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Cannabinoids for Pain Modulation in Orthopedic Surgery

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abstract

Cannabinoid compounds are being increasingly used as an analgesic adjuvant in the orthopedic population, but little data exist to either support or oppose this practice pattern. A review of all contemporary (2000-2020) studies on the use of cannabinoids in orthopedics is presented. Physicians and patients are optimistic that cannabinoids can decrease pain scores and perhaps opioid use; however, their application in orthopedics is not well characterized. In addition to the social stigma regarding the use of cannabis, there is limited high-quality evidence of the efficacy of cannabinoids in treating orthopedic-related pain. As cannabis becomes more accessible, well-designed trials are needed to better understand cannabinoids and guide orthopedic practice. [*Orthopedics*. 202x;xx(x):xx-xx.]

Use of cannabinoid compounds as therapeutic agents dates back at least 4000 years, with medical references documenting the first medicinal use in 2737 BC in China.[1] More recently, cannabinoid compounds and their analgesic properties have gained attention in the last decade because of a changing legal landscape and the continuing opioid crisis in the United States. Orthopedic surgeons are the third highest prescribers of opioids among all physicians and therefore need to be well informed about therapies that could reduce or eliminate the need for opioids.[2] However, the combination of patient expectations and fragmented information about the use of cannabinoids in orthopedics poses significant challenges to practitioners.[3] Although cannabis is the most widely used illicit recreational substance in the United States,[4] the US Food and Drug Administration (FDA) does not regulate the production of these compounds, leading to uncertainty and inconsistency in the effect of cannabinoid formulations. Therefore, we sought to review the existing literature and present relevant information to guide orthopedic surgeons as they counsel patients on the use of cannabinoids for pain.

Basic Science

The endocannabinoid system is a lipid signaling system in the body that includes the endocannabinoids, their receptors, and enzymes, and it is involved in returning the body to and maintaining physiologic homeostasis.[5,6] This function of the endocannabinoid system theoretically may be harnessed to improve sleep and appetite as well as reduce pain and inflammation. Cannabinoids are naturally occurring compounds found in the *Cannabis sativa* plant, the most well known of which are tetrahydrocannabinol (THC) and cannabidiol (CBD).

These compounds act on the cannabinoid receptors (CB1 and CB2) that normally bind endogenous cannabinoids (anandamide and 2-arachidonoylglycerol) to affect appetite, mood, and pain.[7] The CB1 receptors are mostly found in the central nervous system and peripheral nervous system, particularly in the nocicep-

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tive centers of the dorsal root ganglion.[8] Conversely, CB2 receptors are located within immune and musculoskeletal cells and are important for the regulation of inflammatory processes. In addition, CB2 receptors contribute to antinociception by inhibiting the release of proinflammatory factors throughout the body.[9-11]

Whereas THC produces psychoactive effects, CBD does not, thus making CBD potentially more desirable for medical use.[12] Patients often do not desire these psychotropic effects; however, studies have shown that the potency of illicit cannabis on the street has increased consistently over the past two decades, from 4% in 1995 to approximately 12% in 2014.[13] According to the potency monitoring program at the University of Mississippi, supported by the National Institute on Drug Abuse, the mean THC:CBD ratio from 2008 to 2017 increased 450%.[14] As the THC:CBD ratio in commercial cannabis compounds continues to increase, patients electing to use cannabis for therapeutic reasons are more likely to experience psychotropic and other undesirable effects. This lack of control and increased uncertainty has highlighted the importance of appropriate research and clinical trials to create maximally therapeutic formulations.

Clinical Applications

Pain Modulation

Pain modulation is among the most cited reasons for cannabis use. In Canada, which has had a medicinal cannabis program since 2001, a survey of 2032 patients identified that 42% of the patients were using cannabis for pain syndromes, including chronic pain (29.4%), arthritis (9.3%), and headache (3.7%).[15] The widespread use of cannabis for the treatment of pain has highlighted the importance of understanding the underlying mechanism of its ability to control pain.

Both CB1 and CB2 receptors are believed to function in pain modulation throughout the body. Interestingly, the human brain has more CB1 receptors than opioid receptors.[16] Through CB1 receptors, cannabinoids modulate nociceptive thresholds by regulating neuronal activity and attenuating synaptic transmission of pain. The presence of CB1 receptors on mast cells also suggests an anti-inflammatory effect, potentially through suppression of mast cell degranulation.[11] Thus, CB1 receptors play a role in inhibiting the downstream inflammatory effects of mast cell degranulation, such as increased blood vessel permeability and recruitment of inflammatory cells to the site of degranulation. Similarly, CB2 receptors also modulate pain through inhibition of proinflammatory factor release because they are primarily associated with immune response modulation. Because cannabinoids bind to the CB2 receptor on inflammatory cells, they dampen the release of inflammatory factors and relieve pain.[11]

There is currently a moderate level of evidence supporting the use of cannabinoids to treat chronic pain.[17] Studies investigating cannabinoids for rheumatic pain have shown some efficacy for rheumatoid conditions; however, there are no randomized studies of degenerative conditions.[18] Similarly, there is little high-quality evidence delineating the use of cannabis and cannabinoids to treat commonly encountered orthopedic conditions, such as low back pain, fractures, knee and hip arthritis, or postsurgical pain.[19]

Decreased Opioid Use

The use of cannabinoids for pain management is increasingly popular as the medical field confronts opioid overuse. In response to the growing issue, the Centers for Disease Control and Prevention published guidelines recommending caution in the use of opioids for pain management.[20-22] Within the context of chronic pain, there have been efforts to explore the potential for cannabis to reduce opioid usage through a multimodal approach. However, many early studies of postoperative pain have shown no benefit of THC alone[23] or any additional analgesia when THC was paired with an opioid agonist.[24] Even novel cannabinoid compounds designed to proffer postoperative relief have not resulted in improved pain control after minor procedures.[25]

In a cross-sectional retrospective survey of 244 patients using medical cannabis between November 2013 and February 2015, study participants using medical cannabis for chronic pain showed a 64% decrease in opioid use and a decreased number of medications and side effects of medications, and 45% of study participants experienced an improved quality of life.[26]

Over the past two decades, numerous states have legalized cannabis use in the context of medical necessity. In a time series analysis of medical cannabis legalization and state-level death certificate data across all 50 states from 1999 to 2010, states where medical cannabis was legalized showed a 24.8% lower mean annual opioid overdose mortality rate (95% CI, -37.5% to -9.5%; *P*=.003) compared with states without medical cannabis legalization. The data also showed that from the date of legalization there was further reduction in the rate of opioid overdose deaths. This finding indicates that as the availability of medical cannabis became more prominent, the number of opioid overdoses declined more significantly.[27]

Anxiolytic Properties

In addition to pain modulation, cannabinoids are believed to have anxiolytic properties. Studies have shown that there are high densities of CB1 receptors located throughout the amygdala, the brain region believed to control anxiety and fear. Additionally, CB1 receptors have also been found in the anterior cingulate cortex and prefrontal cortex, 2 areas that are involved with emotional regulation.[28] Kathuria et al[28] showed that a disruption of CB1 receptor activity in rodents led to anxiety-like behaviors, suggesting that CB1 receptors and endocannabinoids have a role in underlying anxiolytic tone. Recent evi-

dence suggests that pain modulation likely exists in the form of a descending pain modulatory circuit with areas that include the hypothalamus and the amygdala, the same regions involved in the modulation of anxiety.[29] The overlap of the neuronal circuits corresponding to pain and anxiety is not redundancy, but instead highlights the intimate relation of these concurrent pathways. Chronic anxiety may lead to susceptibility to chronic pain, and vice versa. Further investigation and research into the relationship between cannabinoids and their anxiolytic properties may make them viable supplements to current treatments for anxiety in addition to the already postulated use in pain control.

Commonly Available Formulations of Cannabis

Cannabis (Marijuana)

Cannabis, or marijuana, is a flowering plant that contains more than 500 different chemical compounds, including many types of cannabinoids. Cannabis contains THC, a substance that, as mentioned previously, has both the greatest psychoactive effect and the greatest analgesic activity of compounds contained within cannabis.[11] Studies have shown that THC administered epidurally, both intrathecally and intraventricularly, produces antinociception similar to that obtained with opioid compounds.[11] Novel products now offer cannabis in various formulations, including herbal, resin, and edible forms as well as lozenges, concentrates, and tinctures. Because of the wide spectrum of chemotypes, cannabis products are available with engineered THC and CBD concentrations for different effects.[30]

Ongoing discussion and research to advance the legal status of cannabis and explore its medical applications led many states to legalize its use. However, it is important to note that the US Drug Enforcement Administration (DEA) still designates cannabis as a Schedule I controlled substance, meaning that it has no currently accepted medical use and a high potential for abuse. This places cannabis in the same category as other drugs such as heroin, lysergic acid diethylamide, ecstasy, methaqualone, and peyote. In states where cannabis has been legalized, physicians can write a recommendation for its usage for conditions such as cancer, multiple sclerosis, and HIV/AIDS; however, because it is considered a Schedule I controlled substance, these are merely recommendations and do not constitute a true prescription.

Dronabinol

Dronabinol (Marinol; Abbvie Pharmaceuticals) is an isomer of THC and was the first FDA-approved cannabinoid drug. Dronabinol is approved for chemotherapy-induced nausea and vomiting for patients with nausea and vomiting refractory to other antiemetic treatment modalities, and it is orally bioavailable. It is a Schedule III controlled substance, allowing medical professionals to prescribe it with up to 5 refills in 6 months. Cooper et al[31] completed a study comparing the analgesic effects of cannabis with dronabinol among healthy volunteers who were daily cannabis smokers. The study subjected these volunteers to hand submersion in cold water to simulate pain sensitivity and pain tolerance. The study showed that dronabinol administration decreased pain sensitivity and increased pain tolerance that peaked later and lasted longer relative to smoked cannabis, whereas cannabis produced a greater attenuation of subjective ratings of pain intensity relative to dronabinol.[31] The ability of dronabinol to induce analgesia, combined with its more lenient DEA scheduling, might make it a more viable option for further research into potentially expanded clinical use.

Cannabidiol Oil

Oil extracted from the cannabis plant has been studied for its potential analgesic, anti-inflammatory, anticonvulsant, antiemetic, and anxiolytic activities, and it is of particular interest because it contains CBD, which does not carry the same psychoactive effects or risk of dependency as seen with THC. Commercially, CBD has been marketed heavily to the public for a variety of conditions and is widely available. It is commonly ingested orally as a pill, absorbed sublingually, or applied directly as a topical agent.

Interestingly, CBD has minimal direct binding affinity for CB1 and CB2 receptors but rather exerts its action through a multitude of other receptors, such as cannabinoid G protein-coupled receptors (serotonin 1A receptor), ion channels (transient receptor potential cation channel subfamily V member 1, transient receptor potential cation channel subfamily A member 1), and peroxisome proliferator-activated receptors.[32] The diverse array of receptors enables the wide-ranging effects seen with CBD. In addition to its potential analgesic, anticonvulsant, and anti-inflammatory properties, research has started to consider CBD as a possible treatment supplement for conditions such as inflammatory bowel disease, graft-vs-host-disease, and severe myoclonic epilepsy.[33] Generic CBD is a DEA Schedule I substance, so it cannot be prescribed by medical professionals.

Cannabidiol (Epidiolex; Jazz Pharmaceuticals) is a 99% pure oral CBD extract that is FDA approved for pediatric epileptic conditions. Although previous studies have not focused on its analgesic effects, its status with the FDA makes it an attractive target for evaluation of CBD.[34]

Nabilone

Nabilone (Cesamet; Valeant Pharmaceuticals) is a synthetic cannabinoid that mimics THC and is used for chemotherapy-induced nausea and vomiting and neuropathic pain.[35-37] It is administered as an oral capsule and is available in the United States, Canada, and Europe. Three randomized controlled trials have been conducted to evaluate nabilone. Levin et al[36] administered a single 0.5-mg dose of nabilone preoperatively to 340 patients

who had undergone elective surgery (47 orthopedic cases) and found that it had no effect on acute postoperative pain scores in the postanesthesia care unit. Beaulieu[35] studied the effect of nabilone on reducing morphine consumption and postoperative pain scores over 24 hours among 41 patients who had undergone major surgery (18 orthopedic cases) and found that it was associated with increased pain scores. Frank et al[37] conducted a trial over a 14-week period comparing the efficacy of nabilone and dihydrocodeine for chronic neuropathic pain and concluded that dihydrocodeine provided better pain relief as well as fewer side effects.

Nabiximols

Nabiximols (Sativex; GW Pharmaceuticals) is an oromucosal spray of THC and CBD that is available in Europe, Asia, Africa, and Canada for neuropathic pain, spasticity, and symptoms of multiple sclerosis. It has been studied by Blake et al[38] for pain relief among patients with uncontrolled pain from rheumatoid arthritis, and results showed improvements in pain scores, although the findings were only preliminary.

Levonantradol

Levonantradol (Pfizer) is a synthetic cannabinoid with 30 times greater affinity for the CB1 receptor than THC.[39] It had previously been investigated for use as an analgesic, but the work was deserted because of a high incidence of central nervous system effects, including euphoria, paranoia, and psychosis. Kantor and Hopper[40] published an abstract describing a randomized controlled trial of 81 postsurgical patients using intramuscular and oral administration of levonantradol and noted improvements in the Sum of Pain Intensity Difference score. However, they noted adverse central nervous system effects. Levonantradol is not currently used in clinical medicine but is widely used for research purposes to explore the effects of cannabinoid compounds.

Cannabis Plant Extract

Cannador (Society for Clinical Research) is a cannabis plant extract of THC and CBD in a 2:1 ratio in the form of an oral capsule. Holdcroft et al[41] studied Cannador for postoperative pain management in a nonrandomized trial in which 65 postsurgical patients (23 orthopedic cases) were administered the study drug after discontinuation of patient-controlled analgesia with morphine. The patients were separated into groups based on the dose of medication they were to receive, either 5 mg, 10 mg, or 15 mg. The study found lower patient-reported pain and decreased need for rescue anesthesia with increased dosing of the study drug.

Palmitoylethanolamide

Palmitoylethanolamide (PEA) is an endocannabinoid that was initially discovered in egg yolks. Therefore, PEA is considered a nutraceutical, a term that applies to any food or food component that has potential health or medicinal benefits.[42] Studies have shown that PEA has activity at both the CB1 and CB2 receptors, although it is not itself a component of cannabis. In addition to its activity at cannabinoid receptors, PEA has also shown activity at peroxisome proliferator-activated alpha receptors, which play an important role in dampening neuroinflammation.[42]

Scaturro et al[43] studied the use of ultramicronized PEA as a supplement to standard treatment for elderly patients with chronic low back pain. The study showed that the use of ultramicronized PEA resulted in a progressive decrease in mean pain intensity score coupled with improvements in the physical and mental components of quality of life as evaluated by the 36-Item Short Form Health Survey questionnaire. Similarly, in a double-blind, placebo-controlled study, Steels et al[44] investigated the use of PEA to treat pain associated with mild to moderate knee osteoarthritis. Pain was measured and standardized by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Patients were randomized to receive 300 mg PEA, 600 mg PEA, or placebo each day, twice daily in divided doses, for 8 weeks. The study showed a significant reduction in total WOMAC score in both the 300-mg PEA and 600-mg PEA groups compared with placebo, highlighting the potential for PEA to be incorporated into pain attenuation treatments for knee osteoarthritis.[44]

Because nutraceuticals, such as PEA, are not regulated by the FDA, they are not under a DEA schedule, nor do they require a prescription. This particular regulatory environment is encouraging for the study of PEA in further research.

Other nutraceuticals have been studied for orthopedic use and have been found to improve osteoarthritic pain, including avocado/soybean extracts, boswellic acids, capsaicin, curcumin, ginger, polyphenols (green tea, pomegranate), and polyunsaturated fatty acids (fish oil, mussels). These all act by reducing inflammation through unique, but noncannabinoid mechanisms. Proponents of nutraceutical drug development believe that these compounds hold potential not only for osteoarthritic symptom management but also for pathology modification.[45]

Disease States

Musculoskeletal Trauma

No trials have investigated the effect of cannabinoids on pain as a result of musculoskeletal trauma, although it is known that cannabinoids have various actions within the musculoskeletal system. As described earlier, pain modulation is believed to occur through cannabinoids affecting the CB1 and CB2 receptors, which attenuate nociceptive signals and mitigate inflammation. Additionally, through various receptors, cannabinoids interact and have effects on bone remodeling and maintenance, leading to other implications within the field of musculoskeletal trauma. A study by Kogan et al[46] showed an increase in the maximal load and work-

to-failure of femurs taken from rats that were given a mixture of CBD and THC for 8 weeks. They also found that the use of CBD led to an increase in the crosslink ratio of collagen at fracture sites, potentially contributing to improved biomechanical properties of fracture callus.[46]

Bhashyam et al[47] found an association between current cannabis usage and an increase in the total amount of prescribed opioids and the duration of opioid use. They hypothesized that patients who use cannabis during recovery have greater psychological distress and less effective coping strategies that lead patients to self-medicate with opioids and cannabis. Although the study did not directly assess whether CBD-based therapies had similar effects on opioid usage, the relatively low risk of dependency and overdose associated with CBD might deem it a good candidate for further research in the context of musculoskeletal trauma.[47]

Postsurgical Pain

Postsurgical pain management is an important component of orthopedic surgical care. However, the legal status of cannabinoids has limited investigation in this area. There have been 4 controlled studies of cannabinoids for postoperative pain: 2 in Canada, 1 in the United Kingdom, and 1 in the United States. Levin et al[36] and Beaulieu[35] both studied nabilone among postsurgical patients and found that it had no effect on postoperative pain scores or increased pain scores. Kantor and Hopper[40] studied levonantradol and found lower pain scores but significant central nervous system side effects. Holdcroft et al[41] found improved patient-reported pain among postsurgical patients receiving Cannador. The 4 trials included all types of surgical patients, but a significant portion had undergone orthopedic surgery. These studies are rare and therefore valuable; however, the heterogeneity in the study drug, study population, dose, frequency, route of administration, and outcome measures make it difficult to draw a unified conclusion about the effect of cannabinoids on postoperative pain. Therefore, improvements in reporting and methods are needed to determine optimal protocols for the use of cannabinoids.[48]

Total Knee Arthroplasty

Research into the relationship between cannabis and arthroplasty has yielded contradictory results. For instance, in a retrospective review of 2,718,023 cases of total knee arthroplasty (TKA) and 247,112 cases of revision TKA, Law et al[49] found that cannabis use led to a significantly greater incidence of revision and a significantly shorter time between primary and revision surgery compared with the noncannabis group. According to Law et al,[49] the TKA revision rate was significantly increased among cannabis-using patients (12.8%; n=18,875) compared with non–cannabis-using patients (9.1%; n=2,718,023), with infection being the most common cause for revision. Conversely, the study found that cannabis use decreased the rate of revision for other reasons, such as periprosthetic fractures, mechanical loosening, implant failure, and osteolysis.[49,50]

Roche et al[50] studied the incidence of drug abuse among patients undergoing revision TKA and found that cannabis users required earlier revision of TKA than users of cocaine, alcohol, and opioids, particularly 30 to 90 days after primary TKA. Further, a study by Moon et al[51] found that cannabis users had a decreased rate of mortality after total hip arthroplasty, TKA, or total shoulder arthroplasty; however, the significance of these findings was unclear. Interestingly, Jennings et al[52] completed a study of the postoperative outcomes of patients with self-reported cannabis use who underwent primary TKA and found no difference in outcomes compared with control subjects. None of these studies addressed the use of CBD alone in the context of TKA. Further research is clearly needed to further identify how cannabinoids can affect patients undergoing joint arthroplasty.

Arthritis

Although there is a dearth of research on cannabinoids for pain in arthritis, patients commonly cite arthritis as their reason for cannabis use.[53] Arthritis is the presence of inflammation within the joints and is often associated with pain and discomfort. Endocannabinoids have been noted to be associated with inflammatory states, and studies have noted the presence of endocannabinoids within joints affected by osteoarthritis and inflammatory arthritis. Likewise, cannabinoid receptors seem to be upregulated within the joints that are currently experiencing inflammation and appear in much lower numbers in the joints of normal volunteers.[9] The upregulation of cannabinoid receptors within inflamed joints opens the possibility of further testing of cannabinoid-based therapy in the management of arthritis.

Spine-Related Pain

Research on the usage of cannabinoid-based therapies in the context of spine pain is limited. Drossel et al[54] found that the use of cannabis for therapeutic purposes did not mitigate prescriptions for other spinal cord injury–related pain medications and instead served only a supplementary function. In an observational crossover study, Yassin et al[55] evaluated improvement in pain and function among a group of 31 patients with low back pain related to fibromyalgia with standard opioid analgesic therapy and medical cannabis therapy. The group found significantly better patient-reported outcomes and range of motion after medical cannabis therapy was added.[55] More specific research is needed to understand cannabinoid-based therapies in the context of spine-related pain.

Route of Administration

There is some debate on the impact of route of administration on perceived or actual pain relief associated with cannabis compounds. Volunteer human partici-

pants in a study evaluating orally ingested cannabis in differing benign pain models did not show analgesia,[56] but a study of inhaled cannabis resulted in marked analgesia and a dose-dependent effect.[57] However, the current body of literature on this topic is not robust, and this is yet another area where further research is needed before recommendations on the route of administration can be made.

Discussion

Cannabinoids are gaining increased attention as a tool for pain management as the United States addresses a continuing opioid epidemic. Previously, the medical use of cannabis had largely been advanced by patients because of its status as an illegal substance, but legislation is now more closely aligning with societal and cultural norms as cannabis has been legalized in 32 states and US territories.[51,58] Despite these legal changes, the application of cannabinoids in orthopedics is still nascent and in need of more supportive high-quality evidence.[19,59] As popular interest continues to rise, orthopedic surgeons should be familiar with the negative and positive attributes of cannabinoids to provide information and guidance to their patients. Although high-quality literature on medical cannabis is scarce, some interdisciplinary work groups have emerged to construct guidelines, including one for perioperative use of cannabis and cannabinoids.[60]

There is little evidence showing the efficacy of cannabinoids for treating core orthopedic issues of arthritis, postoperative pain, back pain, and trauma-related pain, posing a challenge for orthopedic surgeons who need to address patient questions. Randomized controlled trials of cannabinoids have not focused on orthopedic patients, but rather their study populations were an amalgamation of patients undergoing any type of surgery or experiencing neuropathic pain. Other studies that have attempted to address the vacuum of information have largely been patient surveys or systematic reviews that have only been able to provide poor evidence to suggest that cannabis can be effective in treating orthopedic pain. The conflicting legal status of cannabis at the state and federal levels is the principal barrier because this situation complicates funding and institutional review board approval, even in states where cannabis is legal.

For now, we can state with certainty that cannabinoid receptors are nearly ubiquitous within the human body. These receptors are part of a complex endocannabinoid system that influences the sensation of pain, nausea, anxiety, inflammation, sleep, appetite, and more. It is essential that we continue to work to understand how this system can be modulated to help patients.

Conclusion

There is great interest in the potential for cannabinoids to be used for pain relief and as a tool for reducing opioid consumption. Although the basic science of the endocannabinoid system and cannabinoids is reasonably well established, there is a lack of clinical evidence on the efficacy of cannabinoids in the treatment of pain from orthopedic pathology. Ongoing changes in the legal status of cannabis in the United States will be an important determinant of the rate and potency of clinical research. The urgency of the opioid crisis will continue to drive efforts to explore nonopioid pain management options, and cannabinoids remain a promising alternative. Orthopedic surgeons will continue to encounter cannabinoid use in their practice and should be receptive to the discussion and knowledgeable about the topic to help guide decision-making.

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