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Medicinal Cannabis in Orthopaedic Practice

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Author Information

Abstract

Cannabis has gained widespread public advocacy since its legalization in several states with recent evidence suggesting that its self-reported use has increased in patients undergoing a primary total joint arthroplasty. The endocannabinoid system has been proposed to play a role in decreasing the inflammatory cascade and enhancing pain management. For these reasons, interest has emerged in the orthopaedic community as a potential treatment or adjunct to treatment in many musculoskeletal conditions. However, the evidence to date is scant and precludes recommendations for its widespread use. Given the current paucity of evidence in the orthopaedic cohort, future research is warranted in this area to determine the efficacy and safety before endorsements can be made by orthopaedic surgeons.

Pain management in orthopaedics remains one of the most challenging realms of clinical care for healthcare providers. The United States is now battling an unprecedented opioid epidemic that cumulatively costs the US economy roughly $78.5 billion annually.1 The US population accounts for only 4.6% of the world population but consumes 80% of the global opioid supply.2 Opioid-related deaths accounted for 1.68 million person-years of life lost in 2016 (a 345% increase from 2001) with the highest incidence in patients aged between 24 and 35 years (20% of all deaths in 2016).3 Studies have shown that approximately 75% of patients seeking treatment for opioid addiction were introduced to them through prescription medications.4 Opioid abuse has been shown to have a notable impact on surgical outcomes. Preoperative opioid use is associated with higher morbidity and mortality following elective orthopaedic procedures 5 with higher revision rates and inferior outcomes following total knee arthroplasty.6 Healthcare providers and government officials must work together to find safe and effective alternatives to control both chronic and postsurgical pain to minimize exposure to opioids. In recent years, cannabis has emerged as a potential alternative or adjunct to opioids in management of pain related to musculoskeletal conditions, but most orthopaedic surgeons have little knowledge on its medical applications or efficacy.7-10

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Outline

Cannabis sativa (or marijuana) has been used globally for several millennia for medical, recreational, and spiritual purposes. The first documented use of marijuana for perioperative pain control was in the second century AD by Chinese surgeons for procedures including organ grafts, laparotomies, and thoracotomies.11 Subsequently, it became popular in Europe for its effectiveness in controlling pain, spasticity, and nausea.11 In 1854, cannabis was added to the US Pharmacopeia with its major indications being appetite stimulation, headaches, sleep disorders, and sexual dysfunction.11 Cannabis' medical use fell out of favor in the early 1900s as its use became associated with crime and violence in ethnic minority groups.11 The US Marijuana Tax Act was passed in 1937 that strictly outlawed marijuana for recreational use.11 In 1970, the FDA passed the Controlled Substances Act, which classified cannabis as a schedule I substance, meaning that it was deemed to have absolutely no medical value and carried high abuse potential.

Since that time, research on the medical applications of cannabis has been limited to chronic pain and nausea management in patients with cancer, appetite stimulation in patients with AIDS and some forms of spasticity.12-14 Cannabis has recently been legalized for medical use in 29 states and the District of Columbia capturing 63% of the United States population 15 (Figure 1 and Table 1). The motion for legalization has been called by some "medicine by popular vote," given the lack of scientific evidence to support the efficacy of cannabis.16 Many states have legalized cannabis for recreational use as well (Figure 1 and Table 1). Meanwhile, the federal government continues to maintain the classification of marijuana as a schedule I substance, deeming its use to be illegal for any purpose. This has limited any organized research efforts or regulation of medical cannabis at a national level.

Figure 1

Table 1

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The Endocannabinoid System

The cannabis plant contains over 60 active cannabinoids with various physiologic effects.12 The most widely known cannabinoids include [delta]-9-tetrahydrocannabinol (THC) (marijuana's major psychoactive cannabinoid) and cannabidiol (CBD) (Figure 2). Cannabinoids act on the body's endogenous endocannabinoid system that contains receptors throughout the human body. The CB1 cannabinoid receptor is found primarily in the central nervous system on the neurons and glia cells of the brain and has high affinity for THC.17 There are high concentrations of CB1 receptors in the hypothalamus (controlling appetite), dorsal vagal complex (regulating nausea), spinal cord (controlling pain signaling), hippocampus (memory), cerebellum, and cerebral cortex explaining some of the unique physiologic effects of THC.17 There is a paucity of CB1 receptors in the autonomic nervous system, so functions such as respiratory drive are not as affected by THC. The CB2 receptors are primarily located peripherally in the immune system, gastrointestinal tract, and spleen and show much higher affinity for CBD than THC.

Figure 2

The body's natural endogenous cannabinoids bind CB1 and CB2 receptors to suppress neurotransmitter release at synaptic junctions and are subsequently broken down by enzymes.18 THC cannot be metabolized by these enzymes, allowing THC to have a more prolonged effect than endogenous cannabinoids. With increased exposure to THC, the number of CB1 receptors at the synaptic junctions decreases, thus dampening the physiologic effects of endocannabinoids. This also leads to tolerance such that chronic cannabis users must increase the frequency or potency of THC in cannabis to elucidate a similar physiologic effect. The mechanism of action and physiologic effects of CBD are less well understood. Given its lack of affinity for CB1 receptors, CBD does not produce the same euphoric or psychoactive effects as THC. It is proposed that effects of CBD are more anti-inflammatory in nature; however, this remains a topic of continued research.19 The current therapeutic applications for CBD include analgesic, antispasmodic, anticonvulsant, and antiemetic purposes.19 Some have demonstrated that CBD can even moderate some of the adverse effects of THC (such as anxiety) and enhance its intoxicating effects; however, there is conflicting literature on this notion requiring further evaluation.20,21

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Cannabis Current Pharmaceutical Applications and Efficacy

Table 2

Various preparations are available for both natural cannabis and synthetic cannabinoids (Table 2). Traditional cannabis can be smoked, vaporized, or ingested orally. The concentration of THC in cannabis plants ranges dramatically depending on the portion of the plant from 0.3% in the hemp 22 to 30% in the flower buds. Over the past few decades, cross-breeding various plant strains by growers has increased the average THC potency of cannabis from 2% in 1980 to approximately 12% in 2012.23 Scientists are now bioengineering strains of cannabis to have higher THC concentrations to enhance their psychologic effects.24 The most rapid delivery of THC is achieved via smoking with peak plasma levels seen within 9 minutes and maximum THC bioavailability ranging between 2% and 56% (depending on smoking behaviors).19 Studies have shown that smoked cannabis is quite effective for neuropathic pain in patients with HIV 25 and can dramatically improve spasticity in patients with multiple sclerosis.26 Some of the adverse effects associated with smoked cannabis, such as euphoria and somnolence, have shown to intensify with higher concentrations of THC.27 Vaporization is potentially a healthier alternative to smoking where the plant is heated to just below combustion such that the active cannabinoids are vaporized but the harmful pyrroles generated from combustion are not released.28

Oral cannabis ingestion has lower bioavailability than smoking at approximately 6% bioavailability and peak levels of THC achieved between 1 and 6 hours depending on the concentration.19 Ingestion has been less favorable for patients than smoking because there is less control on dosing and first-pass hepatic metabolism can cause unpredictable amounts of active ingredients exerting target effects. Dronabinol (Marinol), a synthetic cannabinoid, and its synthetic analog nabilone (Cesamet) are two oral capsule preparations of synthetic THC available in the United States (Table 2). Dronabinol has been approved for treating nausea and vomiting in patients with cancer and appetite stimulation in patients with HIV.29 Nabilone is approved for managing nausea and vomiting from chemotherapy. Limited evidence is available on the benefits of these medications for pain management at this time.30,31 Some synthetic compounds are available as concentrated sublingual or oromucosal extract preparations to avoid the first-pass hepatic metabolism. The three types of extract preparations include Tetranabinex (high in synthetic THC extracts), Nabidiolex (purified CBD extracts), and Nabiximols or Sativex (equal amounts of Tetranabinex and Nabidiolex)19 (Table 2). Sativex is not currently available for use in the United States but is licensed in other countries as an oral mucosal spray for management of spasticity in patients with MS. It has also been studied for management of depression and sleep disorders; however, very low quality of evidence exists from these studies to support its efficacy.14 Any evidence on the use of these extracts for pain management is lacking at this time.

Several states allowing medical marijuana have passed restrictive laws to limit the content of THC in cannabis. At present, there are 13 states with "low-THC, high-CBD" marijuana laws; however, the limit of THC and minimum requirement of CBD varies widely from state to state.32 The indications for use of these products are quite specific and are only available in certain preparations depending on the state.32 Cannabinoid and hemp oils are legal in these states as long as they contain less than 0.3% THC content. Cannabis oils on the other hand are made from the cannabis plant flowers and leaves which usually contain higher amounts of THC. These products are usually not available in "low-THC, high-CBD" states unless their THC content is below the legal threshold.33

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Cannabis Safety and Adverse Effects

Table 3

As interest for medical cannabis and cannabinoid products grows, it is important to understand the health risks associated with their use. The adverse effects of cannabis and synthetic cannabinoids can be just as severe and limiting to their medical application as opioids (Table 3). Some of the most common adverse effects reported with medical cannabis use include dizziness, euphoria, confusion, disorientation, somnolence, dry mouth, nasopharyngitis, paranoia, and nausea.14,34 Cannabis can have serious psychomotor effects that are dose-dependent in severity and can last for hours depending on the form of ingestion. These effects are more commonly seen with recreational cannabis or high THC concentration preparations and include attention difficulties, impaired visuospatial selective attention, delayed reaction time, short-memory impairment, and slowed motor control.35 This is of particular significance when it comes to operating motor vehicles with one study of 49,000 subjects showing that acute cannabis use doubled the risk for major injury or fatality from motor vehicle accidents.36 Patients should be cautious in using "full spectrum" products that combine several different cannabinoids. Although the individual ingredients may have undergone trial testing, the combined preparations have not been subjected to safety or efficacy testing.33

The literature indicates that patients with underlying cardiovascular diseases are at increased risk for ischemic events with cannabis use.37 Cannabis stimulates systemic hypotension and tachycardia via mechanisms not fully understood but presumable via CB1 receptors on arterial vessels.23 One study identified 35 vascular events associated with acute cannabis use, 26% of which resulted in mortality.37 Smoking may have notable long-term risks to the respiratory system. Chronic marijuana smoking can cause airway inflammation and bronchitis,34 but the dose-dependent decline in pulmonary function seen with tobacco smoke has not been observed.38 Similarly, chronic marijuana users do not seem to have the same risk of lung cancer as tobacco smokers;39 however, more long-term data are needed to verify this finding.

There is growing literature that long-term cannabis use can lead to addiction or cannabis use disorder. The addictive potential of cannabis seems to increase the earlier in life an individual is exposed. Adolescents being in a state of rapid brain development (which includes their endocannabinoid system) are the most susceptible. Roughly one in 11 people in the general population who are exposed to cannabis becomes addicted; however, this number increases to 1 in 6 individuals when cannabis exposure is before the age of 18.40 There is concern that early cannabis exposure also predisposes adolescents to abuse other illicit substances because cannabis can dampen the brain's native reward pathways.23 Early exposure may also have irreversible effects on brain development. Individuals who started using cannabis during adolescence have shown decreased neural connectivity in certain areas of the brain involved with integration, learning, memory, and executive function.23 Although this has not yet been demonstrated for cannabis products with lower THC content or CBD products, more high-quality studies are needed to better understand their addictive potential.

Cannabis usage also appears to exacerbate underlying metal illness, specifically schizophrenia. Although no causal relationship has been established, many studies support that cannabis use can precipitate psychotic symptoms in vulnerable patients at an earlier age and potentially worsen the course of their illness 41 (Table 4). Studies also show that cannabis use increases the risk of developing anxiety and depression disorders later in life. In a study of 1,600 students aged 14 to 15 years old followed up over 7 years, weekly cannabis users had a twofold increased risk for later depression and anxiety, whereas daily users had a fivefold increased risk.42 These safety concerns pose notable challenges when it comes to ensuring safe dosing, distribution, and monitoring of cannabis products legalized for medical use.

Table 4

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Cannabis Use in Orthopaedic Surgery

Since legalization of commercial cannabis sales in Colorado, the self-reported use of cannabis has increased from 1 to 11% in patients undergoing total knee (TKA) and hip (THA) arthroplasty procedures. Patients more likely to report cannabis use were younger in age, more likely to be men, currently smoke tobacco, have a history of substance abuse, report preoperative opioid use, and carry Medicaid insurance.10 These results suggest that either more users or more patients are willing to report the use of cannabis without legal consequences.10 In addition, a survey at two orthopaedic trauma centers in Massachusetts showed that patients perceived that medicinal cannabis could be helpful to treat their postoperative pain and anxiety. Of the patients in this study who used cannabis during their recovery, 90% believed that it reduced the symptoms of pain and 81% believed that it reduced the amount of opioid medication they used.7

Limited data exist on the effect of cannabis and other cannabinoid products on orthopaedic outcomes. The existing studies are highly heterogeneous and are mostly retrospective reviews that rely on self-reported marijuana use (Table 5). The National Inpatient Sample database explored the relationship between cannabis use and mortality in common orthopaedic procedures from 2010 to 2014. Cannabis was associated with decreased mortality in patients undergoing major joint arthroplasty and femur fracture fixation.43 There was an increased odds of medical complications with cannabis use in the patients with TKA and THA including cardiac disease, heart failure, and stroke. Similarly, patients undergoing spinal fusion using cannabis had increased odds of stroke and cardiac disease.43 Another study evaluated outcomes after TKA in patients using cannabis using a large central database (PearlDiver Supercomputer).44 They found that patients using cannabis products had higher revision rates at 30 and 90 days after their index surgery. They were unable to account for confounding factors such as narcotics or illicit substance abuse. Additional evidence is needed to determine whether use of cannabis or cannabinoid products have a notable impact on medical or surgical outcomes.

Table 5

Cannabis and cannabinoid products for postoperative analgesia is an area of great public interest but with very little data to support its efficacy. Hickernell et al 9 retrospectively reviewed 81 patients undergoing THA and TKA who were given dronabinol in addition to their standard multimodal pain regimen compared with 162 control patients (Table 5). The dronabinol group had a shorter hospitalization and lower morphine equivalent consumption compared with controls; however, these findings did not reach statistical significance. A prospective study by Bhashyam et al 8 of patients undergoing treatment of musculoskeletal trauma injuries studied the effect of self-reported cannabis use on pain control. Marijuana use during recovery was associated with higher prescription opioid consumption and longer duration of use compared with patients not using cannabis during recovery. Of note, patients using cannabis before their injury had overall higher opioid use when compared with never users. Additional research in cannabis-naive patients is needed to better understand any potential correlation between medical cannabis and opioid abuse behaviors. Jennings et al 45 found conflicting data when they studied self-reported marijuana use in 71 patients undergoing TKA compared with 71 matched controls. They found no difference between groups in regard to length of stay, morphine equivalent consumption during hospitalization, readmission rates, reoperations, Knee Society Scores, range of motion, or VR-12 mental and physical component scores. No major adverse effects with marijuana were reported in this study.

Finally, although not reported in the orthopaedic literature, the use of cannabis may have deleterious effects on other areas of perioperative care. A recent study on patients undergoing endoscopic procedures demonstrated much higher requirement for sedation medications in patients with daily or weekly cannabis use.46 Cannabis users used 14% more fentanyl, 19.6% more midazolam, and 220.5% more propofol for the procedures than nonusers.46 The exact mechanism for this observation is not understood but will certainly become a safety focus moving forward.

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Challenges in Cannabis Policy Development and Research

Performing high-quality research studies on the efficacy of medical cannabis and implementing policy changes has been challenging. The federal government maintains cannabis as a schedule I substance, so no supervising government agency exists to fund cannabis research or regulate state-level policies. Many cannabis products sold in states with legalization have not undergone rigorous clinical testing by the FDA, and no policies exist to regulate the quality, consistency, potency, or medical indications for distributed products.47 Even at the state level, a major disconnect exists between the scientific community, government officials, and the public in developing cannabis policies. The current policies have taken into little account for scientific evidence, and current research in the field is of mixed quality.48

Studies in orthopaedics are limited and fail to account for cofounding variables shown to adversely affect outcomes (ie, opioid use, drug use). In addition, most of these studies have been retrospective in nature, which are unable to control the type of cannabis use (ie, inhalation versus edible), frequency, or duration of use. Furthermore, there certainly may be a difference with regard to the efficacy of cannabis in the treatment of chronic versus acute pain. To date, no studies have compared the two. Finally, with the lack of regulation, the variable amount of THC and CBD in these preparations makes the comparison of results difficult. Future studies may target cannabis-naive patients to see if the lack of "tolerance" leads to a potential decrease in opioid consumption. As such, the results of the current literature should be exercised with caution by the orthopaedic community.

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Guidance for Orthopaedic Surgeon on Medical Marijuana

Orthopaedic surgeons should understand their role in counseling patients on medical marijuana as the public interest continues to grow. Because of the federal restrictions on cannabis, physicians cannot legally prescribe marijuana, but they can "certify" it to patients for the appropriate indications. The Federal State Medical Board has provided several recommendations on how and when to certify medical marijuana.49 The physician must have a well-established relationship with the patient and provide thorough documentation of the patient's history including specific ailments and failed response to other treatments. Patients should be screened for potential exacerbating medical conditions such as addiction, mental illness, psychotic disorders, anxiety disorders, or upper respiratory illnesses.49,50 Patients need to be counseled on the risks of marijuana use and lack of standardization in product preparation along with limited clinical data to support its efficacy for certain conditions. A treatment agreement should be established with duration of use no longer than 12 months. The physician is then responsible for frequent monitoring and thorough documentation of the patients response to medical marijuana including any adverse effects. Unlike FDA-approved medications where physicians prescribe dosage and frequency, the dispensaries guide the patient in selecting the strain and dosage to use for their condition.50 Patients should also understand that medical marijuana is not covered by insurance companies. Dronabinol and nabilone are covered by insurance when used for their FDA-approved indications (Table 2); however, even then, these can be costly medications.

Unlike medical marijuana, recreational marijuana does not require physician certification and can be purchased at dispensaries in legal states (Table 1). Recreational marijuana usually contains higher THC concentration to enhance the intoxicating effects, whereas medical marijuana contains higher CBD content. Patients must be careful in choosing products at dispensaries as sometimes the THC potency in medical preparations is higher than recreational varieties.

Cannabidiol and hemp oils are managed differently than medical marijuana as they contain low levels of intoxicating THC. With the exception of three states (Idaho, South Dakota, and Nebraska), CBD and hemp oils are legal for sale without physician certification as long as they have less than 0.3% THC content.33 Unfortunately, several CBD and hemp oil products available online have been inaccurately labeled and contain lower than reported amounts of CBD and high levels of THC.51 These products have become popular for musculoskeletal aches and pains; however, limited evidence exists in the literature to support this. A recent systematic review stated moderate quality evidence that CBD was beneficial for chronic pain and spasticity, but only four trials were available for review.14 If orthopaedic surgeons want to recommend CBD or hemp oils to patients, they may consider directing patients to imported products from Europe as these are more strictly monitored and required to have THC levels below 0.2%.33 US products should be certified by the US Department of Agriculture as organic, contain no pesticides or heavy metals, and have undergone laboratory testing to ensure less than 0.3% THC content.33 Although these products are currently experimental treatments for musculoskeletal conditions, orthopaedic surgeons should remain open-minded about their therapeutic potential with more rigorous trials.

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Summary

Medicinal cannabis has been proposed to have potential opportunities for pain management; however, current literature is sparse and of limited quality. Because of the disconnect between the medical, scientific, and political communities when it comes to cannabis policy development, little regulation provides the foundational framework for well-controlled research studies. If a clear benefit can be proven with respect to pain management, there may be potential to help stem the opioid epidemic which continues to be a growing concern in our healthcare system. Finally, the potential synergistic effects and safety with opioid medications warrant further exploration before recommendations can be made by orthopaedic surgeons.

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IMAGE GALLERY

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Figure 1

Table 1
List of States in the US With Legalized Marijuana

Legalized Medical and Recreational Use	Legalized Medical Use	Legalized Medical Use—CBD/Low THC Program	Illegal
Washington	Arizona	Wyoming	Idaho
Oregon	Arkansas	Texas	South Dakota
California	Louisiana	Iowa	Nebraska
Nevada	Oklahoma	Wisconsin	Kansas
Alaska	Montana	Indiana	
Colorado	North Dakota	Kentucky	
Michigan	Minnesota	Tennessee	
Illinois	Ohio	Mississippi	
Maine	West Virginia	Alabama	
Vermont	Pennsylvania	Georgia	
Massachusetts	New York	South Carolina	
District of Washington	Maryland	North Carolina	
	Delaware	Virginia	
	New Jersey		
	Connecticut		
	Rhode Island		
	New Hampshire		
	Hawaii		
	Florida		
	Missouri		
	New Mexico		
	Utah		

Table 1

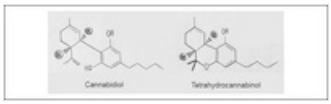

Figure 2

Table 2

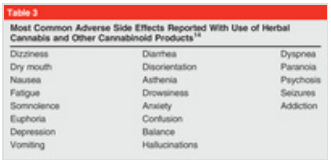

Table 3
Most Common Adverse Side Effects Reported With Use of Herbal Cannabis and Other Cannabinoid Products[14]

Dizziness	Diarrhea	Dyspnea
Dry mouth	Disorientation	Paranoia
Nausea	Asthenia	Psychosis
Fatigue	Drowsiness	Seizures
Somnolence	Anxiety	Addiction
Euphoria	Confusion	
Depression	Balance	
Vomiting	Hallucinations	

Table 3

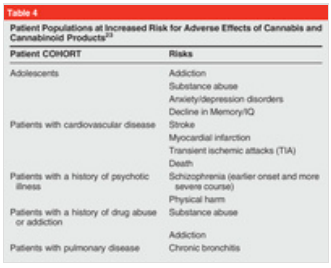

Table 4
Patient Populations at Increased Risk for Adverse Effects of Cannabis and Cannabinoid Products[23]

Patient COHORT	Risks
Adolescents	Addiction Substance abuse Anxiety/depression disorders Decline in Memory/IQ
Patients with cardiovascular disease	Stroke Myocardial infarction Transient ischemic attacks (TIA) Death
Patients with a history of psychotic illness	Schizophrenia (earlier onset and more severe course)
Patients with a history of drug abuse or addiction	Physical harm Substance abuse Addiction
Patients with pulmonary disease	Chronic bronchitis

Table 4

Table 5

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