Therapeutic Potential for Cannabinoids in Sports Medicine: Current Literature Review

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Abstract

Cannabidiol and other cannabinoids are being used more frequently for sports medicine–related conditions. This review will help sports medicine clinicians answer questions that their athletes and active patients have about the potential effectiveness of cannabinoids on common sports medicine conditions. In the article, the authors compare cannabidiol and delta-9-tetrahydrocannabinol effects, noting the difference on the endocannabinoid and nonendocannabinoid receptors. The theoretical benefits of these two compounds and the current legality in the United States surrounding cannabidiol and delta-9-tetrahydrocannabinol use also are addressed.

Introduction

Recent changes in federal and state laws have affected the use of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) by sports medicine patients. The goal of this review is to help sports medicine clinicians answer questions from their patients who are athletes or active people. Patients are asking about the wide variety of uses in sports medicine and how THC and CBD may be beneficial. There is little human research concerning the use of these cannabinoids in sports medicine, and further studies are needed because of the potential benefit.

Differences Between CBD and THC and Cannabis

Cannabis is a group of three plants, known as cannabis sativa, cannabis indica, and cannabis ruderalis. Cannabis plants are made up of more than 100 cannabinoid compounds. THC and CBD are the most abundant phytocannabinoids in the cannabis plant. Although CBD and THC are chemically similar, their chemical properties differ with CBD having a hydroxyl group and THC having a cyclic ring (1). This difference affects how CBD and THC interact with the endocannabinoid system (ECS) and its receptors. THC is the primary psychoactive cannabinoid constituent, which gives users a "high" versus CBD being nonpsychoactive (2).

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Unlike the psychoactive properties associated with THC, CBD has been shown to have very low toxicity in humans. Ingested and absorbed CBD is rapidly distributed, and because of its lipophilic nature, can easily pass the blood-brain barrier. Because, both THC and CBD are metabolized in the liver, the potential exists for pharmacokinetic drug interactions via cytochrome P450, particularly isozymes CYP2C9, CYP2C19, and CYP3A4 (2). The terminal half-life of CBD is about 9 h and is preferentially excreted in the urine as its free and glucuronide form (3). CBD can be consumed in many forms, including oil (most commonly), gel capsules, herbal extracts, beverages, candy, or baked products, and may be applied topically.

A comprehensive safety and side effect review of CBD in 2016 on both animal and human studies described an excellent safety profile of CBD in humans. This is thought to be due to the lack of direct agonist effect of CBD at cannabinoid receptors. The most commonly reported side effects were tiredness, diarrhea, and weight gain (4).

The ECS

The ECS is neuromodulatory and plays a critical role in maintaining homeostasis of the human body by affecting the central nervous system (CNS), endocrine system, immune system, musculoskeletal system, gastrointestinal (GI) tract, as well as the peripheral nervous system (PNS) (5). The ECS is comprised of the receptors, endogenous cannabinoids (endocannabinoids), and the proteins that are used in the synthesis and degradation of those endocannabinoids (6). These endocannabinoids act as retrograde messengers synthesized postsynaptically to regulate neurotransmitters at the presynaptic level (7). Once neurotransmitters are released they bind to postsynaptic receptors which allow for entry of Ca^{2+} into the cell, leading to the activation of phospholipase and diacylglycerol lipase (8). Exogenous cannabinoids, phytocannabinoid (plant based), and synthetic, interact with the cannabinoid receptors to produce their effect.

Clinical endocannabinoid deficiency has been an area of discussion by Russo (9) since the early 2000s who concluded that "migraine, fibromyalgia, irritable bowel syndrome (IBS), and related conditions display common clinical, biochemical,

and pathophysiological patterns that suggest an underlying endocannabinoid deficiency that may be suitably treated with cannabinoid medicines." This theory was then investigated by Smith and Wagner (10) in 2014 who reported confirmation, based on new evidence, which "underlying endocannabinoid deficiencies indeed play a role in migraine, fibromyalgia, IBS, and a growing list of other medical conditions". Russo (11) revisited this theory in 2016 after a decade's worth of supportive evidence that ECS hypofunction is present in fibromyalgia, major depression, PTSD, migraine, and IBS.

Cannabinoid Receptor 1 and Cannabinoid Receptor 2 location

Cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) receptors in the ECS are coupled through G-protein inhibition. CB1 receptors are located on the neurons' axon and synaptic terminals extensively in the CNS. They are expressed to a lower extent in the cardiovascular system, liver, musculoskeletal system at the skeletal sympathetic nerve terminals, reproductive organs, GI tract, and the PNS (12). Because of their ample expression in the brain, the psychoactive effects of THC are attributed to the activation of CB1 receptors. CB1 receptors are predominately located on presynaptic terminals, thus, modulating neurotransmitters' release. Therefore, it suggests that CB1 receptors suppress neuronal excitability and inhibit neurotransmission (13). On the other hand, CB2 receptors are primarily expressed in the immune system, specifically B cells, tonsils, spleen macrophages, and the thymus, and show little expression in nervous tissue (12). There is expression of the CB2 receptors in osteoblasts, osteoclasts, and osteocytes of the musculoskeletal system (14).

THC exhibits partial agonist activity at both the CB1 and CB2 receptors. Conversely, CBD binds poorly to CB1 and CB2 receptors. CBD act as an allosteric modulator, altering how the receptors site works (15). It causes an inhibitory effect on CB1 agonists, such as THC. Alternatively, it acts as an inverse agonist at the CB2 receptor. In addition to CB1 and CB2 receptors, CBD additionally modulates several noncannabinoid receptors and ion channels, including vanilloid receptor 1 (transient receptor potential cation channel subfamily V [TRPV1]), 5-hydroxytryptamine, adenosine receptors, glycine receptors, opioid receptors, and G-protein coupled receptors (GPR55, GPR3, GPR6, and GPR12) (16).

TRPV1 Receptor location

CBD can promote analgesia by activating TRPV1 and serotonin (5-HT) receptors (17). TRPV1 receptors are located in vascular tissue, neural circuits, chondrocytes, and osteocytes (12,18). They are inotropic receptors for endocannabinoids, as well as direct targets of cannabinoids (19). TRPV1 is known to mediate pain perception, inflammation, and body temperature. CBD binds to TRPV1 and suppresses inflammation by decreasing pro-inflammatory cytokines: IL-2, TNF-a, IFN-c, IL-6, IL-12 (p-40), IL-17, MCP-1, and eotaxin-1 (CCL11) (20).

Serotonin Receptors Locations

Serotonin receptors are G-coupled protein receptors implicated in anxiety, sleep, addiction, pain perception, nausea, and vomiting. CBD directly activates the 5-hydroxytryptamine (HT1A) serotonin receptor at high concentrations in the peripheral and CNSs. Studies show that CBD reduces anxiety through 5-HT1A receptor activation and recovers impaired 5-HT neurotransmission in neuropathic pain conditions (21).

GPR55 Receptors

GPR55 is a G protein-coupled receptor that is extensively expressed in the brain, GI tract, and adrenals. GPR55 regulates bone cell function due to its presence on osteoblasts, osteoclasts, and chondrocytes (22). Elevated levels of GPR55 were found in patients with inflammatory bowel disease, suggesting that it may have a proinflammatory role. In a study by Staton et al. (23), there were lower inflammation levels in mice that were genetically unable to produce GPR55 receptors, suggesting that GPR55 may have therapeutic potential in treating inflammatory pain. CBD blocks the activity of GPR55 by binding to the receptor (24) (Fig. 1).

CBD Market and U.S. Legality

There has been increased interest and questions around therapies and products derived from cannabis and its component, including cannabidiol (17). The Agriculture Improvement Act of 2018 at the federal level changed some rules concerning hemp production and marketing. Hemp is defined as "the plant *Cannabis sativa* L. and any part of the plant, including seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3% on a dry weight basis" (25). In addition, this bill removes hemp from being a controlled substance if there is no more than 0.3% THC on a dry weight basis (25). The FDA, however, still has authority to regulate products containing cannabis or cannabis-derived compounds under the FD&C Act and section 351 of the Public Health Service Act (PHS Act), which it explicitly states in the 2018 Farm Bill (26).

It is important to note that many states have now removed restrictions on the medical use of cannabis and its derivatives, and many other states are considering changes to the state laws (Fig. 2). Although this is true, and many people are recommending THC and CBD. It is essential to recognize that there is still a large gap in research that supports the use of these products for a wide variety of medical conditions.

The Controlled Substances Act was decreed by congress as part of the Drug Abuse and Prevention Control Act in 1970. Marijuana is listed as a schedule I drug because of its high abuse potential, attributed to the psychoactive effects of THC. Conversely, CBD, after the passage of the Hemp Farming act of 2018, which is derived with less than 0.3% of THC on dry weight, is no longer a category I substance (25).

This section of the article is focused on the U.S. CBD market and legality because of the target audience we have in mind.

Disease Entities

Osteoarthritis

The most common joint disease globally is osteoarthritis, with it being the leading cause of disability in the United States, affecting 27 million people (27). Knee OA is explicitly ranked within the top 10 noncommunicable diseases for global disability-adjusted life years (28). Many factors contribute to osteoarthritis, including age, previous joint injury, overuse, obesity, weak muscles, genetics, and sex (females > males). There

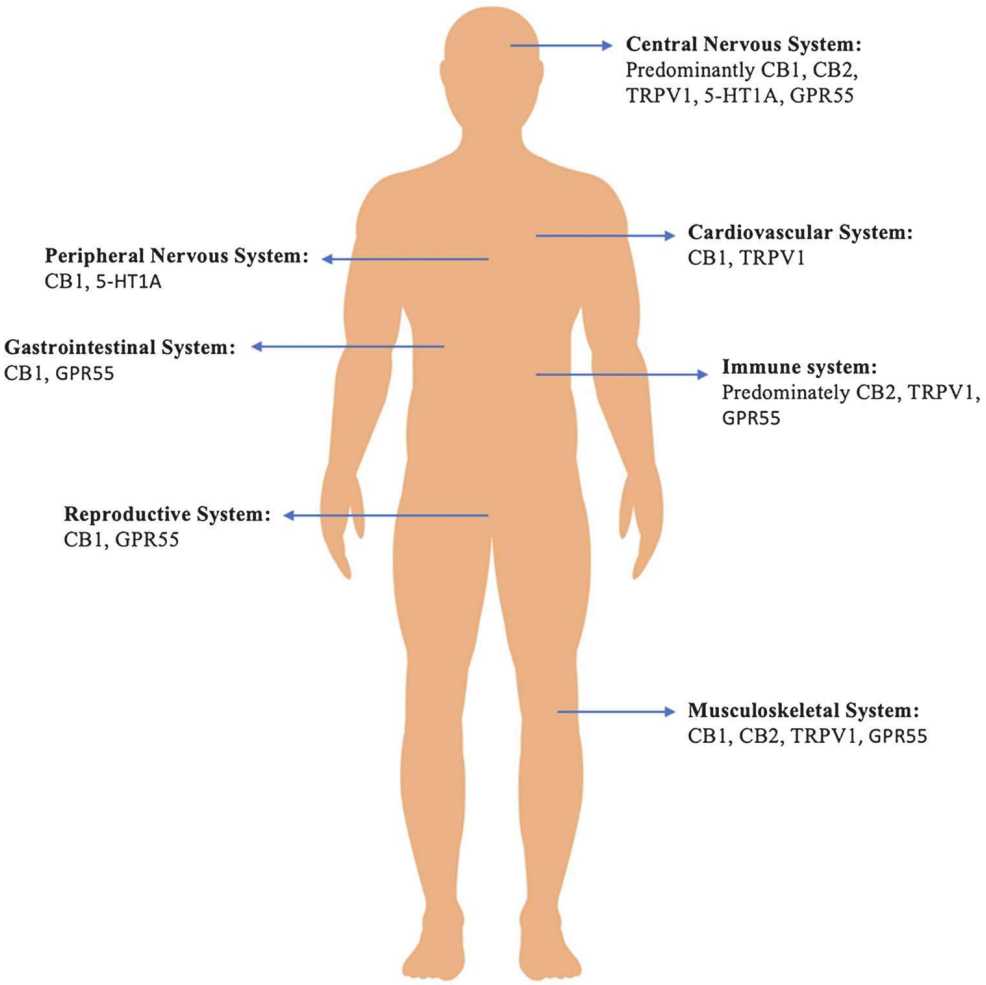

Figure 1: Visual depiction of where the ECS receptors are located.

is a known age-related increase in the prevalence and incidence of osteoarthritis. Osteoarthritis is a degenerative disease of the synovial joint that causes loss of articular cartilage and underlying bone. The breakdown of these tissues eventually leads to pain and joint stiffness, resulting in loss of joint function and partial or permanent disability (29). Pain reduction of cannabinoids in different animal models of osteoarthritis and the possible role of ECS in the pathophysiology of this disease makes THC and CBD possible treatment medications for OA (30).

Symptomatic control is the current mainstay of osteoarthritis treatment. Although some treatments like platelet-rich plasma and viscosupplementation injections are directed toward limiting the progression of joint damage, maintaining and improving joint mobility, reducing joint pain and stiffness, reducing physical disability, and improving health-related quality of life (31). The infrapatellar fat pad is proposed to secrete a variety of inflammatory chemicals to participate in the local inflammation of the knee joint, thus contributing to the development of knee OA (32).

A study from 2016 by Dunn et al. (18) found that CB1, CB2, GPR55, and TRPV1 receptors were present in single chondrocytes, chondrocyte clusters, and osteoclasts. In comparison, more expressions of the receptors in the chondrocytes than osteoclasts suggest that CBD would affect the chondrocytes. As previously mentioned, TRPV1 receptors are expressed at nociceptive neurons and have been implicated in the pain associated with arthritis. Barrie and Manolios (34) reported similar findings in which CB1 and CB2 receptors were expressed in the synovium of patients with osteoarthritis, suggesting that targeting these receptors can be chondroprotective in osteoarthritis. Multiple animal and human preclinical and clinical studies have found that cannabinoids provide therapeutic effects to patients with osteoarthritis. In addition to modulating inflammation, these studies also suggest that targeting these endocannabinoid receptors can mediate disease progression and reduce joint damage (35). In 2014, researchers in Barcelona found increasing evidence from preclinical studies that pointed to the ECS as a therapeutic target for osteoarthritis pain (30). In addition, health researchers in Sydney found that endocannabinoids — the endogenous organic compounds produced in our bodies — have an effect on both pain modulation and inflammation (34).

In September of 2020, the Arthritis Foundation released new guidelines on CBD use. They noted that more than 50 million Americans report using CBD, and the global cannabidiol (CBD) market is predicted to grow 700% and be worth $2.1 billion the following year (17). With this growing

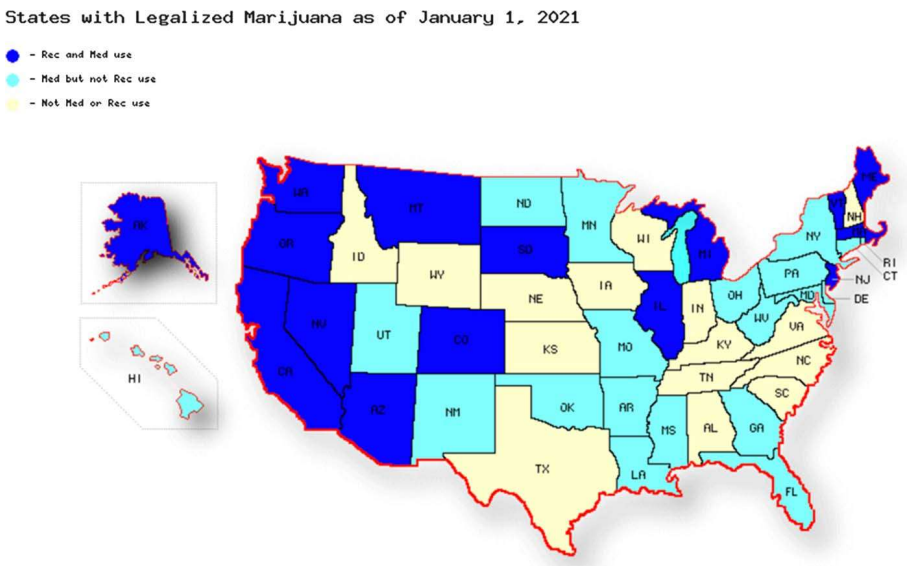

Figure 2: Current map of the United States of America labeled based on each state's current restrictions. Dark blue — recreational and medical marijuana use is legal, cyan — medical but not recreational marijuana use is legal, and beige — medical or recreational marijuana use is not legal.

popularity, we are likely to see more patients ask about the use of CBD and whether it can help manage osteoarthritis. Although literature to date does show therapeutic and disease-modifying benefits to CBD in osteoarthritis, it is still not an FDA approved treatment of choice.

Concussions

Concussions are defined as mild traumatic brain injury (TBI) as per the latest consensus statement without structural abnormalities on conventional neuroimaging modalities (36). 6% to 36% of high school and collegiate athletes in the United States have had more than one concussion (9). There are two components in TBI, the first is the biomechanical force, and the second is a cascade of events (hypoxic-ischemia, cerebral edema, increased intracranial pressure, and hydrocephalus) (7). The most common acute symptoms of concussion are headache and dizziness, which usually resolve within 7 d to 10 d. However, in 10% to 15% of concussions, persistent symptoms are reported (8). Postconcussion syndrome can have adverse effects on the individual's day-to-day activities, as shown through its negative associations with health-related quality of life, assessed by the 36-item Short-Form Health Survey Perceived Quality of Life Scale (37).

As previously discussed, CB1 receptors are abundantly found in the CNS, and although CB2 receptors are predominantly in the immune system, they also are found in brain microglia. Microglia activation can result in a release of proinflammatory cytokines and reactive oxygen intermediates, and the presence of the CB2 receptor at the microglia suggests a neuroprotective purpose (38). Activation of the CB1 receptor is thought to be responsible for the common psychosis symptoms associated with THC (39), while activation of the CB2 receptor can attenuate inflammation and accelerate regeneration in many disease states (33). There is a neurometabolic cascade and other physiologic consequences secondary to concussion (38). The ECS is thought to have neuroprotective properties that could prevent the neurometabolic cascade (38). Multiple studies confirm that the ECS function is markedly increased in response to pathogenic events like trauma (38,40). Supporting the role of cannabinoids and their interactions with CB1 and CB2 as part of the brain's compensatory and repair mechanisms following injury (40).

In an *in vitro* study CBD has been shown to provide a reduction in cell death, neurogenesis, enhanced neuroplasticity, and inhibition of excessive neuroinflammatory responses affecting mechanisms such as oxidative stress, immune mediators, PTSD, postconcussion syndrome, depression, and anxiety (40,41). An *in vivo*, cannabinoids decrease hippocampal neuronal loss and infarct volume after cerebral ischemia, acute brain trauma, and induced excitotoxicity (42). CBD also has been found to increase brain adenosine levels by reducing adenosine reuptake. Increased adenosine is associated with neuroprotection and decreased inflammation after brain trauma (43).

Cerebral blood flow is impaired in patients with postconcussive syndrome. Although it has not been studied to date, the presence of CB1 on cerebral circulation and TRPV1 receptors at the vagal afferent neurons and the tunica of the blood vessels provide suspicion that CBD may have an effect on reductions in hemodynamic disruptions (38).

Patients may ask about CBD use for concussion, and it is important to understand that trials do not exist. Our role is to discuss with our patients the evidence and lack thereof for the use of THC and CBD in concussions. The authors are not recommending their use in concussions, at this time, but acknowledge that this is a promising area of research.

Chronic Pain Syndromes

Although there are limited human trials, animal studies show an apparent reduction of pain and allodynia when animals were treated with cannabinoids (44). Cannabinoids modulate pain by stimulating adenosine reuptake, increasing adenosine levels in the brain, and inhibiting pain sensations. It also has been demonstrated that CB2 activation by CBD induces the peripheral release of b-endorphin, which might contribute to CB2-induced analgesia (19). Outside the ECS, CBD directly binds to the nociceptors TRP vanilloid 1

(TRPV1) and TRP Ankyrin 1 (TRPA1), which is responsible for pain and inflammation (45,46).

With these finds in current research, athletes and active individuals will likely approach us as clinicians requesting information on use and benefits in acute pain and inflammation after an injury. The current literature shows that CBD acts as a pain-relieving and anti-inflammatory agent.

Performance

Cardiovascular

A paper in the *British Journal of Clinical Pharmacology* by Stanley et al. in 2012 reports that CBD protects against the vascular damage caused by a high glucose environment, inflammation, or the induction of type 2 diabetes in animal models and reduces vascular hyperpermeability associated with such environments (47). There is suggestion that CBD plays a role in reduction of systolic blood pressure and baseline heart rate however, studies investigating the cardiovascular (CV) impact that CBD has, to date, are inconsistent. Therefore, it is difficult to determine the role of CBD on lowering pulse rate for sports like rifle, biathlon, and golf. The studies were done with people at rest not during exercise. Therefore, further work is needed to see if CBD could lower heart rate and produce an ergogenic effect for certain sports (48).

Sports Performance Anxiety

The concept of a decrease in athletic performance due to perceived stress is known as sports performance anxiety (49). It is widespread and often multifactorial, including the pressure of people watching, the increased expectations to perform well, get a scholarship, and/or the fear of letting down oneself, teammates, coaches, and parents. This perceived stress is often internally driven and has less to do with outside influences. It is more commonly seen in organized sports (*i.e.*, collegiate, travel teams) because the athletes want to perform well under pressure and meet the competition demands (50).

Multiple studies have investigated the use of CBD in anxiety, although there have been inconsistencies in their findings. A study done by Linares et al. (51) in 2019 reported a U-shaped dose-response relationship of CBD treatment and subjective anxiety, where 300 mg compared with 150 mg or 600 mg had a more substantial anxiolytic effect. As well, Hundal et al. (52) found that 600 mg of CBD caused increased anxiety in paranoid groups. Evidence would support less than 600 mg of CBD in people with anxiety.

Under low-stress conditions, the effect of CBD has had little influence on anxiety. Numerous studies have demonstrated anxiolytic effects in stress-inducing situations (51,53,54). On the other hand, several studies have shown no CBD effect on anxiety in this similar situation (52,55). These discrepancies may be attributed to individual differences in anxiety levels at baseline and the amount of stress-response generated in stressful situations. Although many studies have been done to evaluate the effects of CBD on anxiety, there have not been any specifically that investigate CBD in sports performance anxiety. Athletes may be requesting information on the use of CBD and possible doses before competition to deal with performance anxiety, it would appear that 600 mg of CBD is not a good choice.

Adverse Reactions

As we are starting to see more of our patients turn toward cannabidiols and come to us with questions, our role also is to be able to advise them as to possible adverse reactions they may encounter. Huestis et al. (56) in 2019 had an article in *Current Neuropharmacology* assessing cannabidiol adverse events and toxicity in both *in vitro* and the few *in vivo* studies. The *in vitro* review noted developments in toxicity, CNS inhibition, hepatocellular injuries, spermatogenesis reduction, male reproductive system alterations, and hypotension. *In vivo* review in studies done for epilepsy and psychiatric disorders reported CBD induced drug-drug interactions, hepatic abnormalities (elevated alanine transaminase/aspartate transaminase), diarrhea, fatigue, hyperemesis, depression, and somnolence.

Conclusions

This review answers questions that clinicians may face from their patients concerning the use of CBD and THC for their sports and exercise medicine problems. As the knowledge of medicinal use continues to evolve, we as practitioners will face numerous inquiries regarding the use of cannabidiols for various diagnoses. Common topics in sports medicine include osteoarthritis, concussion medicine, pain control, and sports performance, all discussed in the review. Research thus far has demonstrated that CBD has anxiolytic, antidepressant, neuroprotective anti-inflammatory, immunomodulatory benefits, and potential for disease-modifying effect (13). As clinicians, our role is to continue to be curious and follow the evolving research to provide our patients with the current recommendations. There is a lack of high-quality human clinical trials o-n cannabidiol in sports medicine. There is a need for more investigation into the dosing, safety, and long-term sequala before any recommendations can be made. Currently, nonprescription THC-related products are not legal federally, and therefore, we are not recommending the use of medical marijuana with THC.

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