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Review Article

Endocannabinoids in Orthopedic Surgery and Musculoskeletal Medicine: Is it Time for a Green Standard?

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Abstract

Cannabis and endocannabinoid agonists have been safely used for decades by a large segment of the United States population for both recreational and medicinal purposes [1]. The medical use of cannabis products has been legislatively restricted for decades in the United States [2]. Due to widespread enthusiasm for cannabis in American Society, no authority can deny the wide margin of safety that exists, even for chronic use [3,4]. Newly enacted legislation over the last several years has decriminalized cannabis consumption and even legalized its use in some states for both recreation and medicinal purposes [5]. Most recently, clinicians' guides to cannabidiol (CBD) and hemp oils have moved to the front seat of many prestigious clinical publications [6]. The translation of cannabinoids from herbal preparations into highly regulated prescription drugs is progressing very rapidly and healthcare practitioners must become familiar with its mechanisms and possible clinical applications [7]. These drugs and supplements may provide an unmet need in the management of patients with osteoarthritis and other musculoskeletal ailments. It may be time for a new gold standard in our approach to the clinical condition of arthritis where these pharmaceuticals play an important role.

Keywords: *Endocannabinoids; Orthopedic Surgery; Musculoskeletal Medicine; Cannabis*

Cannabis preparations are available in legal and illegal formats and may or may not include the active agent, delta-9-tetrahydrocannabinol (delta-9-THC) found in traditional cannabis sought out by the counter-culture [8]. Availability of the legal pharmaceutical and the legal and illicit formats of the drug/supplement in the United States varies widely and is largely dependent upon constantly changing state and federal laws [9]. This constantly changing climate has left many orthopedic surgeons and other healthcare providers to speculate on the appropriate way to answer questions patients present regarding endocannabinoid agonists [10].

This article seeks to familiarize the orthopedic surgeon and other musculoskeletal healthcare providers with the information they need to be able to counsel patients appropriately about the potential risks, benefits, alternatives and complications associated with endocannabinoid management and dosing. While endocannabinoids are well tolerated, they are not benign, with the two most common side effects being anxiety and mood alterations and more serious complications have been reported [11]. These complications are likely to be patient specific and may be difficult to predict due to cognitive variability in the general population and to uncertain dosing in unregulated preparations. Some authors have suggested a maintenance dose of 10 - 20 mg/kg CBD administered daily in divided dosing based on clinical response, while others have recommended adhering to the same "start slow and go slow approach guidelines" published for cannabis by the state of California [12]. We agree with the concept of starting low and proceeding in a slow and deliberate fashion with treatment. We believe that an understanding of the generally tolerated dose response curves suggested in the current literature may represent a good 'starting point' for that approach.

While the sativa plant contains at least 113 phytocannabinoids, for the purposes of this discussion, the two primary molecules that have been recently exploited for their medical uses in the United States and elsewhere are delta-9-THC and CBD. The psychotropic effects of endocannabinoids are distinct from the anti-inflammatory and immunomodulatory effects. CBD exceedingly antagonizes psychotropic effects from the D9THC molecule through competitive inhibition for the same receptor. This is an important point for understanding accurate endocannabinoid dosing of different preparations and potential indications for management with different preparations and how CBD functions in biological systems.

The endocannabinoid system

Delta-9-Tetra-hydrocannabinidol is the psychotropic drug that is derived from the cannabis sativa plant. CBD also comes from the cannabis sativa plant, however in that setting becomes illegal for study, distribution, or use unless permission to study cannabis sativa

is provided by the DEA and application to obtain samples from the University of Mississippi to study have been granted [13]. There is no psychoactive substance present in hemp alone, from which the molecule, CBD, can be harvested, concentrated and distributed without fear of prosecution.

Cannabidiol is a phytocannabinoid discovered in 1940. It is one of 113 identified cannabinoids in cannabis plants and accounts for up to 40% of the plant's extract [14]. From 2018 until present, clinical research conducted includes preliminary studies on the correlation of cannabidiol and the effect it has on cognition, movement disorders, anxiety, and pain [15]. Recently there has been a deluge of literature, as well as additional supportive studies on the topic, however, well-designed scientific studies are lacking [16].

CBD is widely recognized due to heavy marketing [17]. Where CBD, THC and Cannabis are concerned, there is much confusion in the general public [18]. This confusion leads to corporate opportunity and patient extortion. Appropriate stewardship on the part of the orthopedic surgeon demands building a reasonable immunology knowledge base to gain the ability to be conversant with patients and colleagues concerning modern immunobiologic concepts and technologies, including cannabinoids. The safety data gleaned from the Epidiolex® biostatistical experience shows that CBD has a broad spectrum of safe dosages with surprisingly few side effects that when present, are very well tolerated by the vast majority of patients [19]. Benefits clearly outweigh risks in this setting.

The hemp plant does not contain the phytochemical Delta-9-THC. Because CBD oil is derived from the hemp plant that does not contain the Delta-9-THC molecule, it is not illegal or subject to regulation. CBD is not psychoactive, meaning it does not provide euphoric effects, because it primarily binds a different receptor than Delta-9-THC. The CBD molecule from the Hemp plant is available for widespread distribution and consumption. Extremely high margins make it desirable from a distribution standpoint and hundreds of US companies have answered the call. Hundreds if not thousands of unregulated CBD preparations are now available in and outside the US, although permits for industrializing hemp must be applied for from state and sometimes federal authorities. The massive income potential has led to early corruption and that is likely to remain a problem [20].

This pathway has opened up novel treatment options for patients who are inundated with online marketing of CBD that can also be purchased at both legitimate pharmacies but also convenience stores everywhere across the nation. Given the lack of regulation and oversight, the chance for pseudoscience is high and the field faces the same potential setback that signaling cell treatments have experienced due to clinician greed and irresponsibility. Careful stewardship is required to maintain field integrity and patient respect.

Most patients will present questions about typical unregulated CBD products that can be found at CVS® or Walgreen's®. It is important to explain that unregulated means there is no guarantee of contents, no matter where it comes from. These companies have no obligation to the FDA, you, or your patients. It's also important to point out to patients that in spite of having a scientific mechanism for functional molecular effects, those quantum changes may have no translation to what is observed at the clinical level where classical mechanics are observed. In addition, studies to date have been primarily anecdotal and unscientific, leading many to shy away from CBD as a legitimate medical treatment option.

Given the potential of these cannabis sativa-derived medications to eradicate suffering and fill a void in treatment that currently exists, further scientific study is needed. Patients should be instructed that no indication for pain management currently exists, although anecdotally there have been too many reports of significant musculoskeletal pain reduction to ignore. Going forward it is impossible to ignore the potential evolving therapeutic role of endocannabinoids in orthopedic surgery.

Cannabis sativa-CBD from Delta-9-THC containing plants

The FDA has approved *Cannabis sativa*-derived CBD drug Epidiolex®, which contains a purified form of the drug substance cannabidiol, for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older [21].

While the market for this drug is small, the availability of and the opportunity for providers to prescribe a pure, FDA approved CBD oil concentrate in an off-label format has not escaped the notice of the medical or patient community.

Epidiolex® costs approximately $1500 - 2000 for a one-month supply typical for an anti- inflammatory effect in the setting of musculoskeletal disease. Dose response curves indicate that the anti-inflammatory/immunomodulatory effect can be consistently achieved in healthy adults by placing 5 - 20 mg/kg/day sublingually, with most adults in our clinic using equal to or less than 5 standard dropperfuls sublingually each day as needed. However, most patients are not obtaining CBD dosing by means of the FDA approved formulation due to high costs of the drug and healthcare practitioners being reluctant to embrace the off-label prescribing required.

General merchandise, over-the-counter CBD varies widely in cost, quality and purity. The lack of federal oversight explains the dozens of confusing brands, applications, formulations and concentrations of CBD products. Scientific study is non-existent with any of the OTC preparations; 1000 and 3000 mg preparations are popular and cost anywhere from $20 - 80 depending on the brand, purity and concentration claims.

Costs for Epidiolex® when prescribed off-label are high. These costs are prohibitive for most patients, leaving a large void in the market that has been filled by mainly low-cost operations acting regionally to maximize profit. These models too often sacrifice purity with little detail to good manufacturing process (GMP) and quality control. With an emphasis on profits instead of patient care, there is high risk for exploitation. Lack of any oversight or regulation complicates conditions.

To review, because CBD from the hemp plant is not regulated as a drug by the FDA, whereas CBD from the cannabis sativa plant is, hemp CBD is not subject to FDA regulation or oversight, leading the buyer to beware, start very low and go very slow until familiar with the effects of the preparation they have selected. This is reminiscent of the labels that have been affixed to prescription bottles for decades warning patients to become familiar with the effects before "attempting to operate heavy machinery".

What is the science?

The desirable clinical effects of endocannabinoid agonists emerge from a scientifically described mechanism that has enabled its classification by the US Food and Drug Administration is an anti-inflammatory, antioxidant and immunomodulatory drug [22]. The endocannabinoid system has emerged as a viable target of pharmacotherapy. This was confirmed by a recent U.S. Government patent on CBD, leading some to speculate that widespread endocannabinoid use has been checked more by technology transfer than legalization issues [23].

The well documented anti-inflammatory and immunomodulatory properties of endocannabinoids have been confirmed by multiple competing labs worldwide [24]. Over the last decade, an eyebrow has been raised towards using endocannabinoid small molecules as pharmacologic treatments for many conditions, including orthopedic manifestations of pain syndromes [25]. This focused interest has only recently surfaced and exploded in the U.S. and has secured a widespread, attentive, nationwide audience. Some authors have suggested a complementary role for endocannabinoids in orthopedic rehabilitation, joint or spinal injections, but they may play a more primary role in symptom management going forward. It may be that these drugs step in front of NSAIDs in the armamentarium of the treating clinician in the setting of arthritis. Given the favorable safety profile and the availability of CBD, consideration should be given to realistically prescribing these supplements where purity is assured. If efficacy is comparable in randomized clinical trials, CBD will emerge the clear winner.

While there is accumulating scientific evidence for the clinical application of endocannabinoids, the scientific guidelines for treatment remain sparse. Viable dose-response curves have yet to be determined. This has led to confusion among both patients and physicians. Scientific evidence for a legitimate mechanism of action can no longer be disputed. However, a predominance of case reports and anecdote

dominate the present 'scientific' literature where endocannabinoids are concerned. This weakens the position of the prescribing physician when managing patients because validated, properly done studies to review the effect of endocannabinoids for musculoskeletal pain are lacking [26].

In a recently introduced publication, The American Journal of Endocannabinoid Medicine (AJEC), the authors present some worthwhile scientific documentation and make noteworthy suggestions about future direction where agonists of the endocannabinoid system are concerned. A textbook is now available on the botany and biotechnology of Cannabis Sativa for interested readers who want to expand their knowledge base [27].

A new green standard?

Currently, there are approved medications to treat musculoskeletal pain that are based on achieving anti-inflammatory effects [28]. NSAIDs and DMARDS both have significant dose and non-dosage related complications [29,30]. NSAIDs are among the most commonly used drugs worldwide and their beneficial therapeutic properties are thoroughly accepted. However, they are also associated with gastrointestinal and cardiovascular adverse events that include a not insignificant risk of mortality [31,32]. NSAIDs can damage the entire GI tract including a wide spectrum of lesions [33]. About 1 to 2% of NSAID users experienced a serious GI complication during treatment. The relative risk of upper GI complications among NSAID users depends on the presence of different risk factors, including older age (>65 years), history of complicated peptic ulcer, and concomitant aspirin or anticoagulant use, in addition to the type and dose of NSAID [34].

While theoretically, enzyme-specific cyclooxygenase-2 (COX-2) specific drugs could eliminate some of the complications associated with traditional NSAIDs, in a recent large study, COX-2 inhibitors were associated with an increased risk of upper gastrointestinal adverse events, especially abdominal pain [35]. Other authors have also found an increased risk of cardiovascular adverse events with COX-2 inhibitors, namely hypertension, heart failure and edema that compares to that found in the setting of traditional NSAID dose administration. At moderate doses, celecoxib was found to be noninferior to ibuprofen or naproxen with regard to cardiovascular safety [36].

Disease modifying anti-inflammatory medications are commonly indicated in inflammatory arthritic conditions. Because the inflammatory pathways in osteoarthritis and inflammatory arthritis involve the same canonical and non-canonical pathways, these drugs have utility in the management of both. The insured population of patients with osteoarthritis is ten times greater than patients with inflammatory arthritis. Patients with inflammatory arthritis are commonly on two separate biologics that cost in excess of $100k yearly. These drugs are expensive and additionally come with a heavy side effect profile that is often poorly tolerated by patients [37].

Currently a void exists for patients with osteoarthritis whose third-party payor will not cover immunobiologics due to limitations imposed by third party fiduciary responsibilities to stockholders and board members. It would be unreasonable to ask third party payors to bankrupt themselves to provide gold standard patient care. Care has become very polarized with the wealthy or 'disposable income' populous often receiving more cutting-edge technological care, which works out when the technology is legitimate.

The safety profile for cannabis as an anti-inflammatory drug appears superior to that of other available pharmacologic options so far, demanding a closer look at the drugs as not only fulfilling a legitimate medical use, but limiting costly and unnecessary complications arising from NSAID and DMARD use. There has never been a marijuana-related death placed on record. Endocannabinoids are not addictive. The addiction profile of CBD in particular is non-existent, confirmed by trials demanded for FDA clearance of Epidiolex.

Adding complexity to clinical treatment recommendations is the fact that available retail preparations are likely to be inequivalent and so dosing may be inconsistent, causing clinical condition to deteriorate. Currently 69% of CBD containing products have inaccurate labels [38]. Typically patients should look for larger brands like those carried by major drug store chains like CVS®. CVS only carries MedTerra® and other specific brands selected for good manufacturing practice (GMP) and demonstrated quality controls.

Endocannabinoids in orthopedic surgery

Endocannabinoids (ECs) have been studied scientifically and the pharmacologic mechanism of action has been discovered [39]. Considerable clinical and administrative challenges persist including purity of dosing, dosing strategy, lack of conformity between state and federal cannabis and hemp laws, product inconsistency and lack of research funding. Many of these problems could be subverted with the designation of an authoritative governing body with the appropriate background and training to represent leadership [40].

Healthcare professionals are being pressed by patients due to direct to patient advertising and massive word of mouth campaigns that have escalated dramatically over the last decade. The discovery of the endocannabinoid system as an endogenous, immunomodulatory, spatiotemporally based, anti-inflammatory pathway that could be modified by safe, readily available exogenous phytocompounds has literally sparked a revolution in health care and given patients a safer alternative to the Non-Steroidal Anti-Inflammatory Drugs and Disease Modifying Anti-Rheumatic Drugs.

The number of complications arising from the use of NSAIDs and DMARDs in the USA are enormous and add significantly each year to US healthcare costs. Some authors have suggested using endocannabinoids before transitioning patients to the harsher pharmacologic treatments, potentially earning ECs a permanent role in the management of osteoarthritis and inflammatory arthritis. Co-administration of ECs may enable patients to lower their dosage of NSAIDS and enhance safety profiles, but studies to demonstrate that potential advantage have not been done to our knowledge.

Recently, a feature article from Orthopedics Today® described how physicians have explored cannabinoids as pain management solutions [41]. Recommendations were made for adjunctive treatment of orthopedic surgical problems with co-administration of cannabinoids. Other authors have independently described how cannabinoids have become valuable as novel anti-inflammatory drugs [42].

The discovery of Delta-9 tetrahydrocannabinol as the major psychoactive ingredient in marijuana as well as the endocannabinoid system and endogenous ligands prompted a search to define the immunomodulatory signaling pathways involved [43]. Recently, the application of CBD in multiple clinical settings has been exploited and demand is at an "all-time high.

The endocannabinoid system, the CB2 TRV1 receptors on immune cells may plan an anabolic role in the inflammatory process and through immunomodulatory pathways, diminishing release of TNF-alpha and IL-1 beta. NSAIDs are the most commonly prescribed medications for arthritis and are the mainstay for symptom management in musculoskeletal disease. However, these drugs are not benign, and complications can be serious including severe gastrointestinal hemorrhage and death.

There is a role for endocannabinoids in the setting of musculoskeletal disease due to their excellent tolerability profile.

The endocannabinoid system follows immunomodulatory transduction signaling pathways. Intrinsic endocannabinoids are made on demand in the cell membrane and are built on G-protein coupled receptors called CB1 and CB2. Normal endocannabinoid system function is required for normal human physiology and cerebral function [44].

Improved behavioral markers of cannabinoid intake are required [45].

Conclusion

Endocannabinoids have been safely used by the public in the United States since 1962 and by cultures around the world for centuries as inebriants and medicines with magical powers often ascribed to their prescribed use. Modern science has taken away the magic potion hysteria wrongly brought about by a 'reefer madness' campaign that needlessly frightened the public and resulted in a decades-long setback in the development of endocannabinoids as legitimate medicines.

It's another of life's ironies that the diseases endocannabinoids seem to address best are those that represent the ultimate scourges of mankind: Cancer and its sinister complications, including glioblastoma multiforme, pediatric electro conduction disruptions in the brain and opiate addiction. It may be worth noting for future endeavors, that if each of these specific indications now verified by the FDA were revoked, a sinister gap in treatment would remain for these patients who would go back to suffering needlessly.

The primary limiting factor when it comes to prescribing endocannabinoids is the unknown dose-response curve. Adding insult to injury, there is no guarantee of therapeutic continuity in treated individuals due to preparation variability and a lack of a strictly standardized preparation protocol designed to assure the availability of a homogenous product of defined stability [46]. To subjugate this problem, experts have recommended a start low and go slow. Based on our preliminary clinical data, patients using the 1000 - 3000 mg tincture preparation typically benefit from administration of 5 - 10 drops sublingually each day in a 70 kg individual corresponding to approximately 10 - 20 mg/kg/day. It is worth emphasizing once again that starting at a low dose and titrating for effect is likely to be the most valuable approach clinically.

Future Directions

The introduction of the American Journal of Endocannabinoid Medicine's may provide a service to the field by introducing the journal for scientists and clinicians interested in these valuable native intrinsic molecules and their immunologic signaling pathways [47]. Understanding these pathways and how they fit into sapiens metabolism in multiple tissue disease states is likely to spur additional research and development into endocannabinoid small molecule agonists and fill additional treatment gaps.

Large word of mouth campaigns and myriad internet offerings troll the high and low ends of the CBD market with alternative products. Patients are actively seeking these preparations and may be particularly vulnerable to exploitation as many have lost hope for obtaining meaningful pain relief and will to try anything, however absurd the price tag. Orthopedic surgeons should develop a well thought out and studied protocol using endocannabinoids as pain relievers in specific settings of musculoskeletal disease.

Endocannabinoids work in at least some patients, we believe, through immunological signaling pathways we are targeting to relieve symptoms. The field deserves further study and we are in favor of these methodologies for many reasons, chief among them being the diminished chance of habituation and efficacy in musculoskeletal pain treatment. We believe this is an ideal class of drug to be studied conservatively, appropriately and with intention to treat based on the established track record. Determining ideal dose schedules, determining monitoring, adverse effect profiles, secondary effects and ease of therapeutic removal are key moving forward.

Patients can consider coming out of pocket for what appears to be a safe alternative to anti-inflammatory medication in the setting of CBD preparations. Patients should understand that anecdotal evidence is not science and that currently a lack of scientific data exists. In our opinion, these drugs could be considered as seemingly safe, non-opioid options that may provide significant pain relief with little risk and certainly less risk than other available anti-inflammatory drugs. Due to the massive downside of complications related to NSAIDs, DMARDS and opioids, we recommend considering endocannabinoids as more than just adjunctive care and think there may be a permanent clinical role for their utilization that will follow patient demand.

Patient FAQs

1. Is this a realistic treatment alternative that is based in scientific fact? Yes. CBD products have a viable mechanism of action and act through immunomodulatory signaling pathways. If you are taking a CBD drug or supplement it will have a biologic effect on you via its small molecule interaction with your cell surface receptors. This causes an anti-inflammatory effect at the nanomolecular level that can translate clinically to symptomatic pain relief.

2. How does it work? CBD sets off immunomodulatory signaling pathways that antagonize inflammation and attenuate the inflammatory response.

3. Is this a safe alternative to other treatment options? CBD is extremely well tolerated with very few patients experiencing nausea or anxiety that required stopping the drug or supplement.

4. What conditions could be considered appropriate for a trial of CBD? While specific indications exist for Epidiolex®, we believe that a trial of CBD may be indicated in cases of osteoarthritis, prior to initiating NSAID therapy or DMARD therapy. Similarly, in the setting of inflammatory arthritis, a trial of CBD may be prudent prior to initiating more complicated pharmacotherapies.

5. What is the best brand of CBD? There is no one 'best brand'. Rather consumers are cautioned to do their own research to determine whether or not products use GMP and exercise routine quality controls. Two companies that have distinguished themselves have been MedTerra®, Charlotte's Web®.

6. Is this a waste of my time and money? CBD preparations are well tolerated drugs and supplements with a notable safety profile thanks to the FDA approval process that Epidiolex® went through. Results following treatment may be more predictable with standard preparations like Epidiolex although treatment costs may be prohibitive.

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