WADA Prohibited List: The Benefits of Combining Pharmacology, Medicine, and Law

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The yearning to win sports competitions has led some athletes to dope. Doping in sports is a real threat to the 'Spirit of Sport' and fairness. The pharmacokinetics of performance-enhancing drugs differ, as do their effects and purposes of use. As one of the most effective and decisive solutions, the idea to issue a prohibited list came to raise the legal awareness level among athletes about the types of prohibited substances and methods they have to avoid and in which time specifically. In addition, for the sake of broader and more comprehensive cooperation between the law, medicine, and pharmacology, to confront the phenomenon, and limit it to the narrowest possible scope on the other hand. The idea to issue the prohibited list came. Historical, descriptive, and legal approaches are employed in conducting this review. Additionally, the method of conceptual analysis is used to discover the exact normative terminology. The most significant finding for this review is that the issuance of the Prohibited List brought greater stability to sporting events. Its annual issuance is legal proof in front of everyone (countries, international sports organisations, and athletes).

Keywords: Doping; Sports Medicine; WADA's List; Banned Substances Prohibited Methods

I. INTRODUCTION

Sports builds personality as it prepares you to perform through the rules and teaches you to apprehend what it feels like to win or to lose. It informs you about life (Harris, 2020). Sport's soul is festivity of the human spirit, body, and mind. This is mirrored in the ideals we reach in and around sport, such as morals, reasonable play, integrity, fitness, performance quality, and fun and satisfaction (Sumner, 2017). However, sports have an eminent history of doping, which can be traced back to antiquated Greece and Roman fighter batting (Breenfeldt Andersen et al., 2021). In any case, regardless of the numerous notorious doping incidents and the number of competitors admitting to doping, there is an implicit misconception that it is "essential for contend" during their dynamic careers (Breenfeldt Andersen et al., 2021). In sports, taking and giving prohibited items are deceptive actions. But not a single contestant will practise such a thing accidentally (Al-Dafrawi, 2020). Albeit medication is a treatment that influences the body's physiological activities and is used for the determination, prevention, and treatment of illnesses. The phrase 'ill-usage points to 'extravagant or malicious use.' (Deeksha 1 et al., 2017). In sport, doping is an example of duplicity and a scrupulous, criminal and health impairment (Mallia et al., 2016). The medications are linked to a variety of negative consequences, varying from gentle to life-menacing, temporary to endless (Schartau, 2020). Sports logicians have developed law-related to aspects of the sport (Croteau, 2020). After the approval of the first version of the World Anti-Doping Agency Code (WADC) during the Second World Congress on Doping in Sport, March 2003, in Copenhagen, Denmark, World Anti-Doping Agency (WADA) presumed that it is responsible for supporting, renewing, and promulgating the banned list of the substances and techniques (the List) in sport (Mazzoni et al., 2011). In this review, our focus is to deeply read the banned items and methods that came in the final version of WADA's 2021 Banned List.
II. DOPING, MEDICINE, AND PHARMACOLOGY

People have attempted to develop their bodies in a fake manner by using legitimate, illegitimate, healthful and unhealthful methods (Mazzeo, D’Elia & Raiola, 2018). Fundamentally viewed, the materials accessible around then may presumably be classified between supplements or dietary enhancements (such eggs, flesh, blood) and true “drug-like” elements with unbiasedly anticipated movement (like bull gonads, or cocktails with them in any case two-edged impact on the action) (Müller, 2010). Basically, the act of human emasculation, which likely started around 2000 BC in Babylon, gave proof that deficiency of the gonads implied that guys lost their richness, yet additionally their intensity, their ability, and their hostility (Yesalis & Cowart, 1998). According to Holt and his colleagues, “One of the first performance-enhancing substances to be tried was testosterone. Having identified the properties of this hormone by examining the behaviour of their animals following castration, the ancients were reported to eat the testes of other animals or humans to improve or heal their own.” (Holt et al., 2009). In the contemporary merciless time of sports, competitors are unhesitant to forfeit their respectability and face a challenge to acquire the joust edge and promote the performance (Malve, 2018). In a similar ruthless contest, the consumption of performance-enhancing substances (PESs) has frequently grown familiar (Malve, 2018). Examining the effect of biologically effective substances associated with sound people as food or medications that enhance impedance to many, harmful, factors, and improve recuperation from natural stressors or prevent ailment, and it is called pharmacosanation (Malve, 2018).

III. LEGAL ACTIONS AGAINST DOPING IN SPORT

Competitors have been prohibited from dope since 1928, and however, with minimal in the method of testing accessible, they needed to depend on the expression of the competitor that they were spotless (Taware & Bansode, 2016). In 1966, the Union Cycliste Internationale (Cycling) and FIFA joined the IAAF in the battle against medications, then trailed by the IOC in 1967 (Taware & Bansode, 2016). Currently, it is apparent that competitors utilise a few different ways of doping in sports like steroids, erythropoietin, and GH. Moreover, the utilisation of energizers, blood doping, diuretics, and beta-blockers have also been added to doping (Ali et al., 2016). WADA was founded under the leadership of the International Olympic Committee (IOC) for the control of doping in 1999 (Altukhov, Li & Nauright, 2019). The doping disgrace in the Tour de France in July 1998 is considered as the fundamental justification for making of WADA later on (Altukhov, Li & Nauright, 2019). The first World Meeting on Doping in Sports was done in Lausanne, Switzerland in February 1999, and it is known as the start of WADA’s action (Altukhov, Li & Nauright, 2019). Different elements prompting the formation of WADA in 1998 and 1999 incorporated another embarrassment associated with debasement and scheme charges of Nagano, Sydney and Salt Lake City bid boards of trustees with commissioners from the IOC as the selection of the Olympic host urban areas occurred during the 1990s (Altukhov, Li & Nauright, 2019). Another ‘threat’ was important to switch public consideration and save contracts with supporters of the IOC (Altukhov, Li & Nauright, 2019). Doping turned out to be such a menace. Subsequently, WADA was made to combat the ‘world corruption’ – doping (Altukhov, Li & Nauright, 2019).

In Malaysia, by November 2006, the Malaysian government ratified the UNESCO International Convention against Doping in Sport after the approval of the Malaysian Cabinet on August 2, 2006 (AL-Dafrawi et al., 2019a). Then, in May 2007, Malaysia approved the Global Anti-Doping Act. The accepted document was signed by the Malaysian Minister of Youth and Sports, and in the same year, ADAMAS was officially launched under the National Sports Institute as an anti-doping unit (AL-Dafrawi et al., 2019a). Since then, ADAMAS operates as the National Anti-Doping Organization (NADO) for Malaysia. Since mid-2016 AD, ADAMAS has been reorganised under the management of the Malaysian Ministry of Youth and Sports (AL-Dafrawi et al., 2019a).

IV. CRITERIA FOR BANNING SUBSTANCES AND METHODS

WADA became a successor to the IOC-MC for handling the List in 2004 (Fitch, 2012). As of now, WADA has 3 criteria...
for including a drug in the List namely, danger of the drug to health, enhancing sports performance and opposing sports spirit (Fitch, 2012). Two of the three standards or criteria are inevitable to insert an element or technique inside the List (Fitch, 2012). The listicle is a dynamic text that is open to continuous revision and adjustments. After deliberations, stakeholders and experts participate in the additions and deletions to the List (Vernec et al., 2017). Notwithstanding, when reviewing the updates, one has to realise the lack of clear scientific evidence regarding lifting energy, or the health risks related to taking a particular substance in specific sports groups (Vernec et al., 2017). The List exceeds sport and frontiers, demonstrating the benefits of the international agreement of rules while producing other difficulties; various medical uses, diverse cultural convictions and sport attitudes nowadays need to be assimilated into one List (Vernec et al., 2017). WADA presents a thorough and detailed list of prevented items and procedures in the forbidden List (Melethil, 2006). Anabolism factors, hormones, beta-2 agonists, anti-estrogenic agents, and diuretics are the 5 classes of illegal materials. Oxygen transference improvements, different ways of intervening in samples, and gene doping are all banned (Melethil, 2006). In general, the just existence of an Illicit item inside the body will present prima facie proof of a violation of the anti-doping rules (Cowan & Abbate, 2020). However, for some chemicals, there may be a threshold above which their quantities in urine must be surpassed before the WADA-accredited laboratories that test the samples declare an “Adverse Analytical Finding” (AAF) (Cowan & Abbate, 2020). The beta-2 agonist salbutamol, as an example, is criminalised if its concentration into the urine is over 1000 ng/mL. The lab will apply a measurement uncertainty of 200 ng/mL as designated by WADA and will not report an AAF for salbutamol unless the concentration surpasses 1200 ng/mL (Cowan & Abbate, 2020). The lab will assure that the measurement uncertainty of its analytical method is smaller than the WADA stipulated value, which is seen to be the pinnacle allowed value (Cowan & Abbate, 2020).

Legally speaking, doping acts of taking, giving prohibited substances in their traditional forms leave metabolic and notable traces in the blood and urine of athletes who use them, thus proving their occurrence is not difficult (AL-Dafrawi et al., 2019a). In contrast, nothing enters the bloodstream or left in the urine with Gene Doping, so proving it is, for the time being, a figment of the imagination (AL-Dafrawi et al., 2019a).

A. Substances and Methods Prohibited at All Times (In-and out-of-Competition)

1. So Non-Approved Substances

According to the Prohibited List, “any pharmacological substance which is not addressed by any of the subsequent sections of the List and with no current approval by any governmental regulatory health authority for human therapeutic use (e.g. drugs under pre-clinical or clinical development or discontinued, designer drugs, substances approved only for veterinary use) is prohibited at all times” (Prohibited List, 2021). Items in this class might be treatments in pre-clinical or clinical development, inert medications, designer drugs, or substances authorised specifically for veterinary treatment (Heuberger & Cohen, 2019). Anyway, they will be chemicals that (at the moment) lack good evidence for (positive) effects in individuals in general, and hence, in almost all cases, the absence of proof for performance enhancement in special (Heuberger & Cohen, 2019).

2. St Anabolic Agents

Androgenic Anabolism Steroids are virile hormones that are produced in a natural way included a variety of physiological tasks. They come in two classes: endogenous or normally, as testosterone, and exogenous or manufactured, such as danazol - clearly pointed out as "steroids" (BARON et al., 2007). In the entire lifetime of both men and women, steroids’ gonads (i.e., androgens and estrogens) play a significant function in bone metabolism. By developing genitals, promoted protein creationism, bringing increased muscle weight and weight, masculinization, overall growth, and bone metabolism, their activities contain growing, developing, and keeping (Malve, 2018).

Dependence and the dejection that follows withdrawal are among the most serious issues related to Testosterone’s utilisation and its derivatives. Dependence on AAS was
identified for more than two decades ago (Medras et al., 2018). A random-effects sample built on ten studies predicts that approximately 32.5 percent of individuals taking AAS will experience dependence. According to other reports, 30% of those who had experimented with AAS will increase dependence, and this implies that millions of men in the globe have been affected (Medras et al., 2018).

3. S2 Peptide Hormones, Growth Factors and Related Substances and Mimetics

Hormones are quickly metabolized and therefore, they have a very short half-life. They are eliminated in lower concentrations in the urine as unaltered chemicals. Growth hormone (GH) or somatotropin is a hormone that is released by the anterior portion of the hypophysis. GH activities comprise increasing skinny body size, power, performance, muscle weight, and intensity, stroke volume, and maximum oxygen absorption. Its sports misuse is growing because it is hard to be discovered (Malve, 2018).

4. S3 Beta-2 Agonists

Catecholamines that are freed from the adrenal medulla and work like neurotransmitters are adrenaline and noradrenaline. Their excretion rises during stress and helps to physiologically respond to a condition. The rise in cardiac output, vasodilatation, ventilation and circulate glycogen is related to it in a sports setting, with the reaction proportionate to training intensities. These catecholamines are caused by the coupling of both ß1-AR and ß2-AR to β-adrenoceptors (ß-AR). 99. The ergogenic properties have been widely used by doping agents in the classes of ‘beta 2 agonists’ and ‘stimulants’ (Bird et al., 2016).

5. S4 Hormone and Metabolic Modulators

Inhibitors of aromatase lead to lower oxidative metabolism for male hormones in converting to estrogens. This in-service reduces the estrogens levels and hence contributes to improving androgen levels by prevention of adverse feedback on the hypothalamus (Heuberger & Cohen, 2019). This rise was reported in healthy men for exemestane to be about fifteen nmol/l. Still, no existing tests for CG and Luteinizing hormone that study the performance effects of these aromatase inhibitors and only increased androgen of about 25 per cent are the indicator of prospective impacts (Heuberger & Cohen, 2019). The adenosine is also released, and it has an extracellular autocrine-paracrine role while energetic stress in the rectal gland, derivative from adenine nucleotide disorder. The mechanism of the intracellular kinase (AMPK) is responding to raise in the AMP and ADP concentricities accompanying the ATP collapse (Neuman et al., 2018). The Kinase protein (AMPK) is activated by adenosine. Both are piece of metabolic processes that respond to cellular energy stress and control tasks in several Mammalian tissues, such as muscles of the skeleton, heart muscle, brain, intestines and kidneys (Neuman et al., 2018).

6. S5 Diuretics and other Masking Agents

Diuretics promote urine production and, as a result, they are supposed to dilute outlawed elements in urine, making them harder to detect. Diuretics’ enhanced water excretion may also ameliorate performance by rapidly minimise bulk, which may provide a competitive advantage (Heuberger & Cohen, 2019). This effect can position athletes in a lighter division in weight-class competitions, while slimmer athletes may have an edge in speed or stamina sports (Heuberger & Cohen, 2019).

In 1985, diuretics were banned due to fears that the resulting urine dilution might allow athletes to take forbidden medications, particularly Anabolic Androgenic Steroids (AAS), to avoid identifying them. Even though WADA continues to consider it an element, most lab supervisors do not have such apprehension currently (Fitch, 2012). This is because, despite the reduced particular gravity, the substantially improved analytical technology and software should allow for better detection and recognition of forbidden drugs from the greater amount of urine. Yet, the foremost considerable reason for banning diuretics is for weight-classified players because diuretics allow an athlete to race in the minimal weight class (Fitch, 2012). This is equivalent to cheating. By 1988, 11 competitors, all of whom were taking furosemide, have been disqualified from Summer Olympic Games, with most of them competing in weight-classified contests, the foremost common of which was weightlifting (Fitch, 2012).
B. Prohibited Methods

1. M1 Manipulation of Blood and Blood Components

Blood enhancement by legal elevation training or illegal blood doping is extensively exercised by athletes. Blood doping includes the transfer of entire blood or concentrated red blood cells and can be autologous (athlete’s blood) or homologous (other’s blood). The IOC describes doping as the employment of physiological materials in atypical quantities and by unusual techniques for the sole purpose of obtaining an unreal and illogical growth regarding performance in the contest (Mottram, 1999). Haemoglobin mass is the crucial agent to maximum training volume. Disallowed methods and items for purpose of increasing haemoglobin mass and physical performance, which are intractable to confirm exactly are tried by a few players. Autologous red platelet bonding cannot be followed on reinforcement, and furthermore, recombinant erythropoietic proteid is noticeable just inside a limited time (Jelkmann & Lundby, 2011). Several competitors misuse ESAs (erythropoiesis influencing factors) such as erythropoietin (EPO), epoetin alfa, darbepoetin alfa, and methoxy polyethylene glycol epoetin beta to boost their accomplishment. This could be discovered by the raised levels of unripe reticulocytes because of their accelerated shot from the ossein marrow, as well as an expand in life span. Synthetic oxygen transporters such as perfluorocarbon emulsions (oxygen, oxyfluor) were utilised as a PED too (Sowjanya & Girish, 2019). The drops are taken by the reticuloendothelial structure after intravenous injection and optimise tissue oxygenation, hence improving efficiency. The most possible side effects are flu-like symptomatic and febrile reactions; at higher doses, however, transient thrombocytopenia is observed in a few cases. This material is hard to be detected in doping analyses because it is primarily ousted from the body through breathing and there are no differences noticed in blood or urine checks (Sowjanya & Girish, 2019).

2. M2 Chemical and Physical Manipulation

This alludes to interfering with a sample obtained as part of anti-doping testing procedures for sake of manipulating its integrity and effectiveness (Bird et al., 2016). Additionally, it requires the conversion of samples by the insert of proteases and extra chemicals that change parameters of the steroid description, which seems to be relatively fit inside individuals, but it is changed by the usage of doping agents (Bird et al., 2016). ‘Intravenous admixtures and/or needles of higher than 50 mL each 6-hour duration excluding those legally taken in the reason of hospital entries or clinical studies’ are forbidden as well (Bird et al., 2016).

For example, the German Katrin Krabbe won the 1991 world contest at 100 and 200 meters. But the next year, the IAAF stopped her after discovering that she and two teammates all had presented the same micturition sample for doping analyses (Todd & Todd, 2001).

3. M3 Gene and Cell Doping

Genetic engineering has presented significant benefits to sports in last years, and it has made a tremendous part in increasing the evolution of sports-connected aspects (Shen & Liang, 2021). The advancement of embryonic engineering has been extremely beneficial, particularly in the remediation of numerous conditions caused by Endogamy, muscular dystrophy, and even ageing.” Because of the positive response of cases to these technologies, a very severe idea has appeared, calling for the application of these technologies to healthy sportsmen in order to create genetically altered players (Al-Dafrawi et al., 2019b).

"Gene Doping", as a term was added to the formal list of prohibited items and techniques in 2003. Following that, WADA has paid notable attention and investments to gene doping discovery analysis (Beiter et al., 2011).

C. Substances and Methods Prohibited in-Competition

In addition to the Classes So to S5 and M1 to M3 defined Above, the following classes are prohibited in-competition:

1. S6 Stimulants

Danish bicyclist Knut Jensen fainted and died in his group timing-test of 175-kilometer distance at the Rome summer Olympic Games in 1960 after he utilised amphetamines and nicotine acid (Møller, 2010).

In 1967, stimulants (S6) were the first class of medicines to be prevented in competitions. Since then, there have been
numerous advancements in the identification and categorization of medications in this category (Beotra, 2013). The combination contains both particularised (ephedrines) and unspecified stimulants (amphetamines), which means that medications that may be utilised unintentionally for healing purposes face milder penalties than the non-specified class (Beotra, 2013). Furthermore, medicines used to remedy cough and colds, such as ephedrines, come into a threshold level that must be quantified by doping labs, with only penalties required if discovered over the threshold level (Beotra, 2013). Methylhexaneamine is a medication that resurfaced in supplements in 2010 and was banned for usage in 2010 in two classes: non-specified and specified. The medication is abused in India as well as in different parts of the globe (Beotra, 2013).

Stimulants are prohibited in competition, with the exception of topical imidazole derivatives and those in the WADA control program and are presently measured in micrograms per litre of micturition. Methylhexaneamine,amphetamine (AMP), cocaine, methylphenidate, and ephedrine were the top five synthetic compounds detected in anti-doping checks in 2011 (Anizan & Huestis, 2014).

2. S7 Narcotics

Strong analgesics, all of which are opioids, fall into the narcotics classification. Unexpectedly, while not all opioids are presently prohibited (tramadol, for example, is legal), morphine and its analogues, as well as fentanyl and its derivatives, are (Heuberger & Cohen, 2019). Even if tranquiliser effects may improve performance, familiar opioid side effects such as nausea, sedation, and respiratory gloominess would dispute versus any useful effects (Heuberger and Cohen, 2019). There have been no cogent clinical studies on the effects of narcotics on athletic stamina, so there is no data for either affirmative or counteractive effects on performance (Heuberger & Cohen, 2019).

On another side, utilising morphine derivatives, for example, can cause drop blood pressure, giddiness, sleepiness, and constipation. Bradycardia, bronchospasm, rash, and blurred vision are fewer common symptoms (Józków, 2017). An uncharted survey of British recreational divers provided that 22% of those polled used illegal materials like benzodiazepines, amphetamines, cocaine, ecstasy, LSD, heroin, or "magic mushrooms,” (Józków, 2017). Buprenorphine, dextromoramide, diamorphine (heroin), fentanyl and its derivatives, hydromorphone, methadone, morphine, oxycodone, oxymorphone, pentazocine, and pethidine are all outlawed as well (Józków, 2017).

3. S8 Cannabinoids

Hemp is the source of cannabinoids, which are used as a recreational medication. Chemically speaking, cannabinoids are referred to as aryl-substituted meroterpenes. They are primarily obtained from the Cannabis Sativa plant. There are above 400 chemical ingredients in this herb (Mottram, 2015). More than 60 of these components are chemically classified as cannabinoids. The psychoactive cannabinoid Δ⁹-tetrahydrocannabinol (Δ⁹-THC) are the highly powerful of these cannabinoids. When herbal cannabis is smoked, two additional cannabinoids, cannabinol and cannabidiol, produce complex pharmacological responses and interplays (Mottram, 2015).

Cannabinoids are illegal, despite the fact that no one thinks marijuana is a medication that promotes performance. Actually, Marijuana is known to impede performance. One highly publicised example involving marijuana abuse in organised sports exemplifies the ineptitude and ambiguity of IOC principles aimed at preventing drug employment in sports (Melethil, 2006). Ross Rebagliati, a Canadian, had gold in snowboarding at the Nagano Winter Olympics in 1998. A metabolomic concentricity for cannabis of 17.8 nanograms per millilitre (ng/ml) was found in his urine sample taken "immediately after his won." (Melethil, 2006). The IOC inventoried him of his trophy because of this discovery. The CAS overturned the IOC verdict, declaring that the IOC "had excluded Rebagliati despite the fact that the IOC has no interdictions or punishments for hiring cannabis" (marijuana) (Melethil, 2006).

4. S9 Glucocorticosteroids

Glucocorticoids influence the metabolic process and the immune system, conceivably are interfering with performance. As a result, systemic dosages are prevented in
competition (Heuberger & Cohen, 2019). GCs have also been extensively employed and abused believing that the numerous useful impacts of GCs will be evoked throughout physical exertion (Pigozzi et al., 2012). Admittedly, GCs may enhance the availability of metabolic substrates in muscles, stop the releasing of pro-inflammatory cytokines as a result of training-induced muscle harm, preparing of the body for the following round of physical activity, and promote the emission of Dopamine in the Central Nervous System with favourable temperament changes, according to their mechanisms of work (Pigozzi et al., 2012). The alleged performance-enhancing impacts of GCs could be explained by these physiological characteristics (Pigozzi et al., 2012).

D. Substances Prohibited in Particular Sports

1. P1 Beta-blockers

Just a few sports are banning the use of beta-blockers during competition (Tandon et al., 2015). The use of beta-blockers is forbidden in-contest just in the precision sports such as Archery (WA), Automobile (FIA), Billiards (all disciplines) (WCBS), Darts (WDF), Golf (IGF), Shooting (ISSF, IPC), Underwater sports (CMAS), and it is also forbidden in Out-of-competition when pointed (Ivanova et al., 2016). Out-of-competition outlawed substances include, but are not limited to, Acebutolol; bunolol; carteolol; esmolol; levobunolol; metipranolol; nadolol; oxprenolol; propranolol; sotalol and timolol (Ivanova et al., 2016). Beta-blockers can help relieve shiver in certain sports like golf and shooting (Hughes, 2015). Sundry inclusive checking procedures were used to evaluate the beta-receptor blocking agent’s category (Thevis et al., 2010).

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VII. CONFLICT OF INTEREST

The author wishes to announce that there is no conflict of interest with anyone or any organisation regarding this review.

VIII. ABBREVIATIONS

This review includes some important abbreviations for Performance-Enhancing Drugs, testing procedures, or refers to some sports federations and international organisations working in the field of Anti-Doping in sports:

AAF: Adverse Analytical Finding.
AAS: Anabolic Androgenic Steroids.
ADAMAS: Anti-Doping Agency Malaysia.
IAAF: International Amateur Athletic Federation (IAAF).
IOC: International Olympic Committee.
IX. REFERENCES


