies indicate there is an association between fibromyalgia and endocannabinoid deficiency and this deficiency may play a role in the sore muscles of this condition.¹⁰⁻¹² For this reason, cannabinoids are thought to be useful in chronic pain conditions such as myofascial pain syndrome and

temporomandibular joint pain (TMJ).¹⁰

CBD has analgesic and anti-inflammatory effects that may prove beneficial in disorders that involve muscle pain.¹³ CBD was first isolated in 1940, but it is only relatively recently that its full potential was realized due to studies showing its antioxidative, anti-inflammatory, and neuroprotective effects.¹⁴ Some of these actions are independent of the CB₁ and CB₂ receptors.¹⁵

In studies using rodent models of inflammation, CBD reduces the migration and infiltration of inflammatory cells (neutrophils).¹⁶ Cannabinoids are also thought to reduce inflammation by increasing the generation of eicosanoids, signaling molecules involved in regulating inflammation and pain.¹⁷ In addition, CBD lowers production of the inflammatory cytokine TNFα and reduces fatty acid amidohydrolase (FAAH) activity, an enzyme that degrades the anti-inflammatory endocannabinoid anandamide.¹⁷ CBD's reduction in FAAH causes a raise in anandamide production.¹⁷ In animal and cell culture studies, CBD has demonstrated an anti-inflammatory effect that is several hundred times greater than aspirin.¹³ CBD's analgesic properties are due to mechanisms that include acting as a lipoyxygenase inhibitor, increasing the release of prostaglandin (PGE₂) from synovial cells, and blocking production of leukotriene B₄ in human polymorphonuclear cells.¹³

Other non-psychoactive phytocannabinoids such as cannabidiol (CBD) and cannabigerol (CBG) also produce an analgesic effect, leading one group of researchers to conclude, "Therefore, there is potential for developing analgesic drugs based on these cannabinoids which do not have the psychoactive properties of THC."¹³

There are a paucity of human studies using cannabidiol in patients with fibromyalgia. Preclinical studies, however, suggest a promising role for this agent. For example, in a rodent model of myofascial pain, intramuscular injection of CBD alone, injection with another non-psychoactive phytocannabinoid (CBN), or the combination of the two reduced muscle pain.¹⁸ The two phytocannabinoids combined appeared to have a synergistic effect, pointing to what is commonly called the entourage effect, the synergistic actions between the phytocannabinoids found in *Cannabis*. The researchers concluded, "These results suggest that peripheral application of these non-psychoactive cannabinoids may provide analgesic relief for chronic muscle pain disorders such as temporomandibular disorders and fibromyalgia without central side effects."

Multiple Sclerosis

Evidence indicates endocannabinoid system activation is beneficial in motor disorders associated with multiple sclerosis, including muscle spasticity. A large number of clinical studies show that a 1:1 combination of THC and CBD in an oral spray reduces muscle spasticity in multiple sclerosis patients. In one study of 50 multiple sclerosis patients, THC/CBD proved effective in 80% of participants at a median dose of 5 (2-10) inhalations/day.¹⁹ Some of the patients experienced adverse effects such as dizziness (11 patients), sleepiness (6), muscle weakness (7), oral discomfort (2), diarrhea (3), dry mouth (2), blurred vision (2), agitation (1), nausea (1), and paranoid ideation (1).

In a double-blind, randomized, placebo-controlled study, a cannabis-based medicinal extract containing

equal amounts of THC and CBD at a dose of 2.5-120 mg of each daily was given in divided doses to 160 patients with multiple sclerosis.²⁰ The participants suffered from at least one of the following symptoms: spasticity, spasms, bladder problems, tremor, or pain. The primary symptom score declined from mean 74.36 to 48.89 following THC/CBD and from 74.31 to 54.79 following placebo. Muscle spasticity scores significantly declined in

stress increases 2-AG in the brain and downregulates CB₁ receptors in sensory ganglia, which control visceral pain.²⁴ Chronic psychological stress changes CB₁ receptor activity by means of epigenetic pathways. This may be the reason why stress often triggers abdominal pain.²⁵ Epigenetics refers to the alteration of gene expression through pathways other than the genetic code. Epigenetic changes occur in our genes due to lifestyle

Cannabidiol (CBD) has strong anti-inflammatory and calming effects.

the patients using THC/CBD compared with the placebo.

Because many patients are uncomfortable with the "high" feeling produced by THC, it is surprising that there are a lack of studies using CBD alone. Dr. Meletis has observed in his own clinical practice that CBD has an analgesic effect on muscle pain and that it is beneficial in patients.

Visceral Pain and Inflammatory Bowel Disease

Visceral pain is pain that affects the area around the stomach, rectum, bladder, or uterus. Abdominal pain that occurs during irritable bowel syndrome (IBS) is a type of visceral pain. Menstrual cramps and pelvic pain caused by bladder infections are also types of visceral pain. The endocannabinoid system modulates visceral hyperalgesia (increased sensitivity to pain) caused by chronic stress.^{21,22} Alterations in this system may play a part in the association between chronic stress and irritable bowel disease (IBD)/IBS.^{21,22} In rodent studies, early-life stress changes the endocannabinoid system, which leads to an increased vulnerability to IBS.²³

As a key player in the regulation of visceral pain, the endocannabinoid system may play a role in the means by which psychological stress impairs GI function.²³ Chronic stress lowers concentrations of the endocannabinoid anandamide. At the same time,

or environmental factors. Through these epigenetic actions, chronic stress impacts the CB₁ gene promoter, resulting in reduced concentrations of CB₁ in sensory neurons in the colon and other pelvic organs.²⁶ In support of this concept, a substance that activated the CB₁ receptor reduced abdominal pain in mouse models that mimicked symptoms of functional GI disorders, such as stress-induced diarrhea.²⁷ The beneficial effects were thought to be due to activation of serotonin receptors.

CBD exerts known anti-stress actions that may be beneficial in inhibiting stress-induced visceral pain. CBD positively impacts the hypothalamus-pituitary-adrenal axis in mice exposed to psychological stress.²⁸ These stress-shielding effects of CBD were due to activation of serotonin receptors.

A number of human studies also support CBD's calming effects. In a double-blind study, scientists investigated different doses of CBD and a placebo in 57 healthy male subjects undergoing a simulated public speaking test.²⁹ Before giving a speech, the men used oral CBD at doses of 150 mg, 300 mg, or 600 mg or a placebo. There was a pronounced reduction in anxiety during the speech in subjects taking 300 mg of CBD. The other CBD doses were ineffective, indicating there is a specific range in which CBD is effective. CBD's ability to have a calming effect indicates it may have a promising role to play in reducing visceral pain caused by stress.



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Conclusion

CBD exerts anti-inflammatory effects that are beneficial in patients with muscle pain, such as that caused by fibromyalgia or multiple sclerosis. This phytocannabinoid also has a calming effect that can play a role in inhibiting stress-induced visceral pain. Although studies investigating CBD and muscle and visceral pain did not report on whether CBD increased energy levels, it stands to reason that reduction in pain would also reduce fatigue. Alteration of the endocannabinoid system through the use of CBD holds great promise in supporting the health of patients with sore muscles and visceral pain. As optimal CBD absorption can be clinically challenging particularly in the cases of pain, enhancing absorption with tested delivery mechanisms such as VESIsorb® or other researched approaches can help achieve clinical therapeutic levels.

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