

High-Performance Sport, Marijuana, and Cannabimimetics

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Abstract

The prohibition on use of cannabinoids in sporting competitions has been widely debated and continues to be a contentious issue. Information continues to accumulate on the adverse health effects of smoked marijuana and the decrement of performance caused by the use of cannabinoids. The objective of this article is to provide an overview of cannabinoids and cannabimimetics that directly or indirectly impact sport, the rules of sport, and performance of the athlete. This article reviews some of the history of marijuana in Olympic and Collegiate sport, summarizes the guidelines by which a substance is added to the World Anti-Doping Agency Prohibited List, and updates information on the pharmacologic effects of cannabinoids and their mechanism of action. The recently marketed cannabimimetics Spice and K2 are included in the discussion as they activate the same receptors as are activated by THC. The article also provides a view as to why the World Anti-Doping Agency prohibits cannabinoid or cannabimimetic use in competition and should continue to do so.

Introduction

The XVIII Olympic Winter Games at Nagano in 1998 featured the case of the Canadian snowboard athlete Ross Rebagliati and brought the issue of use of marijuana in sport to international attention. At the inaugural year of snowboarding at the Olympic Winter Games, Rebagliati had a confirmed positive drug test for 11-nor- Δ^9 -tetrahydrocannabinol carboxylic acid (THC-COOH) at 17 ng/mL. The International Olympic Committee (IOC) Executive Committee disqualified the athlete and stripped him of his Gold Medal. This decision was immediately appealed to the Court of Arbitration for Sport (CAS) by the Canadian Olympic Association. Rebagliati's claim was that he had ingested second-hand marijuana smoke at a going-away party in Whistler, Canada a few days earlier (January 31), while the date of the specimen collection was February 8. In addition, he stated he had not actively used marijuana since April of 1997. The claim of inhalation of second hand smoke was of interest; however, the CAS members did not delve into the metabolism of Δ^9 -tetrahydrocannabinol (THC) and the possi-

bility of a positive result from passive inhalation over the time frame stated. The CAS decision turned on the status of marijuana as treated by the IOC Medical Code which provided "Marijuana: In agreement with the International Sports Federations and the responsible authorities, tests may be conducted for cannabinoids (e.g., marijuana, hashish). The results may lead to sanctions (1)." At that time, THC was not prohibited for Giant Slalom Snowboard by the International Federation (IF) for skiing, which was Fédération Internationale de Ski (FIS). The CAS ultimately overturned the IOC Executive Committee decision to strip Rebagliati of the Gold Medal, and the win was officially awarded to Mr. Rebagliati (2).

The World Anti-Doping Agency (WADA) was established by the IOC in November 1999 and maintains a list of prohibited substances and methods, known as the Prohibited List International Standard (3). The current list is for 2011; however, for future reference, the list may be obtained at www.wada-ama.org along with the World Anti-Doping Code (4) and other international standards. A substance may be included on the Prohibited List if it meets two of three major criteria defined by WADA, or if it is a potential masking agent to impede detection of a prohibited substance. The criteria are as follows:

1. The substance is performance-enhancing.
2. There are potential health risks to the athlete with use of the substance.
3. The use of the substance violates the "spirit of sport".

Of particular note is the policy of "strict liability" which means that the mere presence of a prohibited substance is a sufficient basis for an adverse finding and there is no requirement for actual performance to be enhanced (or impaired). The current wording which applies to THC (Figure 1A) in the 2011 prohibited list (3) under section S8. CANNABINOIDS is "Natural or synthetic Δ^9 -tetrahydrocannabinol (THC) and cannabimimetics [e.g., Spice (containing JWH-018 and JWH-073) and HU-210] are prohibited." The classical cannabinoids with the partially reduced dibenzopyrene structure are clearly prohibited; however, the definition of synthetic cannabinoids is somewhat vague although the prohibition may well be considered by WADA to apply to certain other cannabimimetics. The National Collegiate Athletic Association (NCAA) prohibits

marijuana use in collegiate sport under the category of street drugs and uses a threshold of 15 ng/mL for laboratory testing (5). In this article, marijuana and cannabis are used to represent the plant or plant materials derived from the leafy annual plant, *Cannabis sativa*.

The use of performance-enhancing substances and methods (PES) in sport is generally thought, in a limited way, to only include those substances that are anabolic and result in muscle growth or that enhance oxygen transport; however, the prohibition on the use of cannabis in-competition must be evaluated relative to the three WADA criteria listed. The prohibition “in-competition” is not solely the use at the competition, but includes the time period before the competition that is necessary for the 11-nor- Δ^9 -tetrahydrocannabinol carboxylic acid (THC-COOH, Figure 1C) metabolite of marijuana to clear from the

urine to a level below the WADA prescribed threshold of 15 ng/mL (6). Also of interest is the in-competition prohibition, as implemented by the IOC for Olympic Games, which applies the entire time the Olympic Village is open and anywhere in the world an Olympic competitor may be training. Thus, an Olympic athlete must be particularly careful prior to and during the entire period of the Games. Saugy et al. (7) addressed cannabis use and sport as a social issue with the primary effect being to allow the athlete to “relax and escape from social pressures” and stated that the long excretion times for the urinary metabolite create significant issues for the athletes and for medical and disciplinary committees. The negative effects listed were mild intoxication, sedative effects, slower reaction times, memory problems, and tendency toward drowsiness. The authors recommended a clear distinction be made between social drugs and PES. In an earlier article, Campos et al. (8) addressed social issues, raised the consideration of safety in dangerous sports requiring quick reactions and careful timing, and pointed out the impact of use of THC on the integrity of sport.

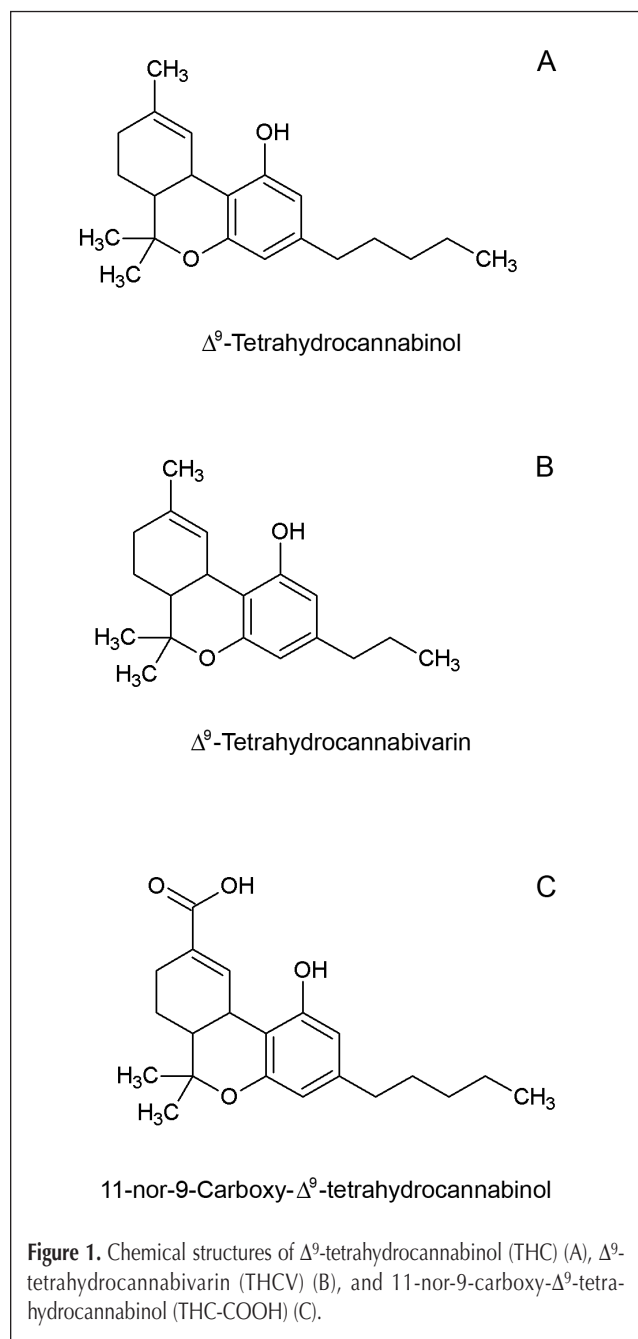
Discussion

Prevalence of use

Monitoring the Future data from a survey (9) of approximately 15,000 U.S. students in each of grades 8, 10, and 12, show that 11.8%, 26.7%, and 32.8%, respectively, of the students report using marijuana in the past year. Initiation of use is in the teenage years, and the percentage of users is highest in the U.S., Australia, and New Zealand. Approximately 1 in 25 adults, worldwide, aged 15–64 years, uses marijuana, despite adverse health effects. Approximately 10% of persons who have ever used cannabis become daily users, and approximately 20–30% become weekly users (10). Annual trends among 12th grade students in the U.S. show the highest use in 1978 as 50.2%, the lowest use in 1992 as 21.9%, and the current use at 32.8%. The “medicalization” of marijuana may have modified students’ view of use and resulted in this slow increase in recent years; however, the disapproval rating among the students toward regular use continues to be rather high at 85.9%, 79.9%, and 80.3% for grades 8, 10, and 12, respectively (9).

The NCAA completes a survey of student-athlete drug use on a recurring basis. The most recently available survey from 2005 (11) found that the percent of student-athletes using marijuana in or prior to junior high increased, most student-athletes used marijuana only 1 or 2 times in the previous 12 months, and the primary source of marijuana was a friend or relative. Marijuana use dropped in Division I student-athletes from 26.3% to 17.3% from 2001 to 2005. Marijuana use in Division III student-athletes appeared to be somewhat higher at 25.8% than either Division I or II student-athletes. The same study reported that college student-athletes are more likely to engage in high-risk recreational drug use than are non-athletes.

Buckman et al. (12), in a preliminary study, found that male college athletes that use PESs are at a higher risk of recre-



ational drug use and exhibit more risk factors for substance abuse than do peers that do not use PESs. In this study 70% of the student-athletes that use PESs had used marijuana in the last year compared to 22% of the student-athletes that did not use performance-enhancing substances. This study, even though preliminary and performed at only one university, clearly demonstrates a relationship between recreational substance abuse (including marijuana) and use of PESs.

From 277,928 specimens tested in 2009, WADA laboratories reported 399 adverse analytical findings for cannabinoids (13). USADA has sanctioned 35 athletes (14) for THC use in the years 2003 through 2009 out of approximately 22,700 specimens collected (15) in competition during that same time period. The important note here is that the athletes had received a great deal of education and fair warning that the testing for THC would be completed in-competition. A laboratory study (16) of marijuana use in sport was completed by the IOC in 1999. Thirty-six specimens out of 7421 urine specimens were found to contain THC-COOH above 15 ng/mL. The results of this study are difficult to interpret because certain IFs prohibited THC and others did not, and the basis for prohibition differed. In some cases, the prohibition followed IOC rules, and in other cases followed the rules of the IF. In addition, some specimens were collected at a competition, and others were collected out-of-competition. The study did show major differences in use among various sports. The positive rate from the laboratory in this study is only 0.5%.

One must be cautious and not assume the prevalence of use rate in a group of athletes is the same as the percentage of positive results from the reporting laboratory. A laboratory positive rate from a random testing program is the same as prevalence (even as an estimate) only if the athletes that are using THC are not casual users and are positive at all times. For example, if the users in the group are uniformly casual users and smoke cannabis only 2 times per month and are therefore positive by drug screening for perhaps 7 or 8 days out of the month, the prevalence rate will increase by 3 to 4 times the laboratory positive rate within that group. This difference between actual prevalence and a laboratory random positive rate will only increase if the athletes are less frequent users of marijuana, are not using prior to a competition and expect to be tested, or are otherwise evading detection. These data all show that marijuana is widely used in the U.S. and that the impact of marijuana use in sport and on the health of the athletes is an issue of significance.

Potency and natural occurrence

The concentration of THC in marijuana has been widely reported to have increased in the past two decades. The results of analysis are somewhat inconsistent and difficult to interpret, although ElSohly (17) does provide a good description of the actual material analyzed and the methods used. A recent report (18) by the Office of National Drug Control Policy indicates that the THC content (average of all samples) of seized domestic cannabis increased from 2.22% (dry weight) in 1985 to 4.80% in 2008. The percent dry weight of THC (average of all samples) for non-domestic cannabis increased from just under 3.48% in 1985 to almost 10.05% in 2008. The THC content of seized domestic marijuana (buds and leaves only) increased in the late

1990s and then declined to about 1985 levels by 2008. For non-domestic marijuana, the THC content almost doubled (3.44% to 7.21%) over the same time period.

Huestis provides a complete discussion of the chemistry and biology of cannabis (19). As a brief summary, THC occurs naturally in the annual herb *Cannabis sativa* as a number of monocarboxylic acids. During heating or smoking, the cannabinoids are decarboxylated to provide THC. The THC is then metabolized to a psychoactive substance, 11-OH-THC, and on to a primary inactive metabolite, THC-COOH. The THC-COOH excreted in the urine makes up a relatively small percentage of the total dose of THC administered and is the metabolite that is most frequently analyzed. THC-COOH occurs in urine free and conjugated. Approximately one-third of the smoked THC dose is eliminated in the feces.

Davis et al. (20) evaluated the fate of THC during smoking of cannabis (1.6% and 3.1% THC) by a cigarette smoking machine and determined that about 30% was pyrolyzed and 40% to 50% of the THC was released in the sidestream smoke. This should be a maximal amount because, in actual smoking, an individual will take a puff more frequently than does the machine (21). In addition, Perez-Reyes (21) did a regression of plasma THC concentration relative to marijuana potency and found a relationship; however, there was wide variability in the plasma THC concentrations, and plasma concentrations did not increase at the same rate as the increasing THC potency. In the case of oral ingestion, only 6–18% of THC is bioavailable (22). In addition, oral ingestion allows first pass metabolism of the THC to the inactive metabolites.

Doping control and analytical processes

Doping control specimens are collected under direct observation and prepared as a split specimen (in containers marked with a permanent number and identified with an A or B to identify the splits) to be shipped to the designated laboratory, generally by overnight courier. Following the report of an adverse analytical finding on the A specimen, the athlete has the right to observe the opening and analysis of the B specimen or have a representative observe that process. Any adverse analytical finding is based on a single urine concentration at a given time, and the information available is limited and does not allow an assessment of impairment or any significant pharmacokinetic modeling.

There are distinct differences between testing for THC-COOH in workplace testing laboratories under the rules of the Department of Health and Human Services (DHHS) (23) and the WADA procedures for accredited laboratories (24). One major difference is the WADA-accredited laboratories are scanning for THC-COOH along with many other potential prohibited substances. For example, the extraction and assay used for THC-COOH may include anabolic steroids, β -blockers, benzoyllecgonine, and certain opiates and β 2-agonists. As a result of the number of compounds being analyzed, the use of a urine immunoassay is impractical, and the THC “screening” is completed using extraction and derivatization followed by gas chromatography–mass selective detection (GC–MS). An example of the type of assay used by the WADA-accredited laboratories is given by Geyer et al. (25):

1. Internal standards are added to 2 mL urine: 11-nor-9-carboxy- Δ^9 -THC- d_9 at 15 ng/mL; 17 α -methyltestosterone at 25 ppm; [2,2,4,4- 2H_4]-etiocholanolone at 25 ppm; [16,16,17- 2H_3]-testosterone at 4.5 ppm; [16,16,17- 2H_3]-epitestosterone at 0.75 ppm; [2,2,4,4- 2H_4]-11 β -hydroxyandrosterone at 12 ppm; and [2,2,3,4,4- 2H_5]-androsterone-glucuronide at 25 ppm.
2. The mixture is hydrolyzed by β -glucuronidase from *E. coli* (pH 7.0, 50°C, 1 h).
3. Target substances are back extracted into tertiary butyl-methyl ether and dried.
4. Target substances are derivatized using MSTFA/ NH_4I /ethanethiol (1000:2:6, v/w/v).
5. Analysis is completed by GC-MS.

The initial assay procedure identifies the presence of molecular fragments indicative of one or more of the prohibited substances, which is then followed by a confirmation procedure to allow the unequivocal identification (and quantitation when required, as for THC-COOH) of the prohibited substance.

Huestis addresses the variety of analytical processes used in confirmation testing for THC-COOH (19). The confirmation procedures used in the doping control laboratories for THC-COOH are similar to the confirmation performed at the laboratories certified under the National Laboratory Certification Program (23) with several significant differences. The WADA-accredited laboratories use a threshold for THC-COOH of 15 ng/mL for an adverse analytical finding but must consider and report uncertainty. On September 1, 2010, a new technical document was implemented by WADA that establishes criteria for reporting of a THC adverse analytical finding (6).

1. The threshold of 15 ng/mL continues to be used.
2. The maximum combined absolute uncertainty allowed is 1.5 ng/mL or a maximum relative uncertainty of 10% is allowed.
3. The decision limit for reporting is 18 ng/mL, which is defined as the threshold plus a guard band of 1.645 times the maximum combined uncertainty rounded up to two significant figures. The guard band corresponds to the expanded maximum uncertainty giving a greater than 95% coverage interval for a result at the threshold concentration based on a one-sided distribution.
4. The quantitative results must be based on three independent determinations.

The reports of analysis are sent to the relevant anti-doping authority (results for most American elite, Olympic, or Paralympic athletes are forwarded to USADA) for results management and any required adjudication process. The athletes under the jurisdiction of WADA have the option of accepting the finding or having an administrative hearing with the CAS through binding arbitration. In addition, the athlete has a right to an appeal of the initial CAS decision at the International CAS (26).

Effect on performance

A number of studies have been completed to assess impairment as a result of use of marijuana. In 2002, Huestis (19) provided a very comprehensive review and discussion of the studies of effects of cannabis on human performance. The au-

thor tabulates epidemiological studies, performance studies, driving and flying simulator studies, and closed/open course driving studies. Many early studies were not definitive and often suffered from the lack of an appropriate control group and from the lack of complete data on the incidence of cannabis use in the general population. In addition, many epidemiological studies are based on widely variable methods of analysis, selection of specimens to be tested for cannabis, and the determination of the role of alcohol or other drugs in the event. Laboratory performance studies are complicated by the manner in which individuals smoke and the resultant variability in blood THC concentrations. Based on the performance studies, Huestis concludes that sensory functions are not highly impaired, but perceptual functions are significantly altered. As a result, the user may have difficulty concentrating and maintaining attention. In simulator and actual driving studies, the subjects apparently were aware of their impairment and compensated by driving at a reduced speed, passing less, and following at a greater distance (27,28). Huestis (19) states: "Cannabinoids are the number one illicit drug detected in motor vehicle injuries, fatalities, and DUID cases; and frequently, are found in combination with ethanol or other drugs. Critical skills needed for the safe operation of motor vehicles and other forms of transport can be impaired following cannabis use. Impaired functioning of psychomotor activities ...has been reported following cannabis use."

Various injury and performance studies reported since the Huestis review provide additional information. Gerberich et al. (29) completed a retrospective study of questionnaires submitted by 64,657 Kaiser Permanente patients during the years 1979 through 1985. Injury-related hospitalizations over a 10-year period from the time of completion of the questionnaire to December 31, 1991, were included. The study adjusted for age, alcohol use, and cigarette use and found increased rate-ratios (with 95% confidence intervals, CI) of all-cause injury hospitalizations for both men and women (1.58, 95% CI 1.29–1.94 and 1.55, 95% CI 1.12–2.10, respectively) among the current users, although other psychoactive drugs may be present as a confounding factor. Mura et al. (30) studied 900 drivers of automobiles involved in injury accidents and 900 age- and sex-matched controls. THC was found in the blood of 10% of all drivers in the injury accidents and 5% of all controls; however, of the under 27 age group 15.3% of drivers in injury accidents and 6.7% of controls had THC in the blood. The results demonstrate a higher prevalence of alcohol, cannabinoids, and the combination of cannabinoids with alcohol in blood samples from drivers involved in road accidents compared with controls. Ramaekers et al. (31) reviewed studies relating blood THC concentration to culpability for accidents and found drivers with higher levels of THC are 3 to 7 times more likely to be responsible for accidents than non-users of drugs or alcohol. Publishing in this same time period, Moving et al. (32) failed to find that cannabis alone contributed to culpability for injury accidents. Drummer et al. (33) studied 3398 fatally injured drivers to assess the effect of drugs and alcohol on the likelihood of the driver being culpable. Drivers with THC in their blood had a significantly higher odds-ratio (2.7, 95% CI 1.02–7.0) of being culpable than drug-free drivers. Drivers

with blood THC of 5 ng/mL or higher had an odds-ratio of 6.6 (95% CI, 1.5 to 28.0) of being culpable. Laumon et al. (34) compared 6766 culpable drivers and 3006 non-culpable drivers in France and had rather similar results with an overall odds-ratio of culpability of 3.32 (95% CI, 2.63–4.18) and an odds-ratio of culpability of 4.72 (95% CI, 3.04–7.33) if the blood THC level was 5 ng/mL or greater. Ronen et al. (35) studied volunteers who smoked cigarettes laced with THC and tested subjective feelings and driving ability after placebo, low dose of THC, moderate dose of THC, drinking, and 24 h after the high dose of THC. There were no effects after 24 h; however, the low and moderate doses of THC were equally detrimental to some of the driving abilities. Karschner et al. (36) followed THC, 11-OH-THC, and THC-COOH in 18 chronic, heavy cannabis smokers and found measureable plasma THC concentrations even after 7 days of monitored abstinence. The significant point to impairment is that previous studies have shown plasma THC levels of 2 to 5 ng/mL may result in impairment and that 4 of the subjects in the study had THC at those levels after 7 days of abstinence. The extended time periods for the presence of THC in plasma may suggest a mechanism for neurocognitive impairment in long-term heavy users after several days of abstinence. Canfield et al. (37) found the number of potentially impaired individuals involved in fatal aviation accidents increased 2.7 times from 1997 to 2006 and that the median THC blood concentration was significantly greater in the 2002–2006 time period compared to the 1997–2001 time period. This was attributed to use of highly potent THC.

Although early studies produced equivocal results on impairment, the recent studies, including the culpability and accident data, indicate that performance is, in fact, impaired and risk of accident or injury is enhanced. Highly potent cannabis, without titration by the user, may exacerbate that impairment, and the impairment may exist for a longer time period than previously estimated. The use of marijuana by the elite athlete prior to competition may result in danger to that particular athlete or others as a result of impairment of response or inappropriate decision making. Elite National and Olympic sports are performed at the highest level of physical coordination and cognitive effort. Despite the implication that if persons are aware of impairment they may compensate by various means in certain situations, the explanation would apparently not apply to elite sport. For success in highly competitive sport, the athlete will be performing at maximum capability and cannot afford compensatory actions.

Products inhaled during smoking

In 1990, Sparacino et al. (38) reported on the chemical substances contained in and produced by the combustion of marijuana. Smoke produced by machine smoking was fractionated into basic, acidic, and neutral fractions and mutagenicity evaluated by in vitro bioassay (39). Sparacino et al. (38) found that a number of condensate fractions were mutagenic to some degree, the basic fraction was most mutagenic, and the high-dose marijuana was more mutagenic than either a comparable tobacco fraction or low dose marijuana. In a recent study, Moir et al. (40) compared mainstream and sidestream marijuana and tobacco cigarette smoke. Using machine smoke pro-

duced under two different conditions, they found qualitative similarities and several quantitative differences between marijuana and tobacco smoke. Ammonia, hydrogen cyanide, NO, and NO_x were found at higher concentrations in mainstream marijuana smoke than in mainstream tobacco smoke, and selected polycyclic aromatic hydrocarbons were found at lower concentrations in mainstream marijuana smoke but at higher concentrations in sidestream marijuana smoke than the corresponding tobacco smoke. Marijuana and tobacco contain qualitatively similar carcinogens, and the burning of any plant material will result in different mixtures of chemicals depending on many variables. Thus, the qualitative similarities are more important than the quantitative differences in assessing the risks (40).

Maertens et al. (41) evaluated matched sidestream and mainstream condensates [as prepared by Moir (40)] of tobacco and marijuana smoke for (geno)toxic responses and found they differ substantially in terms of their cytotoxicity, *Salmonella* mutagenicity, and ability to induce chromosomal damage (i.e., micronucleus formation). Specifically, the marijuana condensates were all found to be more cytotoxic and more mutagenic than the matched tobacco condensates. Following correction for total particulate matter yield, the investigators found little difference in the mutagenic activity of samples smoked under the extreme or the standard regimen for both tobacco and marijuana condensates. The authors also note that the variations in the physical-chemical properties of the tobacco and marijuana smoke will likely modify the relative (geno)toxicity. As an example, THC may inhibit cytochrome CYP1A1 function and reduce the activation of polycyclic aromatic hydrocarbons.

A recent study using commercial cigarette tobacco has shown that smoking may result in direct exposure to many bacteria, including human pathogens (42). Considering the similarities in smoke produced by tobacco and cannabis, there is a reasonable expectation that bacteria would be inhaled from smoking of marijuana as well. Other studies using marijuana have found contamination with bacteria and fungi and a related increase in *Aspergillus* fungi in the lungs of marijuana smokers (43,44), although cause and effect cannot be established.

The athlete will thus be exposed to carbon monoxide, numerous chemical products of combustion, a variety of bacteria or fungi, and even pesticides if used in the growing process. The effects of carbon monoxide on the binding of oxygen to hemoglobin are well known and would potentially impact the physical performance of the athlete in a negative manner. In addition, smoking has adverse effects on the respiratory system.

Passive inhalation

The possibility of exposure of non-smokers to sidestream smoke from marijuana was identified as a concern very early as the process of developing assays to detect THC-COOH progressed. Zeidenberg et al. (45) found that a single subject exposed by passive inhalation was positive above 50 ng/mL for 11 days; however, the study has been criticized for not being well controlled and for the methods of analysis. Perez-Reyes et al. (46) completed various exposures, including the exposure of 2 subjects by 4 persons smoking 2 (2.8% THC) cigarettes each in

a station wagon for 1 h. All analyses for all exposures were by immunoassay, and only 2 of 80 samples collected exceeded a 20 ng/mL cutoff for the immunoassay in use. Other studies were completed using rather severe exposures to sidestream smoke from marijuana of low-to-moderate potency and with rather similar results (47–49). Mulé et al. (50) pyrolyzed about 108 mg of THC (total of 4 cannabis cigarettes) in an unventilated room of 21,600 L of air and exposed 3 subjects by passive inhalation for 1 h. Twenty-four hours postexposure, the subjects had less than 6 ng/mL cannabinoids by radioimmunoassay.

Cone (51) provides a summary of three extreme exposure studies (52,53) on passive inhalation. Study 1 exposed 5 subjects to 16 (2.8% THC) cigarettes for 1 h/day for 6 days in a small unventilated room (12,225 L). The range for the urinary THC-COOH was 15–35 ng/mL. Study 2 exposed 5 subjects to 4 (2.8% THC) cigarettes for 1 h/day for 6 days in the same room. The range for the urinary THC-COOH was 0–12 ng/mL. Study 3 exposed 2 subjects to 16 (2.8% THC) cigarettes for 1 h/day for 6 days in the same room. One subject had 10 ng/mL urinary THC-COOH, and the other reached 87 ng/mL.

In the studies using artificial smoking, the mainstream smoke was removed from the room; however, the subjects were exposed to conditions so severe that goggles were worn to protect the eyes.

In recent work, Rohrich et al. (54) followed eight healthy volunteers who were exposed to cannabis smoke for 3 h in a coffee shop in the Netherlands. The study could not obtain information about the cannabis being used by the visitors, the concentration of THC in the air, or ventilation as the study area was an active coffee shop. The environment was described as being not too smoky. Blood samples were taken up to 14 h and urine samples were taken up to 84 h. Samples were analyzed by immunoassay and by GC–MS for THC, 11-OH-THC, and THC-COOH. THC-COOH could be detected in blood samples by 1.5 h after start of exposure, and after 14 h, three of the eight blood samples had remaining THC-COOH concentrations between 0.5 and 1.0 ng/mL. None of the urine specimens produced an immunoassay response above the threshold of 25 ng/mL, but total THC-COOH up to 7.8 ng/mL was found by GC–MS. Of note is that two subjects whose urine specimens each contained 11 ng/mL of cannabinoid equivalents by immunoassay at zero time also had the highest single point urinary THC-COOH concentrations by GC–MS when tested following the exposure; however, no THC-COOH was detected by GC–MS in those subjects in the zero time urine, and the subjects claimed no association with cannabis prior to the study.

The potential for passive inhalation is subject to many variables, such as the potency of the cannabis, the quantity of THC released in sidestream smoke by the smokers (the manner in which the cannabis is smoked), the percentage of THC destroyed by pyrolysis, the individual metabolic characteristics of the person exposed and, most significantly, by the size of the room and the type of ventilation. Hayden (55) reviewed the published data and concluded that there appeared to be data to support the possibility that passive inhalation could produce enough THC-COOH in the urine to exceed the 15 ng/mL threshold. Giardino (56) has proposed a model to link an in-

door air quality model with a pharmacokinetic model to predict a passive marijuana smoker's resultant concentration of THC-COOH.

These data are reviewed to bring forward the consideration of the impact of the increasing concentrations of THC in *Cannabis sativa* seen in past years and the use of a variety of THC containing materials. Yonamine et al. (57) discuss passive inhalation as a possibility for a non-intentional doping violation in sport and Busuttill et al. (58), prior to the Rebagliati positive in 1998, raised the issue of passive inhalation as a novel defense strategy (the passive inhalation strategy is not so novel and has, in fact, been used for the past 28 years in a variety of jurisdictions and with very limited success). Busuttill et al. (58) cover the potential conditions that would allow an athlete to approach the testing threshold, including an exposure approaching 16 (2.8% THC) cigarettes being smoked in 1 h in a small, unventilated room. The authors state that anyone willing to endure the exposure required is, in fact, a willing participant and raises the issue of “deliberate passive exposure” because unknowing passive exposure to produce a THC-COOH concentration above the 15 mg/mL threshold is essentially not possible. When the actual laboratory conditions required to approach a level close to a threshold are examined, passive inhalation does not have a major effect in actual exposures and should not affect doping control. In addition, in the case of testing in sport the concept of “strict liability” applies and the athlete is ultimately responsible for the presence in the body of any prohibited substance. One can safely say that the presence of THC-COOH in urine at any level approaching the 15 ng/mL confirmation threshold could not occur without the knowledge of the athlete. Despite these considerations, an actual study under the most realistic conditions possible and using cannabis of a higher THC concentration and hashish for inhalation exposures would provide beneficial information concerning plasma THC and urine THC-COOH levels following passive inhalation.

Health effects

The health effects of chronic exposure of athletes to cannabis are not the primary focus for WADA, because the prohibition on THC only applies in-competition. Despite the limited prohibition in sport, certain adverse health effects are of significance. Dependence is defined as increased tolerance, compulsive use, impaired control, and continued use in the presence of physical or psychological problems. The lifetime risk of becoming dependent on cannabis is approximately 7% to 10% for regular users, and the early onset of use is a strong predictor of future dependence (59). Compton et al. (60) examined changes in use, abuse and dependence on marijuana from 1991–1992 to 2001–2002. The investigators found that overall use had not increased remarkably; however, abuse and dependence had increased in past-year users from 30.2% to 35.6%. A second effect of interest is the gateway effect or the possibility that cannabis users will be more likely to use harder drugs. There are several possible explanations for the gateway effect: 1. cannabis users have better access to other illicit drugs because cannabis has the same suppliers; 2. the pharmacologic effects of cannabis increase the propensity to use the other illicit

drugs; and 3. the common cause explanation that those who are cannabis users are more likely to use other illicit drugs for reasons other than cannabis use. At this time, the explanation for the gateway effect is not clear; however, the association between cannabis use and other drug use is clear (61). There are other adverse health effects of use of cannabis such as the potential contribution to development of schizophrenia and other mental health conditions, reproductive effects, chronic respiratory conditions, and increased opportunity for certain cancers (61).

The American Society of Addiction Medicine (ASAM) recently published a public policy statement on the use of marijuana as a medication (62). Most physicians recognize the need to dispense medications in a known dose and composition and by a means of delivery that is not harmful to the patient. The physician is the controller of access to the cannabis but does not have the knowledge or information to control the quality, dose, or composition of the prescribed medication. The use of medical marijuana creates a situation where a physician must ignore the basic tenants of evidence based medicine and cannot use monitoring and follow-up to ensure appropriate utilization of a prescribed medication. "ASAM asserts that cannabis, cannabis-based products, and cannabis delivery devices should be subject to the same standards that are applicable to other prescription medications..." ASAM rejects smoking as a means of drug delivery based on safety considerations. In particular, ASAM states that the physician and patient should have a bona fide relationship and adhere to established professional tenets for proper patient care such as doing a good faith examination, developing a treatment plan, doing a periodic review of the efficacy of treatment, providing record keeping, and consulting as necessary.

Therapeutic use exemptions

The WADA Code (4) establishes that signatories to the Code must establish a process for submission and consideration of therapeutic use exemptions (TUEs). The procedures are included in the International Standard for TUEs (63). This article will not address the procedures or forms required, but will summarize the criteria for decisions on a request for an exemption and their applicability to marijuana. The Code requires that physicians (a TUE Committee) review the request for the exemption and establishes the criteria for consideration of a request for a TUE. The criteria are as follows:

1. Would the athlete suffer significant impairment without the use of the prohibited medication?
2. Will the medication produce significant performance enhancement above what would be obtained with a return to normal health?
3. Are/is there a reasonable therapeutic alternative(s)?
4. Is the need a result of a prior non-therapeutic use of an otherwise prohibited medication or method?

The TUE request must include diagnostic and current treatment data as well as a statement by an appropriately qualified physician describing the necessity of the otherwise Prohibited Substance or Prohibited Method in the treatment of the athlete. In particular, the request must describe why an alternative permitted medication cannot, or could not, be used, and the

criteria must be covered completely for the TUE committee to consider granting an exemption for cannabis. There is little unequivocal evidence for the therapeutic efficacy of smoked marijuana, and there are many alternative medications. In consideration of the statement of the ASAM, the TUE committee will find the approval of a request for a TUE for smoked marijuana to be a very difficult and unlikely event.

Pharmaceutical THC is available as dronabinol (64) for the treatment of anorexia at a usual dose of 5 mg/day and as an antiemetic for chemotherapy-induced emesis at a higher dose, usually 15 to 20 mg/day. Dronabinol is a schedule III medication in the U.S. Sativex (65) is available in Canada and the U.K. as a buccal spray for the treatment of pain associated with multiple sclerosis. The principal active components of Sativex are THC and cannabidiol (CBD). In the case of a pharmaceutical THC, the dose is controlled, the mode of administration is not toxic, and the effects of treatment are known and can be monitored. However, any request for a TUE must meet all the criteria and document that no permitted medication will suffice; the decision is entirely at the discretion of the TUE Committee. The concern is that the use of a pharmaceutical THC can open the way to use of cannabis by the athlete and with no reliable way for laboratories to always distinguish between the two modes of use. In the TUE process, the anti-doping organizations do approve or disapprove the request for a TUE; however, it is not the medical treatment that is approved or disapproved. The TUE committee is only following the rules of sport on the use of that particular medication.

ElSohly et al. (66) noted that Δ^9 -tetrahydrocannabivarin (Δ^9 -THCV, Figure 1B) would be useful to distinguish between cannabis use and use of dronabinol and then published an analytical procedure for the carboxylic acid metabolite of Δ^9 -THCV (67). De Boer et al. (68) developed a GC-MS-MS method for the detection of the metabolite 11-nor- Δ^9 -tetrahydrocannabivarin-9-carboxylic acid (THCV-COOH). De Boer et al. (68) also noted that the presence of THCV-COOH establishes the use of cannabis rather than dronabinol; however, the absence of THCV-COOH does not establish use of dronabinol because some cannabis contains only a very small amount of the Δ^9 -THCV. As a result, the laboratories may, in some cases, have the possibility of distinguishing between use of cannabis and pharmaceutical THC.

THC receptors

Although these topics have only an indirect impact on sport at this time, they provide additional explanation as to the physiological and pharmacological effects of THC. In addition, they outline a challenge to the World Anti-Doping Agency and the many anti-doping organizations that must develop an appropriate response to the many cannabimimetics (cannabinoid receptor agonists) that are available, even at this time. Decades of research have led to significant advances in the understanding of the effects of THC in humans. The appearance and use of the cannabimimetics on a large scale is relatively recent.

Following the elucidation of the structure of THC (69), more than 20 years passed before cannabinoid receptors were identified. CB₁ (70) was first found in rat brain as a G-Protein coupled receptor, cloned, and the primary structure determined

(71). An essentially homologous (97%) receptor was later found to occur in human brain (72) and has been accepted as the receptor through which the physiological effects of cannabinoids are mediated (73,74). CB₂ was soon discovered (75) and found to occur primarily in the immune system. The CB₂ receptor has 44% identity with the CB₁ receptor, although there appears to be greater homology with the transmembrane portion of the receptor. With the discovery of endogenous receptors and the idea that animals do not make receptors for exogenous plant substances without a specific purpose, work proceeded to identify the endogenous substances that would bind to the receptors and the mechanism of action of those substances. The first endogenous cannabinoid to be identified was anandamide (76). CB₂ has since been found in tissues other than the immune system, including some areas of the rodent brain (77) and in primary sensory neurons (78).

The outcome of early receptor studies was the identification of structure activity relationships and the interpretation of binding of cannabinoids in terms of ligand-receptor interactions as comprehensively summarized by Seltzman (79). With the identification of the structure of the receptors, the field was open for the application of modern computational capabilities to the development of specific substances that had the desired pharmacologic effect and limited negative side effect; however, the methods to differentiate between the binding affinity at the two endogenous receptors had to be developed. This was done by using preparations that specifically included only one of the receptors and measuring displacement of a known ligand from that receptor. Although various methods have been used, an example for the study of CB₁ is the displacement of a high affinity tritiated cannabinoid from the receptor on the cell membrane by the ligand of interest (73).

Affinity for the CB₂ receptor is determined, for example, by the displacement of the same or a similar high affinity tritiated cannabinoid from transfected cell lines (80) or a mouse spleen membrane preparation (81). The functional effect of the binding of a cannabinoid to either CB₁ or CB₂ receptors is evaluated by several different methods, including the ability of a ligand to reduce the forskolin-induced stimulation of ATP (82) or the ability of the ligand to activate the G-Protein coupled receptor using [35S]GTPγS binding (83).

Following the discovery of CB₁ and CB₂ and the development of methods for assessment of receptor binding affinity and the pharmacologic effect subsequent to binding to one of the receptors, the search for cannabinoid agonists and antagonists expanded. Synthetic cannabinoids were developed many years ago with the objective of finding pharmacological effect with a reduced psychoactive component following administration. During the development of nonsteroidal anti-inflammatory drugs, Pfizer found a series of nontraditional cannabinoids that lack the dibenzopyren ring of THC but exhibit the typical pharmacology of THC (84). In essentially the same time period, Sterling-Winthrop reported the development of aminoalkylindoles (AAIs, Figure 2A) and other cannabimimetics (Figure 2B and 2C) which were found to interact with the G-Protein coupled cannabinoid receptor in the brain with high affinity (85). Of particular importance is WIN-55,212-2 (Figure 2D),

which is a rigid AAI and has been used extensively, as described here, in studies of the cannabimimetics.

The chemistry and pharmacology of cannabimimetics were reviewed initially in 1999 (86). A second review, completed in 2005, focused on the cannabimimetic indoles, pyrroles, and indenenes (Figure 2). In this review, Huffman and Padgett (87) concluded that the cannabimimetics reviewed probably interact with the cannabinoid receptors at a different site than the classical cannabinoids or the endogenous cannabinoids and that the interaction may well be aromatic stacking. The authors also conclude that the development of ligands with greater specificity for each type of cannabinoid receptor would be beneficial. A recent article by Hanus and Mechoulam (88) provides an extensive review and listing of the endocannabinoids, cannabinoid receptor agonists and antagonists, and various other related substances.

The CB₁ receptor has been primarily localized in CNS and found to mediate the psychotropic effects of cannabinoids. The "tetrad model" of cannabimimetic activity represents one of the best available measures of cannabimimetic activity and has been used to identify and classify cannabinoids (89). The model includes a specific array of effects including hypolocomotion, hypothermia, antinociception (reduction of sensitivity to pain), and catalepsy (reduced ability to initiate movement). In studies of THC, Monory et al. (90) have found that several of the important pharmacological actions of THC are dependent on the CB₁ receptor but that effects are mediated by different neuronal subpopulations. For example, GABAergic neurons (releasing gamma aminobutyric acid) influenced locomotion and hypothermia, whereas glutamatergic neurons mediated the cataleptic effect.

The CB₂ receptor is of particular interest because of the possibility of finding a substance that will control neuropathic pain but not contribute significant psychotropic effect. After the finding of CB₂ receptors in sensory tissue, research efforts have proceeded in two directions. One is to find a cannabinoid that is restricted to peripheral tissue (and will thus not be psychotropic), and the second is to find an agonist that is selective for the CB₂ receptor. Anand et al. (91) have provided a review of these topics and a summary of various compounds that influence the endocannabinoid system. Their conclusion is that a number of possibilities exist to provide an analgesic without the psychotropic effect. Of particular note is the interaction of CB receptor activation with the μ-opioid receptor with the possibility of synergistic effects and the increase of analgesia of non-steroidal anti-inflammatory agents with co-administration of cannabinoid agonists.

These receptor studies provide insight to the addictive behavior that develops in some of the regular users of marijuana and of the cross-talk that occurs with the opioid receptors (92). The co-localization of the CB₁ receptor with the opioid receptor provides a possible explanation for the gateway effect and demonstrates several interesting properties (93):

1. Animals will self-administer THC in a manner similar to other drugs of abuse.
2. Administration of the CB₁ receptor antagonist SR141716A blocks heroin self-administration in rats.
3. The same CB₁ receptor antagonist (SR141716A) induces a

partial opioid-like withdrawal symptoms in morphine-dependent animals.

4. The opiate antagonist naloxone precipitates a mild withdrawal syndrome in cannabinoid-dependent rats.
5. CB₁ knockout mice will not self-administer morphine (different than other drugs of abuse).
6. Cannabinoids will induce relapse in heroin-dependent animals that have been abstaining.
7. Heroin will induce cannabinoid seeking behavior in rats abstinent for a prolonged period.

Non-CB₁ or non-CB₂ receptors

Although strictly beyond the scope of this article, but of great interest, is the work of the last 15 years on non-CB₁, non-CB₂ receptors for cannabinoids, endocannabinoids, and cannabimimetics. The superficial summary included here is from a recent review by De Petrocellis and Di Marzo (94), which includes comprehensive discussion, tabulation of substances and effects, and original references detailing the current status of research. The background is that CB₁ and CB₂

mediate most of the pharmacological effects of THC; however, they are not the unique targets of the endocannabinoids such as anandamide, nor are they the receptors for other plant cannabinoids. In particular anandamide and cannabidiol seem to be candidates for this atypical binding. THC and synthetic cannabinoids produce the expected pharmacological effects in the wild-type mouse and the effects are blocked by CB₁ receptor antagonists and the effects are absent in the CB₁ receptor “knockout” mice. For anandamide, these typical cannabimimetic effects can still be seen in transgenic mice lacking the CB₁ receptor and some effects are not blocked by the CB₁ receptor antagonists. These findings indicate the possibility anandamide is interacting with non-CB₁, non-CB₂, G-protein coupled receptors (GPCRs, based on sensitivity to pertussis toxin). Two GPCRs have emerged as potential non-CB₁, non-CB₂ GPCRs for the endocannabinoids. One of those receptors, GPR55, has been found to be targeted by a number of cannabinoids and to be activated by THC with greater efficacy than is the CB₁ receptor. Anandamide activated GPR55 with potency equivalent to that activating CB₁ and CB₂ receptors and

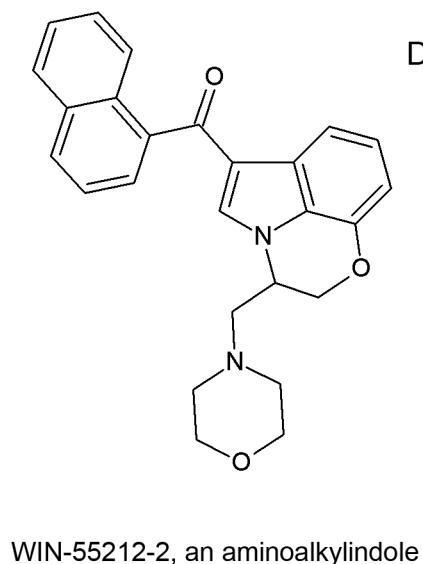
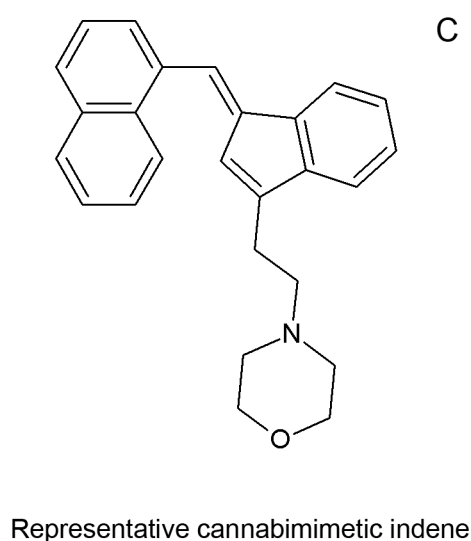
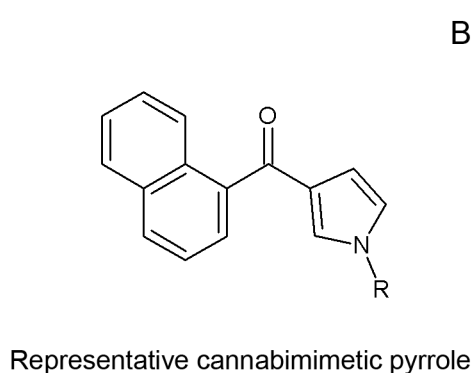
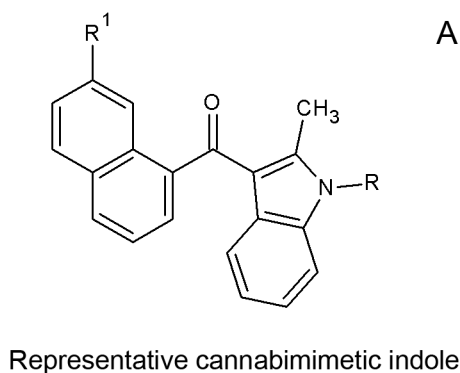


Figure 2. Representative chemical structures of cannabimimetic indoles (A), pyrroles (B), and indenenes (C). The structure of the cannabimimetic (D).

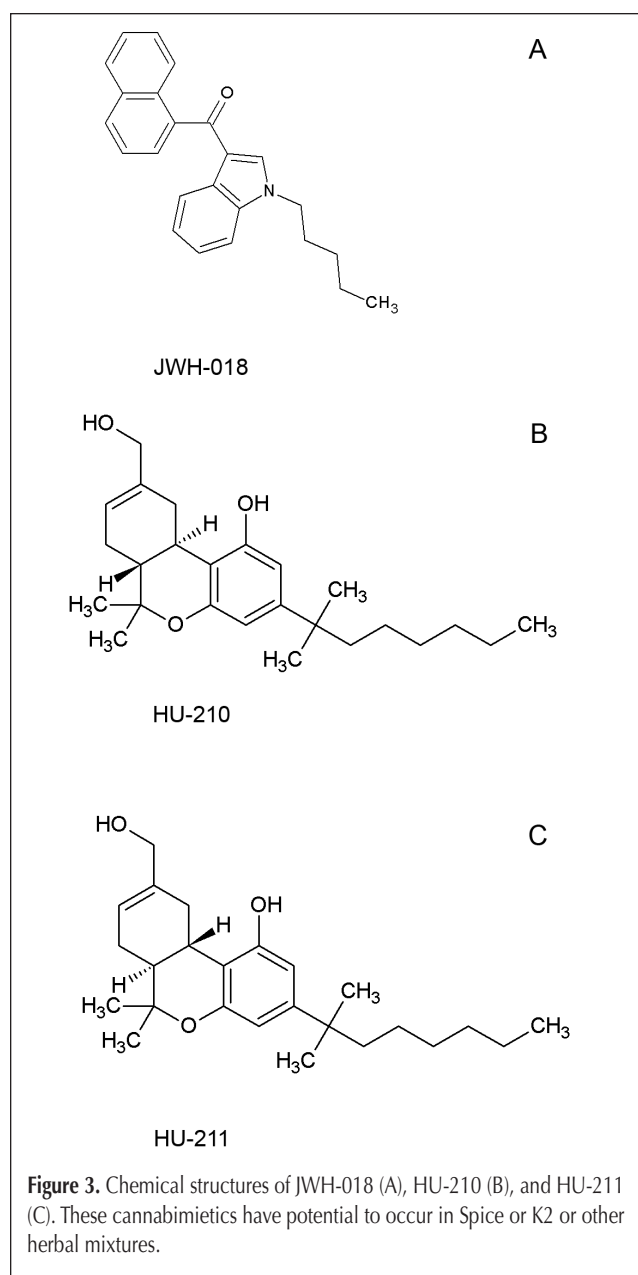
demonstrated that this ligand may equally influence signaling by all three receptors. Anandamide also activates certain transient receptor potential (TRP) channels which gate the passage of several types of cations, including calcium, following various physical or chemical agents. In the case of endocannabinoids the existence of several potential receptors may provide flexibility and allow them to participate in various physiological and pathological conditions depending on the distribution of their receptors in tissue. The authors point out that much of the work described was “in vitro” and that “in vivo” studies must be used to conclusively demonstrate the role of these unique receptors in the pharmacology of the compounds (94).

Spice and K2 as cannabimimetics

The producers of illicit substances are exceedingly adept at identifying chemicals of interest from syntheses performed many years ago. This has been the case with novel anabolic

steroids and is now a process that is seen with “legal” cannabinoid and cannabimimetics as alternatives to THC. Many synthetic procedures are published, and the producers of illicit substances are using those methods for products that are being introduced at many outlets for illicit substances, such as the internet. The recent introduction of “Spice” falls into this category and was the subject of a DEA intelligence alert (95). The Customs and Border Protection Chicago Laboratory received and analyzed “Spice Silver”, “Spice Gold”, “Spice Diamond”, “Genie”, and “Yucatan Fire”, which were purportedly laced with cannabinoids or cannabimimetics. Upon derivatization with *N,O*-bis(trimethylsilyl)acetamide, HU-210 (Figure 3B) was identified at a low level (not quantitated) in every packet analyzed. The DEA intelligence alert provides the ions that were used in the identification process. HU-210 is a Schedule I substance in the U.S. (96), and products containing HU-210 and similar cannabinoids are controlled in the U.S. and other countries including Austria, Canada, Germany, Netherlands, and Switzerland. A report from European Monitoring Centre for Drugs and Drug Addiction (97) found JWH-018 (Figure 3A), HU-210 (Figure 3B), CP 47497, and related cannabimimetics and stated that the JWH-018 had a binding affinity for the CB₁ receptor that was 100 times that of THC. The DEA has added HU-211 to the list of Spice Chemicals of Concern (98); however, HU-211 is not currently controlled by the Controlled Substances Act. HU-211 (Figure 3C) varies from the structure of HU-210 in the configuration of two hydrogen atoms. Despite these findings, the identification of HU-210 in the cannabimimetics sold over the internet is relatively rare (99).

Auwarter et al. (100) identified a series of cannabimimetics in various “Spice” products. Although the author did not find HU-210 or THC, three of the substances identified were similar with one being a trans diastereomer and the other a homologue (dimethyloctyl) of the cannabimimetic CP 47497. Of particular note is the identification of JWH-018. The activation of signaling pathways by JWH-018 has been evaluated using in-vitro preparations (101). Using cultured hippocampal neurons Atwood et al. (101) found that JWH-018 inhibited excitatory post-synaptic transmissions, a finding in accord with previous work on cannabinoids and endocannabinoids (102). In addition, Atwood et al. (101) found that JWH-018 increased the phosphorylation of extracellular-signal-regulated kinase (ERK 1/2) mitogen activated protein kinase (MAPK), which is a typical consequence of CB₁ receptor stimulation (103). Atwood also found significant CB₁ internalization following activation of the CB₁ receptor. The conclusion is that JWH-018 is a potent activator of the CB₁ receptor and produces the consequent effects on cellular signaling and neurotransmission, even though the binding may be at a somewhat different location than cannabinoid binding. Thus, HU-210 and/or JWH-018 are likely to account for the psychotropic effects of Spice by activation of the CB₁ receptor and JWH-018 is likely to account for the psychotropic effect of K2. K2 is a herbal smoking blend made of herbs and spices sprayed with cannabimimetics (probably JWH-018) that mimic the effects of cannabis. K2 is a product similar to Spice and comes in many varieties with names such as Blue, Blonde, Summit, Standard, and Citron. On Tuesday, March 1,



2011, the DEA placed five synthetic cannabinoids into Schedule I of the Controlled Substances Act. The order is temporary and applies to JWH-018, JWH-073, JWH-200, CP-47,497, and CP-47,497 C8 homologue (104).

Conclusions

With the use of cannabis in-competition there is the increased possibility of injury or accident and the possible violation of law in a number of countries, both of which may impact directly on sport and the spirit of sport. In addition, there are potential health risks to the athlete, including the gateway effect of increased possibility of use of other drugs, dependence, and adverse psychological effects. Despite the inclusion of marijuana on the WADA prohibited list, athletes continue to use marijuana and to be sanctioned for that use, which again emphasizes the willingness of athletes to participate in risk taking for a variety of reasons and to use substances that may, in fact, reduce their athletic performance. Despite the widespread social use of marijuana and a general societal view that marijuana does no harm, the opposite is true, and there are appropriate reasons for the WADA to prohibit cannabinoids in sport. Marijuana/THC use may appropriately be classified as prohibited by WADA under the criteria applied in assigning a substance or method to the prohibited list. Pipe (105) has written on the effect of many doping substances on the health of the athlete which reiterates the appropriate concern WADA has for the health and safety of athletes. Pipe emphasizes that prevalence of abuse is difficult to determine among athletes, clear evidence of the adverse effects of substances is difficult to establish when the use is surreptitious, and we would be naïve to assume that knowledge of the side effects of doping substances or methods would necessarily deter the drug taking behavior when the abuse is tolerated or encouraged in certain circles.

Recent data show a trend of increased use of marijuana (106). The rate of current marijuana use among youths aged 12 to 17 increased to 7.3 percent in 2009 and 7.4 percent in 2010 and the use among young adults (aged 18–25) increased from 16.5 percent in 2008 to 18.1 percent in 2009 and 18.5 percent in 2010. This may be due in part to the “medicalization” of marijuana, but shows an increase in use that may impact on sport, because the age groups shown are primary participants in sports.

Marijuana may not be performance-enhancing in the traditional sense; however, there may be effects in certain sports which create an unfair advantage, create a safety hazard, adversely impact the health of the athlete, or violate the spirit of sport.

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