Understanding Cannabis-Based Therapeutics in Sports Medicine

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Context: With increased use of cannabis-based products by the public for both recreational and medical use, sports medicine clinicians should be informed of historical context, current legal considerations, and existing evidence with regard to efficacy, safety, and risks in the athletic community.

Evidence Acquisition: A review of ClinicalTrials.gov, MEDLINE, and CINAHL from 2015 to present was conducted with emphasis on the most recent literature using search terms, *cannabis*, *nabiximols*, *cannabinoids*, *pain management*, *THC*, *CBD*, and *marijuana*. Bibliographies based on original search were utilized to pursue further literature search.

Study Design: Clinical review.

Level of Evidence: Level 3.

Results: At present, limited high-quality studies exist for use of cannabinoids for acute pain, chronic pain, or concussion. None of the trials involving cannabinoids included the athletic population. Thus, results from this clinical review are extrapolated to conditions of the sports medicine population. For acute pain, 2 small-randomized double-blinded crossover trials concluded no immediate effect of cannabinoid therapy. More robust evidence exists for treatment of chronic pain conditions through meta-analysis and systemic reviews. Cannabinoid therapy exhibits moderate efficacy as a treatment for some chronic pain conditions. Investigations included a broad spectrum of chronic pain conditions, including neuropathic, musculoskeletal, inflammatory, and central pain conditions, and reveal reduction in pain and improvement of quality of life with limited adverse effects. For concussion, evidence is based on preclinical in vitro and animal models revealing possible neuroprotective effects as well as 2 clinical studies involving the presence of cannabinoids for concussion (some sports-related), but there are no high-quality trials evaluating efficacy for treatment with cannabinoids at this time.

Conclusion: Although various biochemical explanations exist on the use of cannabinoid therapy through modulation of the endocannabinoid system for several medical issues affecting athletes, recommendations from clinicians must be extrapolated from a majority of research done in the nonathletic population. Lack of strong-quality clinical evidence, coupled with inconsistent federal and state law as well as purity issues with cannabis-based products, make it difficult for the sports medicine clinician to widely recommend cannabinoid therapeutics at present. Future larger, higher quality clinical research studies with standardized pure extracts will better guide appropriate medical use going forward. At present, evidence for a multitude of therapeutic applications is emerging for cannabinoid treatment approaches. With emphasis placed on patient-centered clinical decisions, cannabinoids hold promise of treatment for athletes with chronic pain conditions. Clinicians who treat the athletic community must consider legal and ethical issues when discussing and recommending the use of cannabinoids, with acknowledgment of inconsistencies in purity of various formulations and concerns of drug testing.

Keywords: cannabinoids; THC; CBD; cannabis; medical marijuana; endocannabinoid system

The use of medicinal cannabinoids has skyrocketed in recent years. Clinical research into the potential therapeutic benefits of cannabinoids derived from the botanical genus *Cannabis* has also been growing exponentially.¹² Athletes and

former athletes alike are using and promoting cannabinoids for treatment of a multitude of ailments and indications without established evidence to support efficacy. This article serves to discuss the major cannabinoids, Δ^9 -tetrahydrocannabinol (THC)

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and cannabidiol (CBD), and provide an understanding of the role and interaction of these phytocannabinoids with the body's endocannabinoid system (ECS).

Cannabis has been used as a traditional medicine for centuries. In light of changing perspectives and legislation in the United States, cannabis medicine has emerged as a possible therapeutic option for athletes. In contrast to recreational use, medical cannabis therapy focuses on enhancing or modulating the body's vast ECS: a complex, interactive, and essential endogenous homeostatic regulatory system with a significant role in modulation of pain and inflammation, which has classically been regarded as the system that contributes to the body's capacity to "relax, eat, sleep, forget and protect."⁷

The 2 major cannabinoids derived from *Cannabis* are THC and CBD; however, over 100 phytocannabinoids have been identified, in addition to a multitude of naturally occurring terpenes, flavonoids, and other chemical compounds that constitute the plant.³⁹ At present, 2 types of cannabinoid receptors have been identified in the ECS; the CB₁ receptor, ubiquitous in the central nervous system, and CB₂ receptor, predominantly present on immune cells. CB₁ receptors are present in central and peripheral neurons and nerves; activation of these receptors appear to regulate excitatory and inhibitory neurotransmitters through retrograde synaptic messaging.³⁸ CB₂ receptor activation leads to alteration in pro-inflammatory cytokine release from immune cells and modulates migration of immune cells to reduce inflammatory response.³⁸ As a result of CB₁ activation, nociceptive sensitization is suppressed, and together both CB₁ and CB₂ receptors have roles in mediation of inflammatory pain.¹⁰ THC interacts with both CB₁ and CB₂ receptors as a partial agonist with less efficacy than endogenous cannabinoids, anandamide (AEA), and 2-arachidonoylglycerol (2-AG).³⁸

On the other hand, CBD interacts with CB₁ receptors as an allosteric modulator, binding to an alternative site and negatively affecting the efficacy and potency of agonists, such as THC or 2-AG.²² CBD is recognized to also modulate other receptors, such as 5-hydroxytryptamine (serotonin) receptor 1A, μ - and δ -opioid receptors as well as transient receptor potential vanilloid type-1, peroxisome proliferator-activated receptor gamma, and fatty acid amide hydrolase, an enzyme responsible for the breakdown of endocannabinoids AEA and 2-AG.²² The promiscuity of CBD among multiple targets may contribute to anti-inflammatory properties by not only acting as an antioxidant but also inhibiting expression of cytokines and transcription factors (interleukin[IL]-1 β , IL-2, IL-6, tumor necrosis factor- α , interferon- γ , chemokine ligand 3, CCL4, and nuclear factor- κ B).²⁸

FEDERAL AND STATE REGULATIONS

Cannabis has been regulated in the United States by a combination of consumer protection laws including the Pure Food and Drug Act of 1906, the Marihuana Tax Act of 1937, and the Comprehensive Drug Abuse Prevention and Control Act of 1970, which included the current Controlled Substances Act

(CSA).¹³ The CSA classifies cannabis as a Schedule I substance, which is the most restrictive category of medications, citing no currently accepted medical use of herbal cannabis.²⁹ Most recently, the 2018 Farm Bill legalized the production of hemp, making it an agricultural commodity, allowing an influx of hemp-derived products into the marketplace, especially CBD products containing less than 0.3% THC on a dry weight basis.^{13,44}

Despite federal regulations outlined above, synthetic THC products, dronabinol and nabilone, were approved by the Food and Drug Administration (FDA) for chemotherapy-induced nausea and vomiting, with dronabinol also approved for AIDS-associated anorexia in 1985.^{45,47} Epidiolex is a CBD extract recently approved and regulated by the FDA for specific pediatric seizure syndromes.⁴⁶ In addition, nabiximols (Sativex), an oral mucosal preparation of 1:1 ratio of THC:CBD extract, is approved in Europe and Canada for the treatment of multiple sclerosis spasticity.⁹ Nabiximols is currently an investigational product in the United States involved with multiple clinical trials for pain, and GW Pharmaceuticals plans on seeking FDA approval for use in the United States.¹⁷ With pharmaceutical grade cannabis-derived products available, clinical research efforts have expanded, with increased strength in methodology due to consistent dosing and administration.

In the United States, criminalization of cannabis is enforced on the federal, state, and local level. Through legislative approach, individual states have adopted medical and recreational access laws. As of June 2019, 33 states and the District of Columbia have approved a comprehensive policy making medical cannabis available to residents. An additional 13 states allow the use of "low THC, high CBD" products for specific medical conditions, leaving only 4 states (Idaho, South Dakota, Nebraska, Kansas) without some degree of medical cannabis legislation.³² Since 2012, a total of 14 states and territories of the United States have passed legislation legalizing cannabis for recreational use for adults older than 21 years.³²

At this time, there is a palpable dichotomy of expanding access to cannabis from both a medical and a recreational standpoint, while simultaneously enforcing strict marijuana possession laws. This polarity of accessibility has put the medical community in a difficult position with regard to making evidence-based recommendations when it comes to the use of cannabis for pain and other chronic conditions.

ATHLETIC COMMUNITY

Cannabinoids have been used for centuries to treat ailments that may affect an athlete. Recently, a community-based cohort of adult athletes was examined using The Athlete Pain, Exercise, and Cannabis Experience (PEACE) Survey to explore cannabis use among 1161 participants with 26% acknowledging current cannabis use; approximately 63% of the current cannabis users reporting exercise 5 to 7 days per week and more than 50% of those athletes reporting chronic pain lasting more than 3 months.⁵³ Physical activity appears to enhance the ECS, with evidence supporting exercise increases levels of anandamide, to

produce analgesic effects and support mental and physical well-being, commonly acknowledged as “runner’s high.”^{6,51}

CONSIDERATIONS FOR THERAPEUTIC USE IN ATHLETES

Acute Pain

Research for treatment of acute pain with cannabinoids in humans has been very limited in the past due to the scheduling of cannabis, with small studies providing limited quality evidence for efficacy. A small, randomized, double-blinded, placebo-controlled crossover study on 15 healthy participants found a dose-dependent response to perception of pain in a capsaicin-induced localized intradermal pain model using cannabis with varied doses of THC.⁴⁹ Findings revealed there was no change in pain perception with all doses after 5 minutes of administration. However, at 45 minutes, participants reported a significant decrease in induced pain with the moderate dose, an increased pain perception with the higher dose, and still no change with the lower dose.⁴⁹ Another small double-blinded, randomized, crossover study of 18 healthy female volunteers with sunburn-induced and intradermal capsaicin pain models determined that oral cannabis extract capsules had no effect on acute pain perception.¹⁹

Recovery

Many products are being marketed for improved recovery time and decreased muscle soreness specifically targeting sleep and anti-inflammatory properties. Unfortunately, there are no studies specifically evaluating cannabinoids as a recovery aid in exercise. Many inflammatory markers have been linked to delayed-onset muscle soreness, muscle fatigue, and inflammation.⁸ Specifically, CBD intake has been linked to decreased levels of the inflammatory marker IL-6, which may be related to accentuated muscle recovery.⁴

Many athletes relate sleep quality to recovery and sport performance.¹⁶ A narrative review in collaboration with the National Collegiate Athletic Association (NCAA) Interassociation Task Force on Sleep and Wellness recently published recommendations for collegiate athletes to focus on sleep improvement for overall health, academics, and athletic performance.²⁰ CBD has been linked to therapeutic improvements in sleep at higher doses, with stimulating effects noted at lower doses.¹

Chronic Pain

Evidence appears more robust for cannabinoid therapy in chronic pain, where pain reduction has been observed and an opioid-sparing effect has been documented.^{2,36} A systematic review including 18 good-quality, randomized-controlled studies revealed that cannabinoids, in various routes of administration and doses, demonstrated modest efficacy overall, without serious adverse effects in the treatment of chronic noncancer pain.²⁴ Another systematic review of 79 trials (28 of which specifically addressed chronic pain) included numerous

preparations of cannabis or synthetic cannabinoids, with varying routes of administration. Trials focusing on chronic pain included a broad spectrum of chronic pain conditions, including neuropathic, inflammatory, central, musculoskeletal, and rheumatologic. The authors concluded that in comparison with placebo, a greater number of patients utilizing cannabinoid-based products experienced a reduction in pain ratings of at least 30%, with conclusive moderate-quality evidence for treatment of chronic neuropathic pain, cancer-related pain, and spasticity associated with multiple sclerosis.⁵² Subsequently, the National Academies of Sciences, Engineering and Medicine created a panel of 16 experts from various specialties in 2016 to evaluate the state of medicinal cannabis through a systematic review process with considerations of primary research articles. The panel concluded that there is conclusive or substantial evidence that cannabis or cannabinoids are effective in the treatment of chronic pain in adults.²⁹ Additionally, retrospective surveys of 185 chronic pain patients on opioids revealed a self-reported 64% reduction in opioid use with medical cannabis therapy. Participants on chronic opioids using medical cannabis reported 45% improvement in quality of life and reduction of opioid-associated side effects.²

The aging athletic population often suffers the painful consequences and limitations of osteoarthritis. Recent investigations into the ECS have acknowledged its role as an important mediator of disease progression; both CB₁ and CB₂ receptors are expressed in cartilage, bone, and synovial tissue, with cannabinoids modulating inflammation and reducing joint damage, suggesting a chondroprotective effect on joints.²⁷ Modifications in ECS activity have been observed in preclinical and clinical investigations during osteoarthritic pain states with an increase of 2-AG and upregulation of CB₁ and CB₂ receptors on plasma lymphocytes of patients suffering from osteoarthritis in comparison with healthy participants.²¹

Concussion

There is limited clinical research investigating the use of cannabinoids in the treatment of sports-related concussion. Proposed therapeutic effects are based on preclinical data demonstrating that modulating the ECS after traumatic brain injury (TBI) can have protective effects from these types of injuries.³⁷ Two recent reviews in both animal models and in vitro studies have demonstrated a wide variety of potential mechanism for this, including reductions in cell death and inflammatory cytokines, enhanced neuroplasticity and neurogenesis, improved calcium channel regulation, and reductions in hemodynamic disruption.⁴⁰

Two recently published studies explore the clinical use of cannabinoids in TBI and concussion populations. An observational study of 538 patients with severe TBI showed that participants who tested positive for THC at the time of their TBI had a lower mortality rate.³⁵ The second study investigated the impact of alcohol, cigarette smoking, and cannabis use postconcussion in 307 patients diagnosed with concussion in the emergency room (77 sports-related). The authors found that

participants who used cannabis after concussions had lower severity scores at 3 and 4 weeks postinjury, but did not lead to quicker resolution of symptoms by 4 weeks.²³

Regulation and Quality of CBD Products

Although not classified as a dietary supplement (DS) by the FDA, CBD has similar issues to DS in regard to mislabeling and contamination. Since consumer CBD-based products are not considered pharmaceutical agents, manufacturing does not have to meet the stricter FDA guidelines of pharmaceuticals for production and testing.⁴³ This mislabeling resulted in 7 warning letters in 2019 stating products did not contain the levels of CBD that were advertised on the packaging and that they were illegally marketing for therapeutic and medical usage.¹⁴

In 2017, 84 products from 31 companies were purchased online and tested for CBD content and contamination, with 69% of the products containing different levels of CBD than advertised and 21% of samples containing THC, with some THC levels that could produce intoxication or impairment.³ Counterfeit CBD products containing a dangerous synthetic cannabinoid were determined to be the cause of 52 sickened patients resulting in 31 emergency department visits in 2017 in Salt Lake City.⁵ For this reason, athletes who consider using CBD products available on the marketplace should be conscious of quality and seek formulations with verified testing of ingredients. By consulting with a physician for medical cannabis certification, patients may obtain products at a dispensary where third-party testing information can be requested, and quality control measures are in place.

Safety and Side Effects

Because of relative infancy in terms of FDA oversight in regard to consumer CBD products, as well as no oversight of dispensary supplied cannabis-based products, information in regard to safety and side effects profiles is relatively scarce and rapidly evolving. The FDA has continued to provide consumer updates with regard to cannabis, stating in part that the regulatory body has only approved 1 CBD product, Epidiolex.¹³ The FDA is clear that CBD, like any substance, has the potential to cause harm, including liver injury, interactions with other drugs (prescription and nonprescription), and increased sedation or drowsiness when combined with other central nervous system depressants such as alcohol.^{14,15} Additionally, short-term side effects of CBD can include somnolence, gastrointestinal distress, and irritability/agitation, all of which can be improved with stopping CBD or decreasing the dose.¹⁵ The unknown long-term effects of CBD use, how CBD affects the developing brain, fetus or breastfed newborn, and any potential reproductive effects are grounds for the FDA to remain cautious at this time about recommending cannabinoid-based products for a broad range of indications outside of limited scope of approval for Epidiolex.¹⁵

For medical cannabis products, THC-mediated side effects are most commonly drowsiness/fatigue, dizziness, dry mouth, cough (with inhalation), anxiety, nausea, cognitive effects,

euphoria, blurred vision, and headache. These dose-dependent and highly variable side effects may be mitigated by slow titration of THC, THC dose reduction, and use of products in combination with CBD.²⁵ As a result, all use of cannabis-based medicine is recommended under the supervision of a qualified and knowledgeable clinician.

Athletic Community

US sports leagues' and amateur governing bodies' stances on cannabinoids vary greatly with regard to testing, policies, and enforcement (Table 1). While several leagues do not have specific language in their collective bargaining agreements with regard to CBD, they often classify it based on its relation to cannabis. The National Basketball Association states CBD is banned under language "marijuana and related by-products," and the NCAA states "any substance that is chemically related to one of the (prohibited substances) classes, even if it is not listed as an example, is also banned."^{30,31} THC is on the banned list for the NCAA. The World Anti-Doping Agency (WADA) and United States Anti-Doping Agency (USADA) removed CBD from their prohibited lists in 2018, while all other cannabinoids remain prohibited in competition.³¹ Very recently, Major League Baseball removed marijuana from its list of drugs of abuse, and violations will be treated similar to alcohol incidents with only mandatory evaluation and voluntary treatment.¹¹

The risk of impurity and poor manufacturing has lead several governing bodies to issue official warnings to their athletes. WADA warns: "while cannabidiol is not prohibited, athletes should be extremely cautious because it is nearly impossible to obtain a pure CBD extract or oil from the cannabis plant. Anyone who buys a CBD oil, extract, or other CBD product should assume that it is a mixture of CBD and other prohibited cannabinoids."⁴⁸ USADA echoes this warning, stating "the use of any CBD product is at the athlete's own risk."⁴¹

Given that athletes are more likely to use DS than nonathletes, athletes are at risk for inadvertent doping and, therefore, potentially failing drug screening.¹⁸ For example, in 2019, a triathlon champion athlete accepted a 6-month ban from USADA after testing positive for THC after using an over-the-counter CBD cream for an ankle injury.⁴² As cannabis use lacks performance-enhancing effects, and athletes are seeking nonopioid pain therapeutics, considerations to lift institutional bans on cannabinoid-based medicine use remain a hot topic among the athletic community.⁵⁰

Limitations

Limitations of this clinical review include lack of consistent high-quality evidence for application of cannabinoid therapy for common athletic related indications. Research involving cannabinoid therapies in athletes is sparse. Topics included in this clinical review attempt to identify conditions that present in the athletic population, specifically pain, concussion, and recovery, but do not capture the full spectrum of possible therapeutic applications of cannabis-based medicines, such as psychiatric conditions. Inconsistencies of cannabinoid

Table 1. Summary of major US sports leagues and governing bodies policies related to Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD)

Sports League or Governing Body	Drug Testing Policy	CBD/THC Policy	Consequences for THC Positive Test	THC Level for Positive Urine Test (ng/mL)
National Football League ³³	Once in offseason Up to 6 times per year	Banned; CBD considered product of cannabis	First offense—Drug treatment program Second offense—Fine 2 game checks Third offense—Fine 4 game checks Fourth offense—4 game suspension	>150
Major League Baseball ^{11,26}	No random tests Only for reasonable cause	Not banned	Mandatory evaluation and voluntary treatment Discipline for certain conduct	>50
National Basketball Association ³⁰	Up to 4 times per year in season	Banned	First offense—League Marijuana Program Second offense—\$25,000 fine Third offense—5 game suspension	>15
National Hockey League ³⁴	Yes	Not banned	Referral for behavioral health	not available
National Collegiate Athletic Association ³¹	At championships and in Divisions I and II	Banned	First offense—Half season suspension Second offense—Full season suspension	>35
World Anti-Doping Agency ⁴⁸		Banned except CBD (off list in 2018)	Suspend 3 months to 1 year	>150
US Anti-Doping Agency ⁴¹	Random, all year	Banned in competition except CBD	Suspension	>150

formulation, routes of administration, purity, and dosing within present research make it difficult to propose universal guidelines for cannabis-based therapy at this time.

CONCLUSION

Athletes and former athletes continue to seek safe and effective therapies for a multitude of medical issues, especially acute and chronic pain. There is increasing use of cannabinoid-based medicine for the treatment of these and other ailments. As good-quality evidence-based recommendations emerge, clinicians should remain curious to understanding the role of

the ECS and its modulation, and remain cautious of the hype. Cannabinoids hold promise as a nonopioid alternative for pain management. With expansion of our understanding of cannabinoids and changing laws to enhance research of and access to cannabis-based medicines, athletes and clinicians should continue to educate themselves on possible positive and negative consequences of choosing this type of therapy. Further high-quality clinical research into efficacy, dosing, safety, and long-term effects is warranted, with many trials recruiting and ongoing in the pipeline. At present, it is difficult to advocate for widespread use of cannabinoids due to concerns for purity and quality, especially for athletes who are subject to drug testing.

Clinical Recommendations

SORT: Strength of Recommendation Taxonomy

A: consistent, good-quality patient-oriented evidence

B: inconsistent or limited-quality patient-oriented evidence

C: consensus, disease-oriented evidence, usual practice, expert opinion, or case series

Clinical Recommendation	SORT Evidence Rating
Athletes considering cannabis-based medicines should understand the governing body's stances and seek guidance of knowledgeable clinicians prior to initiation. ^{25,41,48}	C
At present, CBD products are not regulated by the FDA and may contain THC or other impurities, therefore athletes should be cautious when considering using these products. ^{3,5,14,42}	A

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