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REVIEW

Cannabis in combat sports: position statement of the Association of Ringside Physicians

Samuel J. Stellpflug [a], Andrew Stolbach[b], Joe Ghorayeb [c], Erik Magraken[d], Eric Twohey[e], Jeff Lapoint [f] and Kevin deWeber[g]

[a]Department of Emergency Medicine, Regions Hospital, Saint Paul, MN, USA; [b]Department of Emergency Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [c]University of Medicine and Health Sciences, New York, NY, USA; [d]MacIsaac & Company, Victoria, BC, USA; [e]Mayo Clinic Department of Physical Medicine and Rehabilitation, Rochester, MN, USA; [f]Southern California Permanente Medical Group, San Diego Medical Center, Department of Emergency Medicine, San Diego, CA, USA; [g]SW Washington Sports Medicine Fellowship, Vancouver, WA, USA

ABSTRACT

Abstract and ARP Position Statement: Based on the available body of scientific evidence and with the goals of promoting safety of combat sports athletes and striving for the advancement of clean sport, the Association of Ringside Physicians recommends the following regarding cannabis:

- Use of marijuana or synthetic cannabinoids by combat sports athletes is discouraged due to unproven benefits and many known adverse effects. Acute use can impair cognition and complex motor function, which likely leads to reduced performance in combat sports. Chronic use can increase risk for heart and lung disease, several cancers, schizophrenia, and can reduce testosterone in men and impair fertility. Benefits from cannabis in most contexts, including athletic performance, have not been proven.
- Use of topical purified CBD is neither encouraged nor discouraged.
- Since acute cannabis intoxication can impair complex cognitive and motor function, any athlete suspected of acute intoxication at the time of competition – based on clinical judgment – should be banned from that competition.
- Wide-scale regulation of cannabis based on quantitative testing has limited usefulness in combat sports, for the following reasons:
  - Cannabis is not ergogenic and is likely ergolytic.
  - Concentrations in body fluids correlate poorly with clinical effects and timing of use.
  - Access to testing resources varies widely across sporting organizations.

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Introduction

Cannabis sativa, grown for grain, recreational, medical, and ritual purposes, is among the oldest cultivated plants in the world. There is evidence of burning cannabis for funeral ritual activities in western China by at least 2500 years ago [1]. Cannabis-derived substances then made their way around the world from China to India, North Africa, and Europe by around 500 AD [2–4]. The term 'cannabis' can be used to refer to parts of the plant (usually excluding hemp or fiber) or drugs produced from the plant. Cannabis-related products have become a topic of frequent discussion in the context of athletics, and specifically within combat sports. The use of cannabis is common in both the general and athletic populations. Legal restrictions regarding cannabis consumption have been softened significantly in some countries (including the United States) in recent years, prompting increased use and an increase in clinical trials examining the safety of cannabis use and its utility and efficacy for a variety of clinical conditions. This has prompted sports governing bodies to reconsider their own regulations. There are some proposed therapeutic indications, with varying degrees of literature support. To date, there have been no written consensus statements regarding the benefits and/or harms of cannabis use among combat sports athletes. This review summarizes the purported indications for cannabis use, along with the analysis of the ergogenic and ergolytic potential, the effects of acute and chronic exposure, testing, and regulatory oversight of cannabis use in combat sports. 'Combat sports' is meant to be primarily inclusive of boxing and mixed martial arts (MMA) but not exclusive to them.

Biochemistry and pharmacology of cannabis

Cannabis is a single species with diverse varieties (including indica, ruderalis, and more). The plant contains over 500 chemical compounds, including more than 100 with a C_{21} terpenophenolic skeleton known as phytocannabinoids, or simply cannabinoids [5]. These are chemically distinct from endogenous cannabinoids (natural ligands of cannabinoid receptors) and synthetic cannabinoids (a diverse group of chemicals designed as cannabinoid receptor agonists, and are not discussed here). The most used and studied cannabinoids for

CONTACT Samuel J. Stellpflug samuel.j.stellpflug@healthpartners.com Department of Emergency Medicine, Regions Hospital, Saint Paul, MN 55101, USA

their potential therapeutic applications are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Other cannabinoids of note include cannabigerols, cannabichromenes, cannabinodiols, cannabielsoins cannabinols, cannabitriols, and others [5].

There are three main phenotypes of cannabis with varying degrees of the physiologic effects discussed below. Phenotype I (drug-type) contains high concentrations of THC, with some CBD. Phenotype II (intermediate-type) contains a high concentration of CBD with some THC. Phenotype III (hemp or fiber-type) contains very low concentration of THC [5].

THC, the most psychoactive of the principal constituents of cannabis, is used primarily for its relaxing and euphoric effects. THC is found throughout the plant, but the highest concentration is found on trichomes, small resin glands that cover the plant but are focused on female plants on the flower ('buds'). The psychoactivity of a plant is commonly measured by concentration of THC on the inflorescence (leaves and buds), which is influenced by growth stage, as well as genetic and environmental factors. Psychoactivity of THC is mediated by activity at cannabinoid receptor 1 (CB_1), a G-protein-coupled receptor predominantly found in the brain and central nervous system [6]. Smoking is the most common method of consumption, but there are a variety of other methods used as well. This includes, but not limited to, vaporizing, ingesting, and applying topically.

CBD is considered to be minimally psychoactive due to the location of its receptors and mechanisms of action [7]. CBD has diverse molecular targets. CBD has low affinity for CB_1 and CB_2 receptors and acts as an inverse agonist, modulating some of THC effects. CB_2 receptors appear to be predominantly expressed in immune cells. CBD also has activity at serotonin 1a, transient receptor potential channels, peroxisome proliferator-activated receptors, and others [6]. CBD is present to the extent of <1% in most high THC grades of marijuana but up to 20% in specially-grown CBD cultivars [8].

Epidemiology of cannabis use in combat sports and other sports

Globally, cannabis is one of the most commonly used intoxicating drugs, and among athletes, the prevalence of its use is second only to alcohol [9]. According to the 2017 United Nations World Drug Report, prevalence worldwide is estimated to be 3.8%, while up to 18% of Americans used it at least once in 2019 [10].

Cannabis is capable of inducing psychological effects on mood, perception, and cognition, as well as somatic effects to the cardiovascular, respiratory, digestive, immune, neurologic, and endocrine systems [11,12]. Like the general population, the majority of athletes report using cannabis for social reasons [13]; however, a significant percentage of athletes used it to improve sports performance via its perceived benefits on pain management, recovery, sleep promotion and reducing anxiety, among other things [14–17]. While the ergolytic versus ergogenic benefits have been hotly debated over the years [18,19], cannabis has been on the World Anti-Doping Agency (WADA) prohibited list since 2004 due to it fulfilling the latter two of the three criteria: potential to enhance sport performance, actual or potential health risk to the athlete, and violating spirit of the sport [20,21].

In a survey of around 23,000 National Collegiate Athletic Association (NCAA) high-level amateur athletes, self-reported use of marijuana among student athletes was 25%. While the majority (77%) reported using it for social reasons, many used it for other reasons as well including to aid in sleep (26%), anxiety/depression (22%), and pain (19%). Wrestling was among the higher users of marijuana, with 29% of wrestlers reporting using marijuana [13]. This is similar to what was found in the systematic review performed by Docter et al., which found 23.4% of elite and university athletes report using marijuana in the past year [22]. Meanwhile, in a large cohort of elite 14–18-year-old German Olympic athletes, 9% of which were weight-dependent athletes (boxing, wrestling, taekwondo, weightlifting, judo), estimated prevalence by self-report was found to be around 3% [23].

In an analysis of multiple sports doping control tests from 2014 to 2017 by WADA, athletes in boxing and wrestling had greater than 2% of their in-competition samples result with adverse analytical findings, which was second only to weightlifting. Out of the total samples taken, cannabinoids were present in 0.11% (boxing), 0.05% (wrestling), and 0.03% (judo), which accounted for 5.4%, 2.5%, and 2.9% of adverse analytical findings, respectively [24]. Looking at 2624 samples representing 1069 Ultimate Fighting Championships (UFC) MMA athletes from 2015 to 2019, a total of 209 adverse findings were found, resulting in 102 anti-doping rule violations (ADRV) committed by 93 (8.7%) of the athletes. Five (4.9%) of the ADRVs were from testing positive for cannabinoids. Of important note, these represent athletes who tested positive in-competition as USADA does not ban cannabinoid use out of competition [25]. Similar results have been seen in Polish athletes, with boxing and wrestling being among the highest disciplines in terms of testing positive for THC in urine at 4.9% and 3%, respectively [26].

Accurately estimating prevalence of cannabis use in athletes has shown to be difficult for several reasons. Athletes may underreport their cannabis use due to fear of retribution since cannabis is still illegal in many parts of the world and considered a banned substance by governing sport bodies. In a study done by Thevis et al., 9.8% of urine samples tested positive for THC metabolites in a sample of sports science students who practiced sports outside of class despite no one reporting marijuana use [27]. Intermittent or sporadic usage may not be captured with lab testing. Additionally, there are many sociocultural and personal factors that go into using cannabis. Geographical location, legislation, age, sex, race, type of sport, in-season verses off-season, and level of sport likely impact the prevalence of cannabis use.

Therapeutic cannabis use

Cannabis has wide-ranging effects on the body that make it an intriguing potential therapeutic substance for several different disease processes. Most studies looking into the benefits of cannabis to date are small and of low quality; however, there are some medical conditions for which the FDA has approved

the use of cannabis-derived and synthetic cannabis-related drug products including seizures associated with Lennox-Gastaut or Dravet syndrome, nausea associated with cancer chemotherapy, and for the treatment of anorexia associated with weight loss in AIDS patients [28–30]. In addition to this, a combination of THC and CBD is also approved for MS-associated spasticity in several countries [31,32]. CBD, in part due to it being a likely minimally psychogenic active component of cannabis, has been studied and shown some potential to treat a wide range of clinical conditions; however, it is not currently FDA approved. These include epilepsy [33], irritability and behavioral problems in autism [34], positive and negative symptoms in schizophrenia [35], anxiety and depression [36], Alzheimer's and Parkinson's disease [37,38], and sleep disorders, among other things.

Cannabis acts via modulating the body's endocannabinoid system (ECS), a system with a significant role in modulation of pain and inflammation. This, along with the growing social acceptance of cannabis use across the United States, may explain why athletes may gravitate toward using cannabis for a variety of ailments. In fact, in a survey of NCAA collegiate athletes, 19% of athletes who used cannabis said they used it for pain management [13]. Among MMA fighters, marijuana use was common, with users citing its ability to help with recovery from training, sleep, pain, and stress management [39]. While limited, there is some evidence that cannabis can improve perception of pain acutely in a capsaicin-induced localized intradermal pain model at moderate doses [40]. Studies for cannabis use in chronic pain are more robust and have shown moderate pain reduction and opioid-sparing effects in several different patient populations including those with cancer and non-cancer related pain, as well as neuropathic pain [41–43]. CBD use has been linked to decreased inflammatory marker IL-6 and improvement in sleep at higher doses [17], which hypothetically may help athletes recover from training [16,44,45]. While it has not been directly studied in the setting of sports related anxiety, CBD has been shown to have anxiolytic effects under 'stress inducing' conditions in both healthy participants and those with social anxiety disorder [17]. Some studies have even postulated that cannabis my play a role in recovery from concussion given the ECS role in traumatic brain injury [16,17,46].

Effects of cannabis

Cannabis use can have acute and chronic impacts. The acute effects described here are those most applicable to athletic performance: cognitive and motor functioning, ergogenic versus ergolytic impact, sleep alteration, and pain modulation. Chronic cannabis exposure has been associated with a range of effects on bodily structure and function. Chronic use data are conflicting at times due to the lack of large-scale, long-term studies and confounders, but some findings are certainly consistent.

Signs and symptoms of acute intoxication

The clinical evaluation for acute intoxication after use of cannabis varies based on timing of use, amount of use, route of administration, and individual differences in expressing physiologic effects of the drug. This variability can make definitive determination of intoxication difficult. This difficulty can be confounded further with concomitant use of other substances with similar or conflicting physiologic impact, especially substances impacting cognition. There are variable psychological effects of cannabis, but users commonly experience a feeling of relaxation (although some experience anxiousness), perceptual alteration, a feeling of well-being, and increased appetite [47,48]. There are some measurable physiologic effects, notably slight increase in heart rate and blood pressure. The effects on heart rate and blood pressure are not typically profound, but have been reproduced in various studies [49–52]. The timing and duration of these effects vary with type and amount of administration, and not all studies show consistent results [53]. Other appreciable findings include slow reaction time, slurred speech, concentration difficulty, lethargy, postural hypotension, sedation, and psychosis. This is not an all-inclusive list of potential signs and symptoms.

Effect on cognitive performance and brain structure

Impact on cognitive abilities can be divided into acute and long-term effects. The impacts are mixed, but acute cannabis use can impact many aspects of cognitive function negatively [54]. There is some evidence of residual effects, hours to days after use, but the data are not as compelling as for acute use [54]. The same goes for extended analysis weeks after use. The time frame of cognitive impacts varies among studies, with various research examining this in different ways, making comparative evaluation difficult. The acute cognitive impacts seem to be more significant with complex tasks [55]. Scott et al. found that cannabis use during adolescence and young adulthood was associated with reduced cognitive functioning [56]. A systematic review by Broyd et al. found that chronic cannabis use was associated with impaired cognition, especially in the domains of verbal learning, memory and attention [57]. These findings are further corroborated by Kroon et al. [58]. Abstinence of cannabis use for 72 h or longer has been shown to diminish the aforementioned cognitive deficits.

There is a dearth of research examining cognitive and motor functioning impact of THC within combat sports, but there is very applicable tangential research to take into consideration. A large review of the effect of cannabis on driving skills exhibited mixed findings, but showed a twofold increase in motor vehicle accidents after acute cannabis smoking, along with deterioration of control with increased task complexity, increased lane weaving and impaired cognitive function [59]. The same review found that divided-attention tasks, reaction times, and tracking tests all showed impairment with cannabis use. Some evidence in that review supports blood concentrations of 2–5 ng/mL being associated with driving impairment. Other research has shown blood testing as likely the most effective test modality to evaluate acute cognitive impairment, although the correlation of even blood testing with acute psychoactive effects and cognitive/motor function needs tremendous expansion in understanding [60]. Another study comparing driving impairment caused by alcohol and cannabis found that both impaired driving function, but in

slightly different manners [61]. This study also demonstrated that driving-related cognitive effects from cannabis occurs in a dose-dependent fashion, but with more variation than alcohol (which has a fair amount of variation on its own), likely due to differences in use techniques, individual tolerance, and greater variance of THC content in use products. The non-linear dose-dependent impact has been verified in other non-driving contexts as well [62]. Another review highlighted the general awareness of intoxication of THC-affected individuals, in contrast to general unawareness of intoxication of alcohol-affected individuals. This has led to a misconception that conscious carefulness by THC-affected individuals can compensate for the acute cognitive and motor effects impairment the driving activity [63]. Primary literature on the topic of cognitive and motor effects on driving, not surprisingly, reflects the findings of the reviews above, notably that cannabis has negative acute effects on effectiveness and safety of cognitive and motor function necessary to drive effectively [64–72].

There is basic physiologic research demonstrating increased cerebral blood flow following administration of THC via intravenous [73] and inhalation [74] routes. Research has suggested that changes in brain morphology arise due to prolonged exposure to cannabis, and the evaluation of these alterations in brain function following chronic cannabis use is often derived from neuroimaging studies. Abnormalities have been consistently detected in brain regions with a high density of cannabinoid receptors, such as the prefrontal regions, hippocampus, amygdala, and cerebellum, as well as overall reduced regional brain volume and increased gray matter [75]. Through use of magnetic resonance imaging (MRI) and positron emission tomography (PET), it was revealed that those commencing cannabis use prior to 17 years of age had reduced overall cortical size and percentage of gray matter volume and increased percentage of white matter volume compared to those who commence use later [76]. Structural neuroimaging studies have identified reduced gray matter in the medial-temporal, orbitofrontal, temporal pole, parahippocampal gyrus, insula, and cerebellar regions [77–79], although the evidence for significant differences between cannabis users and non-users is largely mixed [79]. Reduced white matter density among regular users [80], dose-dependent reductions in hippocampal and amygdala volumes [81], and shape alterations to the nucleus accumbens have also been reported [82]. There is some evidence that there may be some neuroprotection in dopaminergic neurons from CBD [83]. There is some evidence of reduction of cerebral blood flow, as represented on single-photon emission computed tomography (SPECT) scan, in the context of chronic marijuana use [84]. This corroborated similar findings in a slightly different patient population [85].

Ergogenic and ergolytic effects

Substances that result in enhanced exercise capacity or athletic performance are referred to as ergogenic, while those that hinder these functions are referred to as ergolytic [86]. There is some research available on the ergogenic/ergolytic properties of cannabis; most of this is outside the realm of combat sports but still applicable to athletics in general. The most compelling evidence for ergogenic or ergolytic potential of cannabis is for the ergolytic effect of the impaired cognitive and motor functioning; this is covered in the previous section. In a review on muscle effects of CBD, authors found multiple links in rodent studies between CBD and metabolic regulators and inflammatory pathways but did not find an impact on anabolism. They summarized that in humans there has been some demonstration of improved muscle recovery and performance related to CBD, but with highly variable dosing [87]. Although cannabis use has become more prevalent among athletes, there are no good human data supporting the performance-enhancing effects [88]. Much of the focus of discussion within athletic performance has been on the potential of cannabis to aid in recovery from athletic activity; however, this is not fully supported and is mostly conjecture at this point [12]. Some of these recovery-related issues, along with slightly better established realms like pain management, deserve further attention from future research to gauge the merit behind current practice [88].

In a study of edible THC vs placebo, 10 mg THC offered no performance enhancement during participant use of a standardized cycle ergometer [89]. There have been similar findings of essentially no difference between chronic cannabis use and placebo with regard to physical performance [90]. Lack of impact on athletic performance is not a new research finding. Despite some difference between subjects with cannabis use versus no cannabis use in some physiologic variables, there was no difference in strength in one study, and actually worse strength in another, although in the latter study, it may have been impacted by fine motor control being worse with cannabis exposure [91,92].

Sleep, pain, and stress

On the competition stage, the smallest difference can be the difference between winning and losing. Because of this, athletes often find themselves looking for tools to help them gain a competitive edge in aspects adjacent to direct performance, notably sleep, pain modulation, and performance stress. Pain is a common experience in training for sport, especially combat sports, and can impact athletic performance if not managed. While there are no studies directly studying the effect of cannabis on pain experienced in training for athletics, nearly 1/5 of NCAA athletes who use marijuana cite its impact on pain management as a reason for its use [13]. Marijuana has been shown to modulate both the acute pain experience in capsaicin induced pain models [40] as well as chronic pain in different populations [42,43,93], so it is plausible that some athletes may perceive a benefit when using marijuana for pain management. Sleep plays an integral role in an athlete's ability to recover and perform. Babson et al. recently reviewed the role of cannabis, cannabinoids, and sleep in several different populations [44]. While results were mixed in non-athletic populations, beneficial mechanisms have been postulated, which may be intriguing for an athlete struggling with sleep. Being able to manage anxiety and emotions is vital when it comes to performance and for

overall general health. Athletes often feel a strong identity with their given sport and thus their self-image may be tied to external things, such as sporting results. The pressure to perform, along with normal stressors of everyday life, can create an environment for anxiety to proliferate. Early-stage clinical studies suggest that CBD may be anxiolytic in 'stress inducing' situations, primarily public speaking [17]. However, one can easily extrapolate how this effect may be intriguing for an athlete dealing with anxiety and/or stress related to training, performance, or other reasons. MMA fighters who have used marijuana cite stress management as one of the reasons for its use [39].

Respiratory effects

The primary route of administration for cannabis is inhalation, either by smoking or vaping, and the combustion or heating of cannabis products can produce harmful by-products that can negatively impact the respiratory system. Cannabis smoke contains many of the same carcinogens and irritants as tobacco smoke, which can increase the risk of respiratory infections. Studies that controlled for the effects of tobacco smoking found a 2.1- to 4.1-fold increased risk of developing lung cancer [94].

In addition to the increased risk of primary lung cancer, chronic cannabis smoking can lead to other air exchange diseases, such as chronic bronchitis and chronic obstructive pulmonary disease (COPD). Chronic bronchitis is characterized by coughing, mucus production, and wheezing. A systematic review of 34 studies conducted by Tetrault et al. found that cannabis smoking was associated with chronic bronchitis, with a higher risk observed with increasing frequency and duration of use [95]. Chronic cannabis use has also been associated with reduced lung function, particularly in heavy smokers, and the effect is dose-dependent [96]. Tan et al. determined that among heavy marijuana users, the risk of developing COPD was significantly increased (adjusted OR 2.45, 95% CI 1.55–3.88). When compared to people who do not smoke marijuana or tobacco, heavy marijuana smokers and heavy tobacco smokers both experience a faster decline in FEV1 [97].

Cardiovascular and cerebrovascular effects

Cannabis smoking has been associated with an elevation in heart rate and blood pressure immediately after use, and this effect may last for up to 3 h [98]. A comprehensive review by Richards et al. demonstrated an increased risk of developing acute coronary syndrome and chronic cardiovascular disease with chronic use [99]. Among patients for treatment of myocardial infarction, marijuana users have been shown to have increased mortality [100,101]. Tachydysrhythmias can occur with cannabis use, both natural and synthetic, including life threatening ventricular tachycardia [102,103]. Jouanjus et al. found a dose-dependent association between exposure to cannabis-based products and ischemic strokes. However, the mechanisms involved to explain this observation remain to be elucidated [104].

Psychiatric effects

Chronic cannabis exposure has been associated with a range of psychiatric effects, including an increased risk of developing psychotic disorders such as schizophrenia, as well as mood disorders such as depression and anxiety. A systematic review and meta-analysis by Figueiredo et al. found that chronic cannabis use was associated with impairments in cognitive function, including attention, memory, and executive function, with deficits more pronounced in heavy users [105]. The association between cannabis use and schizophrenia has been extensively studied, with a systematic review by Patel et al. finding a causal relationship between cannabis use and an increased risk of developing schizophrenia, particularly in those who use cannabis at an early age or have a family history of schizophrenia [106]. Similarly, a meta-analysis by Gibbs et al. found that cannabis use was associated with an increased risk of manic symptoms in bipolar disorder [107].

Cancers

There appears to be an association between cannabis use and the incidence of various cancers often seen in tobacco smokers among marijuana smokers. Llewellyn et al. reported an increased rate of oral cancer in marijuana smokers [108]. Similarly, Aldington et al. and Zhang et al. found increased rates of lung and head/neck cancer, respectively [109–111]. Moreover, the WHO reported data regarding an increased risk of gastrointestinal cancers, respiratory cancers, testicular cancer, and prostate and cervical cancer [112].

Effect on the reproductive system

Chronic cannabis use has been associated with various adverse effects on the reproductive system. These effects can occur in both males and females and can be caused by the active compounds in cannabis, such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). In males, chronic cannabis use has been linked to decreased testosterone levels, reduced sperm count, and impaired sperm motility. Studies have found that THC can decrease testosterone levels by affecting the hypothalamic-pituitary-gonadal (HPG) axis, which regulates testosterone production. This effect obviously has the potential to impact athletic performance, but can also lead to a decrease in sperm count and motility, which can impair fertility. One study found that chronic cannabis use was associated with a 28% reduction in sperm concentration and a 29% reduction in total sperm count compared to non-users [113]. A systematic review by Payne et al. found that chronic cannabis use was associated with abnormalities in sperm morphology, and reduced sperm motility and viability [114]. The scientific literature supports some degree of effect from cannabis use on ovulation and menstruation [115,116]. Though in females, the literature is less consistent, with findings ranging from no effect to increased anovulation and suppressed reproductive hormone levels [117,118]. The literature does not offer a strong association between prenatal cannabis exposure and long-term offspring outcomes at this time.

Regulatory oversight of cannabis in combat sports

There is no universal regulatory standard in the United States and Canada for the oversight of combat sports. Within some sports, organizations, and promotions, there is no regulation at all. Even in the highest levels of competition, regulatory bodies and standards vary. Regulation varies by different state commissions in the US, provincial commissions in Canada, tribal commissions in both countries, and even municipal commissions in the Province of Alberta. With dozens of different regulators each in charge of their own jurisdiction, there are scattered laws and rules for combat sports and this applies to anti-doping rules and the legality of cannabis. The lack of universal standards makes it difficult to summarize all the legal ways cannabis is treated by regulators. Generally, however, cannabis products are prohibited substances and use of cannabis can bring consequences ranging from minor penalties to substantial fines and periods of suspension from competition. In some jurisdictions, a bout winner can have their victory overturned due to a positive cannabis finding.

Although there is no universal standard for how cannabis is treated by combat sports regulators, the most common anti-doping standards adopted by athletic commissions are those created by the WADA. WADA keeps an ever-evolving list of prohibited methods and substances (the Prohibited List). Under the 2023 WADA Prohibited List, cannabinoids, with the exception of cannabidiol, are banned [119]. As a prohibited substance, cannabinoids have three unique characteristics:

(1) They are only banned in-competition.
(2) They are a threshold substance, meaning that if cannabinoids are detected in an athlete's sample below a specific concentration, it will not be considered an anti-doping rule violation.
(3) They are categorized as 'Substances of Abuse,' meaning that they attract the lowest of possible penalties among the prohibited substances.

The WADA Prohibited List gives the following definition of the in-competition time frame [119]. 'In-Competition period shall in principle be the period commencing just before midnight (at 11:59 p.m.) on the day before a Competition in which the Athlete is scheduled to participate until the end of the Competition and the Sample collection process.' WADA provides a urine testing threshold of 150 ng/mL for prohibited cannabinoids in competition (with an allowable guard band up to 180 ng/mL and slight adjustment for dense urine) [120]. A violation can occur even if cannabis is not necessarily ingested during the in-competition window but a sample is collected during this window which exceeds this specified threshold. The WADA Prohibited List notes the following as 'Substances of Abuse' as 'substances that are identified as such because they are frequently abused in society outside of the context of sport. The following are designated Substances of Abuse: cocaine, diamorphine (heroin), methylenedioxymethamphetamine (MDMA/'ecstasy'), and tetrahydrocannabinol (THC) [121].

WADA provides the following more lenient punishment for anti doping violations for 'Substances of Abuse' where the Anti-Doping Rule Violation involves a Substance of Abuse and 'the Athlete can establish that any ingestion or Use occurred Out-of-Competition and was unrelated to sport performance, then the period of Ineligibility shall be three (3) months [122]. In addition, the period of Ineligibility calculated may be reduced to one (1) month if the Athlete or other Person satisfactorily completes a Substance of Abuse treatment program approved by the Anti-Doping Organization with Results Management responsibility.' Additionally, WADA allows athletes who use cannabis medically to apply for a therapeutic use exemption ('TUE'), which will exempt the athlete from an anti-doping violation even if they exceed the in-competition threshold. The following broad test must be met for an athlete to obtain a TUE for cannabis [123]:

a. The Prohibited Substance or Prohibited Method in question is needed to treat a diagnosed medical condition supported by relevant clinical evidence.
b. The Therapeutic Use of the Prohibited Substance or Prohibited Method will not, on the balance of probabilities, produce any additional enhancement of performance beyond what might be anticipated by a return to the Athlete's normal state of health following the treatment of the medical condition.
c. The Prohibited Substance or Prohibited Method is an indicated treatment for the medical condition, and there is no reasonable permitted Therapeutic alternative.
d. The necessity for the Use of the Prohibited Substance or Prohibited Method is not a consequence, wholly or in part, of the prior use.

Both in the United States and Canada, there are examples of Athletic Commissions providing athletes with a TUE for permission to use cannabis in-competition. With the ever-increasing legality of both recreational and medical cannabis use, there has been a deviation from WADA standards by several athletic commissions. The trend of having cannabis violations attract lighter penalties is also endorsed by the Association of Boxing Commissions (ABC) whose medical advisory committee released a position statement in 2021 noting that a modest fine should be sufficient punishment for violations [124]. In 2021, both Nevada and Florida removed cannabis as a banned substance [125,126]. The same year, Kansas announced they will stop testing for cannabis in competition, limiting their regulatory concern only to athletes who demonstrate signs of impairment [127]. In 2022, Colorado also removed cannabis from their list of banned substances [128].

Other jurisdictions that do not follow WADA standards are too numerous and varied to summarize easily here. Across these jurisdictions, cannabis generally is a banned substance with a broad spectrum of potential penalties. Many jurisdictions prohibit cannabis in competition, but some also ban it out of competition.

Private anti-doping organizations also play a role in combat sports. There are examples of both promoters and fighters contracting with private anti-doping watchdogs to provide

oversight beyond that provided by athletic commissions. Most notably, the UFC had a private anti-doping contract with the United States Anti Doping Agency (USADA) for a number of years [129]. While USADA generally follows WADA standards, their private contract with the UFC had numerous modifications of these standards. In 2021, USADA and the UFC varied their anti-doping policy to treat in competition cannabis violations as attracting lesser penalties than other violations similar to the Substances of Abuse model created by WADA [130]. The Voluntary Anti Doping Association (VADA) is a private organization used by many athletes, including some boxers and mixed martial artists [131]. Most notably VADA partnered with the World Boxing Council (WBC) to test various ranked and championship fighters [132]. VADA does not test for cannabis in their anti-doping program. Private anti-doping programs are free to adopt whatever standards they want, but the above trend shows that, similar to regulatory agencies, cannabis violations are moving to be treated as less serious doping violations to outright not being tested for at all.

In summary, cannabis is treated differently depending on the jurisdiction in question. Generally, cannabis is a banned substance in competition. While there are examples of athletes being suspended for many years and being fined hundreds of thousands of dollars for cannabis violations [133,134], current trends are to reduce penalties for cannabis violations and even outright removal of cannabis from the list of prohibited substances.

Testing

Detecting and quantifying substances in the human body is a complex topic. There are multiple aspects to testing, including which body fluid to test, which testing modality to use, how to determine the threshold for qualitative testing, how to best get a quantitative measure, availability of various testing modalities, and testing standards of athletic governing bodies. The discussion of testing is important, especially when there is a recommended substance restriction of any kind, which implies a way to determine use to be able to enforce such a restriction. It is important to note that a positive qualitative test does not necessarily correlate with toxicity, clinical impairment, or degree of drug exposure. A positive result of a drug test is reported when the analyte (drug or metabolite) concentration exceeds the established reporting threshold or cutoff. The cutoff has been determined by a scientific advisory panel to distinguish drug use from environmental exposure. Testing for cannabis compounds and metabolites cannot be used in isolation to establish impairment or Intoxication [135]. Even positive quantified results are only loosely correlated with clinical impairment from cannabinoids.

Cannabinoids can be detected in many areas of the body, but blood and urine are the two testable body fluids relevant to sporting regulation. Those fluids are readily obtainable and testable by multiple modalities. In general, substances are more concentrated in urine than blood and a qualitative positive test may be reproducible for a longer time after use in urine than blood. There are many applicable testing modalities. The simplest and most widely available is immunoassay testing [136]. This is the type of testing used in most rapid drug screening, both in and out of health care facilities. It is important to know this basic level of testing, and you may encounter organizations with limited resources utilizing it; however, testing by high-level regulatory bodies on elite athletes is not done this way. Enzyme-multiplied immunoassay technique (EMIT), in isolation, is typically used for qualitative screening as opposed to quantifying drug or metabolite amount in the tested fluid. Because of how this type of testing works, in general, there is a great potential for false negatives and false positives; this is less of an issue with cannabinoids than some drugs, but it is still possible [137]. Immunoassay testing essentially uses antibodies designed to detect a relatively specific epitope of a compound; the specificity of the test depends on how ubiquitous that epitope is [135]. Immunoassay testing is relatively widely available, more so than the options for confirmatory testing that are often used after immunoassay screening. The amount of time between cannabinoid use and a negative EMIT urine test (often set at less than a detection limit of 20 ng/ml) can depend on amount of use, fat stores, and many other factors. In short-term, low-amount users, the time between initiation of cannabinoid abstinence and a negative EMIT test can range from a few days to a few weeks. In chronic heavy users, the abstinence time to a negative EMIT test can range from days to over 2 months [138].

Confirmatory testing following EMIT, and testing that is more accurate for quantitative results, typically includes some sort of chromatography followed by mass spectrometry. Gas chromatography–mass spectrometry (GC-MS) is the most specific for natural cannabinoids, specifically delta-9-tetrahydrocannabinol (typically via carboxy-THC as a delta-9-tetrahydrocannabinol measurable metabolite), and it is considered the gold standard. It would be unusual for EMIT to be used on its own for regulatory purposes in athletic competition. For some cannabinoids, such as nabilone, other modalities are necessary for detection, such as high-performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS) [139]. There are hundreds of known synthetic cannabinoids with varying geographical prevalence [140], and most commonly available immunoassays will not detect them; HPLC-MS/MS or GC-MS will if the testing site is cataloged to identify them; this is notable because the identification, calibration, and cataloging often do not keep up to date with the development of new synthetics [48,141–143].

Developing a testing threshold, or a body fluid concentration over which a governing body determines that an athlete has violated a rule regarding a restricted substance, is a difficult and imperfect process guided by both evidence and expert opinion. WADA and USADA currently set the in-competition threshold for THC (delta-9-tetrahydrocannabinol via measurement of carboxy-tetrahydrocannabinol) at 150 ng/mL tested in urine by GC-MS [20,144]. This is an increase from a prior much lower threshold. Having a regulation like this requires that organizations governed by it have access to advanced testing; this is appropriate at the highest levels of competition, but might be very difficult for resource-low organizations to apply.

Discussion

Cannabis has been used for hundreds of years, and the use is increasing, both inside and outside sporting contexts. Societal approaches to this use have changed, and those changes have been reflected somewhat within sportive regulation, including combat sports regulation. There are a number of published sources discussing why cannabis-related products should remain banned in sport in the same manner it has been historically, and these sources vary from recommending banning because of the illicit nature of the various form of the drug, because of the negative acute cognitive impact, and because of the less than well-validated recovery and pain relief properties of cannabis [21,145–147].

Rationale for regulation of this substance must focus on the impact to the individual athletes, and the impact on the integrity of combat sports. The impact to the individual athletes includes primarily the altered risk to them within the fight as impacted by cannabis, and the risk of the cannabis itself. The impact of the integrity of the competition includes the ergogenic and ergolytic properties of cannabis, the acute impact of cannabis on the ability to compete, and the impact of cannabis on training and recovery.

The impact on the individual athlete

- There is a compelling body of literature demonstrating worsened cognitive and motor function, especially with more complex tasks, potentially putting the athlete at risk in the context of cannabis use in close time proximity to the fight due to a reduced ability to defend oneself.
- There is a compelling body of literature demonstrating worsened cognitive and motor function, especially with more complex tasks, potentially putting the athlete at risk in the context of cannabis use in close time proximity to fight training, especially striking sparring, due to a reduced ability to defend oneself.
- There is more controversial evidence demonstrating worsened cognitive and motor function in the context of subacute cannabis use, more removed in time proximity from the fight or combat training, indicating at least a possibility of safety risk from lack of ability to defend oneself.
- There are proven chronic deleterious effects of cannabis use, including, but not limited to effects on respiratory functioning, cardiovascular functioning, psychiatric stability, reproduction, testosterone levels, brain structure, cognitive functioning, and the likelihood of developing cancer.
- There may or may not be benefit from cannabis use to the athlete due to improved sleep.
- There may or may not be benefit from cannabis use to the athlete due to reduced emotional stress.
- There may or may not be benefit from cannabis use to the athlete due to pain perception modification; the literature supports this slightly better than it does alteration to sleep and stress

The impact on the integrity of combat sports competition

- There is a compelling body of literature demonstrating worsened cognitive and motor function, especially with more complex tasks, potentially putting the athlete at risk in the context of cannabis use in close time proximity to the fight due to a reduced ability to defend oneself.
- The literature on ergogenic and ergolytic impact of cannabis is not particularly compelling in either direction.

From the standpoint of performance impact, acute cannabis use, in a variable dose-dependent fashion, has the potential of creating a scenario where a fighter has less ability to protect him or herself due to reduced cognitive and motor execution ability, especially with complex tasks. Fighting clearly presents a host of tasks that would be considered complex, and thus this indicates a potential safety hazard. This could compromise both the athlete and the integrity of the sport. Subacute use may or may not present similar risk, although clearly less than acute use. Ongoing chronic use may also present similar risk, given existing evidence of brain structure modification. From the standpoint of overall positive and negative health impacts, there may be some positive health aspects to cannabis, although the data are mixed even with many accepted therapeutic use applications, and there are certainly potential overall long-term health risks.

Limitations and areas of exploration

The recommendation (below) based on the potential acute risk to athletes, and to a lesser extent the long term risks, is technically an enforceable ban limited to in-competition use. This is based on clinical interpretation of the on-site ringside or cageside physician. Clinical evaluation of cannabis related intoxication can be difficult, and introduces gray area to regulation. However, the clinicians making this determination are experienced and fully capable of making this determination when necessary. There are a couple of issues that need further exploration, and if understanding were expanded, these aspects could bring about cleaner regulation related to testing in conjunction with clinical evaluation. If body fluid testing were developed such that the temporal relationship between cannabis use and time of testing was reliable, if the clinical effects and quantitative results were better correlated, and if accurate testing required only widely available resources, then testing-based regulation within combat sports would be more applicable.

Conclusion

Cannabis use is increasing and is an issue important in combat sports. From the standpoint of individual athlete risk and ergolytic impacts, the acute and possibly subacute cognitive and motor effects of cannabis exposure potentially increase risks of trauma during fighting in competition and training. There are underwhelming data on ergogenic impacts. The acute negative side effects of cannabis use along with the long-term effects associated with chronic use appear to outweigh the purported performance enhancing effects. It is recommended that in-competition use

should be prohibited when keeping the best interest of combat sports athletes in mind, along with the integrity of the competition. This agrees with the current general athletics WADA classification. There are complex issues with this recommendation, including the variability and inconsistency of clinical evaluation of acute intoxication along with testing aspects including timing, testing modality, and violation concentration threshold.

Based on the available body of scientific evidence and the above discussion, and with the goals of promoting safety of combat sports athletes and striving for the advancement of clean sport, the Association of Ringside Physicians recommends the following regarding cannabis:

- Use of marijuana or synthetic cannabinoids by combat sports athletes is discouraged due to unproven benefits and many known adverse effects. Acute use can impair cognition and complex motor function, which likely leads to reduced performance in combat sports. Chronic use can increase risk for heart and lung disease, several cancers, and schizophrenia and can reduce testosterone in men and impair fertility. Benefits from cannabis in most contexts, including athletic performance, have not been proven.
- Use of topical purified CBD is neither encouraged nor discouraged.
- Since acute cannabis intoxication can impair complex cognitive and motor function, any athlete suspected of acute intoxication at the time of competition – based on clinical judgment – should be banned from that competition.
- Wide-scale regulation of cannabis based on quantitative testing has limited usefulness in combat sports, for the following reasons:
  - Cannabis is not ergogenic and is likely ergolytic.
  - Concentrations in body fluids correlate poorly with clinical effects and timing of use.
  - Access to testing resources varies widely across sporting organizations.

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ORCID

Samuel J. Stellpflug http://orcid.org/0000-0002-2378-5280
Joe Ghorayeb http://orcid.org/0000-0001-5386-3035
Jeff Lapoint http://orcid.org/0000-0002-1780-3614

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