Cannabinoid Use in Musculoskeletal Illness: a Review of the Current Evidence

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Abstract

Purpose of Review The use of cannabinoids has increased since legalization of recreational and medical use in the USA. It is likely that many orthopaedic patients consume cannabinoid products during the traumatic or perioperative period. The purpose of this study was to investigate the pre-clinical data evaluating the mechanism of action of cannabidiol (CBD) and Δ^9 -Tetrahydrocannabinol (Δ^9 -THC) and to evaluate the current clinical data on the use of cannabinoids in musculoskeletal illness.

Recent Findings Recent pre-clinical studies have demonstrated that cannabinoid use and the endocannabinoid system (ECS) has an important role in bone healing and bone homeostasis. There is data that suggests that the use of cannabidiol (CBD) may increase bone healing, whereas the use of Δ^9 -Tetrahydrocannabinol (Δ^9 -THC), the major psychoactive ingredient in marijuana, likely inhibits bone metabolism and repair. The clinical implications and consumption of marijuana by orthopaedic patients have not been thoroughly evaluated. Studies have demonstrated concern for negative cardiovascular and psychiatric effects caused by marijuana use, but have not yet elucidated outcomes in the orthopaedic literature.

Summary With the recent increase in advertising of CBD products and legalization of marijuana, it is likely that many orthopaedic patients are consuming cannabinoid products. The clinical implications and consumption of these products are unclear. We need more robust and well-designed clinical studies prior to making further recommendations to our patients on the consumption of these products.

Keywords Cannabinoid · Marijuana · Cannabidiol · CBD · Orthopaedic surgery

Introduction

Marijuana, otherwise known as *Cannabis sativa*, is the most commonly used illicit drug in the USA [1]. Self-reported use of cannabinoids has increased since legalization of recreational and medical use [2•, 3•]. Approximately 3.1 million individuals reported daily use in 2013 and 8.1 million reporting using marijuana most days in the last month in 2013 [4]. Data demonstrates that the number of marijuana users has steadily increased from 2002 and that in 2016 it was estimated that over 22 million Americans over the age of 12 used marijuana [2•].

Cannabidiol (CBD) is an active ingredient in marijuana, but has recently gained popularity due to extensive marketing and advertising. The Food and Drug Administration has only approved highly purified CBD for the treatment of epilepsy. However, many companies make unproven claims that CBD

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can treat a variety of medical maladies including acne, anxiety, opioid addiction, pain, and menstrual problems [5•]. With the increased popularity of marijuana use and advertising surrounding CBD, it is likely that many orthopaedic patients consume cannabinoid products during the perioperative period [5•, 6•].

It is known that cannabinoids have a number of effects on the body and specifically on the musculoskeletal system. There is a growing body of literature on cannabinoid use, its biomechanical impacts on the musculoskeletal system and on the effect of cannabinoids in orthopaedic surgical outcomes. The primary purpose of this review is to critically analyze the current data on cannabinoid mechanism of action on the musculoskeletal system and its use in the treatment of musculoskeletal illness.

The Endocannabinoid System Positively Affects Bone Mass and Cellular Differentiation

The endocannabinoid system (ECS) is comprised of two G protein–coupled receptors: CB₁ and CB₂, activation of which inhibit adenylyl cyclase activity. Current research suggests that both receptors serve a common role in the modulation of chemical messengers from various cell types [7]. High concentrations of CB₁ receptors have been identified on neurons and CB₂ receptors on immune cells, suggesting their role in both neuro- and immunomodulation. Furthermore, the CB₁ and CB₂ receptors and their associated endogenous cannabinoid ligands have been shown to be cytoprotective in many cell types [8, 9].

CB₁ and CB₂ receptors are associated with endogenous ligands, termed endocannabinoids. These are eicosanoids, derived from fatty acids, and include anandamide and 2-arachidonoylglycerol and their degradative enzymes fatty acid amide hydrolase and monoacylglycerol lipase [7, 10]. The endocannabinoids along with their corresponding receptors make up the endocannabinoid system (ECS).

Recent studies suggest that the ECS affects regulation of bone mass maintenance through CB₁ and CB₂ receptor activity. Another G protein–coupled receptor, GPR55, is activated by certain endocannabinoids and antagonized by CBD, and appears to inhibit CB₁ and CB₂ receptor activity. Inactivation of the GPR55 receptor in male mice produces phenotypes with increased bone mass and increased bone resorption [11]. The complete physiologic function of the GPR55 receptor at this time is yet largely unknown [12, 13].

CB₁ receptor activity appears to serve a protective role in regulating bone mass and osteoporosis through adipocyte and osteoblast differentiation, as well as expression of multiple intracellular signaling proteins [14]. CB₁ deactivation in knockout mice has demonstrated short-term in vivo increased bone mass with ovariectomy-induced bone loss [15]. Further

investigations have shown age-related osteoporosis at 12 months in CB₁ knockout mice. It is believed the increased bone mass at 3 months is secondary to reduced osteoclast activity and at 12 months, the osteoporotic changes are the result of defects in osteoblast differentiations and the accumulation of adipocytes in the bone marrow [13, 16]. Cannabinoid receptor deficiency in mouse models is confounded by the fact that the effects of cannabinoid receptor deficiency are age and sex dependent [13].

CB₂ receptor function also appears to affect bone mass maintenance, first through direct stimulation of osteoblasts and stromal cells, and second through inhibition of RANKL expression [17]. CB₂-deficient mice have a low bone mass phenotype, similar to CB₁ knockout mice at 12 months. Conversely, activation of the CB₂ receptor has been shown to increase bone mass by increasing the number and activity of osteoblasts, inhibiting osteoclast proliferation and stimulating fibroblastic colony formation by bone marrow cells [17–19].

The ECS also appears to affect mesenchymal stem cell (MSC) differentiation through cannabinoid receptors on mesenchymal stem cells [16, 17, 20]. Research has demonstrated a functional increase in the CB₁ receptor during osteogenesis. Based on an in vivo model, it is likely that the CB₁ receptor also has a functional role in the survival of the differentiated MSCs [7].

ESC activation may enhance not only MSC survival but also migration and chondrogenic differentiation of MSCs. Among other benefits, this has potential for use in mesenchymal stem cell–based tissue-engineered cartilage repair strategies; however, data on the role of the cannabinoid system in cartilage tissue is currently lacking [21].

Δ^9 -THC Activates CB₁ and CB₂ but Has Cytotoxic Properties

The *Cannabis sativa* plant otherwise known as marijuana contains more than 100 cannabinoids; the major constituents are Δ^9 -Tetrahydrocannabinol (Δ^9 -THC) and cannabidiol (CBD) [10, 20]. The psychoactive ingredient in cannabis is Δ^9 -THC and although it also has analgesic and anti-emetic effects, it is best known for its psychoactive effects [10, 22].

Δ^9 -THC is a partial agonist of the CB₁ and CB₂ receptors, but has higher affinity for the CB₁ receptor. The effects of Δ^9 -THC are largely due to the activation of CB₁ receptors in the nervous system affecting control of synaptic activity, motor function, pain perception, and appetite [23]. This nervous system activation gives rise to marijuana's euphoric effects, but carries the frequent side effect of memory impairments and an increased risk of psychosis [23].

Despite its activation of CB₁ receptors, Δ^9 -THC may have a detrimental effect on bone healing. Δ^9 -THC has a dual

toxicity profile that prevents osteogenesis and induces cell death in a number of cell types, including neurons and mesenchymal stem cells, likely via a proapoptotic downstream signaling mitochondrial pathway [7]. For this reason, Δ^9 -THC is being investigated for possible use as an antitumoral agent [7, 23–26].

Cannabis smoke inhalation, similar to tobacco smoke, has been shown to reduce bone healing around titanium implants in a rat fracture model [27]. This raises concerns for implant survival and bone healing in patients after fracture fixation. In particular, the impact of Δ^9 -THC on mesenchymal stem cell differentiation suggests a negative effect on osteogenic potential and resultant bone healing [7].

The effects of marijuana on bone homeostasis and fracture healing are under current investigation. Heavy cannabis use has been linked to low bone mineral density, low BMI, high bone turnover, and increased risk of fracture [13]. It is currently unclear to what extent this is caused solely by the ingestion of Δ^9 -THC.

Cannabidiol Antagonizes GPR55 Thereby Facilitating CB₁ and CB₂

Cannabidiol (CBD) is another popular cannabinoid of the *Cannabis sativa* plant. CBD has no psychoactivity and is primarily an anti-inflammatory [1, 28]. CBD has been well studied for a number of illnesses including neurodegenerative disease, epilepsy, and immune disorders such as multiple sclerosis, arthritis, and cancer [29•]. Currently, it is FDA approved only for the treatment of epilepsy [29•].

CBD antagonizes cannabinoid receptor GPR55, and is thus an inverse agonist of the CB₂ receptor. Compared with Δ^9 -THC, CBD has lower affinity to the CB₁ and CB₁ receptors. In vivo studies have demonstrated that CBD can inhibit bone resorption via modulation of GPR55 signaling and activation of CB₂ receptors. It is unknown whether Δ^9 -THC acts on the GPR55 receptor, and if so, whether it has similar or opposing effects to CBD.

The effect of CBD in fracture healing has been investigated in a rat model evaluating callus formation about femur fractures. This data demonstrated enhanced biomechanical properties of healing rat mid-femoral fractures in rats given CBD compared with a control group. This effect was not shared by rats given only Δ^9 -THC; moreover, attenuation of the osteogenic CBD effect was seen in rats given equal amounts of CBD and Δ^9 -THC. This favorable biological effect of CBD is believed to occur via enhancement of osteoblastic expression of lysyl hydroxylase 1, a collagen crosslinking enzyme [28]. Similar in vivo research has shown that CBD incorporated into an osteoconductive scaffold can stimulate MSC migration and osteogenic differentiation [28]. Further studies are needed to better evaluate the role of CBD in human bone

healing and metabolism, as well as the long-term effects of CBD ingestion [30•].

Minimal Evidence Regarding Orthopaedic Surgical Outcomes in Marijuana Users

While recent pre-clinical data has demonstrated promising effects of CBD on bone healing and bone metabolism, clinical studies are insufficient and inconclusive. A retrospective review of the National Hospital Discharge Survey (NHDS) evaluated patients who underwent primary total joint arthroplasty and found that patients who abused substances preoperatively had higher rates of surgery-related complications. Significantly, this study was not limited to marijuana users and included patients using opioids, cocaine, cannabis, amphetamines, inhalants, and sedatives [31].

Research surrounding marijuana in the total joint arthroplasty cohort is contradictory. In a recent series, Law et al. performed a retrospective review of the Medicare database on total knee arthroplasty (TKA) patients evaluating those who used marijuana compared with those who did not. This study found a significant increase in reoperation rate due to infection in the cohort that used marijuana. This study was limited as they relied on accurate coding for data collection and further did not stratify patients based on additional risk factors [32••].

In comparison, a recent retrospective cohort study using a matched control and selected patients only using marijuana versus other substances found no difference in complications after primary TKA in patients that did and did not use marijuana [3•]. The limitations of this study must be appreciated as well, as not all patients report use of substances, and frequency and type of use may not be properly recorded [3•].

A recent review analyzed data from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (HCUP-NIS) database to evaluate the effect of marijuana use by orthopaedic patients on inpatient mortality, heart failure, stroke, and cardiac disease. A decreased mortality rate was seen in patients who used marijuana compared with those who did not [2••]. Similar to previous studies, this study did not stratify by comorbidities, nor by demographics of marijuana users. Furthermore, the heart failure, stroke, and cardiac disease codes generated during hospital visits were likely in part preexisting conditions rather than complications of hospitalization.

Marijuana use does not only affect the musculoskeletal system, nor is marijuana ingestion limited to CBD and Δ^9 -THC. The smoke from cannabis has been shown to contain many of the same carcinogens as tobacco, and heavy cannabis use has been associated with an increased risk of developing lung cancer [1]. Patients using marijuana are at increased risk of psychiatric effects including anxiety, agitation, and even

acute psychosis [33]. Other studies report potential increased risk of cardiac events, atherosclerosis, and even stroke in patients that smoke marijuana [34–38].

The current conflicting data on marijuana use in an orthopaedic surgical population demonstrates the need for future well-designed prospective studies evaluating outcomes and potential complications. It is possible that the perioperative use of marijuana or CBD alone may significantly impact healing, recovery, and complication rates after orthopaedic procedures.

Cannabinoid Use for Musculoskeletal Pain

Opioid over-consumption among patients with musculoskeletal pain is of top concern to orthopaedic surgeons given recent trends in morbidity and mortality associated with chronic narcotic use [3•]. Accordingly, alternatives to narcotic use have recently gained substantial attention. Many patients with complicated surgical history, large-scale procedures, or multiple comorbidities require multimodal pain medication regimens [3•]. Cannabinoids, if effective for pain relief, could potentially reduce the opioid burden [3•, 39•].

Pre-clinical studies demonstrate that cannabinoid signaling has an integral role in the nociceptive system and that CB₁ and CB₂ receptor agonists have antinociceptive properties. Δ^9 -THC has also been shown to have euphoric and psychoactive effects, both of which have a role in pain modulation and experience [7]. Clinical evidence has not demonstrated similar findings in human experiments [40•]. No clear benefit from the use of cannabinoids has been shown to be better than placebo [41•]. This result is due in part to a lack of high-quality evidence to support the use of medical marijuana therapy for acute or chronic pain indications [41•]. The paucity of high-quality data is not only an issue in musculoskeletal pain, but is part of the larger lack of evidence supporting the common use of marijuana for chronic rheumatologic, oncologic, or arthritic pain [33, 39•, 41•].

Conclusion

Pre-clinical studies demonstrate that the ECS has an important role in bone healing and bone homeostasis. There is promising evidence that CBD may increase bone healing through activating cannabinoid receptors, whereas Δ^9 -THC likely inhibits bone metabolism and repair. Current mouse and rat models are age and sex dependent, limiting generalizability and applicability to human cannabinoid receptor function [13]. It is currently unclear whether the pre-clinical evidence demonstrated in this review will correlate with clinical evidence in bone formation and homeostasis in humans.

The perioperative consumption of marijuana by orthopaedic patients has more relevant factors to consider than only the ingestion of specific cannabinoids. Marijuana smoke contains carcinogens similar to tobacco smoke, and has not been thoroughly evaluated as a cause of perioperative or long-term complications. Studies have demonstrated concern for negative cardiovascular and psychiatric effects caused by marijuana use, but have not elucidated similar orthopaedic complications. Future areas for research include age- and comorbidity-stratified analysis of clinical outcomes in marijuana users to non-users. The consumption of CBD alone or in combination with Δ^9 -THC as conventional marijuana may have significant clinical effects in the realm of bone metabolism and fracture healing.

Compliance with Ethical Standards

Ethical Review Committee Statement The study has been performed in accordance with the ethical standards in the 1964 Declaration of Helsinki and has been carried out in accordance with relevant regulations of the US Health Insurance Portability and Accountability Act (HIPAA).

This work was performed at The Albany Medical Center, Albany, NY.

Conflict of Interest Casey M. O'Connor, Afshin A. Anoushiravani, Curtis Adams, Joe Young, Kyle Richardson, and Andrew J. Rosenbaum declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects. Informed consent was not required for this study as it did not study human subjects.

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