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Performance Enhancing Drugs and Methods of Doping: Mode of Action and Dope Testing Methodologies

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ABSTRACT - World Anti-Doping Agency (WADA) monitors each sport worldwide to ensure freedom from drug abuse. Abuse of Drugs or procedures specifically which are banned by WADA to artificially enhance the efficiency of sports-person is called DOPING. The ban is imposed due to the side-effects of performance-enhancing drugs (PEDs), lack of fairness in sports, and the deterioration of sport for the public. The use of PEDs damaging the spirit of sport, and therefore banned, by WADA and the International Olympic Committee. Fair play is a prerequisite to promote clean and safe sports. Doping is the intentional use of banned PEDs by athletic competitors that may be overtly or covertly assisted by Athlete support personnel. Besides, athletes (or athletic programs) taking unambiguous actions to escape exposure make worse the fair disobedience with dishonesty and cheating. Immunoassay, Gas Chromatography-Mass Spectrometry (GC-MS), Liquid Chromatography-Mass Spectrometry (LC-MS), Isotope Ratio Mass Spectrometry (IRMS), Gel Electrophoresis, and Bio- /Chem-iluminescence technologies have been traditionally used in dope testing. There is a strong continuous requirement for further improving the quality of dope testing setups, processes, and procedures. Adoption of emerging technologies like metabolomics and the use of other omic technologies shall play a big role in continual improvements in dope testing. The present system in Doping Control is required to function in a more globally competitive, coordinated, and proactive manner. This review will outline a brief overview of the PEDs, their health impacts, history of their use, and their pharmacological impact. It also analyses comprehensive information on the Dope Testing Technologies available and in the offing.

Keywords: Drug Abuse, Doping, Performance-Enhancing Drugs, Dope Testing

I. Introduction

The use of drugs to enhance performance is considered unethical as it goes against the 'spirit of sport' and, therefore, prohibited [1]. The general worldwide trend amid sport organizations and anti-doping authorities has been to strictly regulate the use of drugs in sport [2]. Also, the athletes with the help of different masking measures evade exposure of doping [3]. At times athlete support personnel are also covertly involved in this clandestine activity [1]. Promotion, coordination, and monitoring the fight against doping menance including improvements of anti-doping capacities, scientific research, education, outreach and harmonizing efforts regionally and worldwide, is a challenge [4].

There is an acute need to develop scientific expertise (skilled and specialized multifarious professionals encapsulating hardcore pharmacology, biotechnology, and chemistry) with analytical capabilities, to evolve innovative concepts, practices, protocols, processes, and devices to inculcate the value for fair play and clean dope-free sports [5-7]. Dope testing agencies must seek to amalgamate multi-disciplinary fields of dope testing with numerous theoretical perspectives, the realm of diversity with the praxis of knowledge, and national issues with a global horizon [1]. An effective system for investigations of anti-doping rules violations, deterrence, curtailments and fair measures to appeal need to be further strengthened.

An innovative set up for improvements in doping controls, awaken intellectual curiosity, and challenge scientific boundaries by creating a networked group working in close collaboration of interrelated disciplines in pursuit of disruptive discoveries, with leading academic and technical Institutions and sports bodies, is required to be institutionalized. Greater expectations will be placed on the governing bodies in sports to help protect the right to doping-free sport. This will include greater cooperation in investigations and the interviewing of athletes and athlete support personnel through amendments to the Anti-Doping Policy. Multiple analytical methodologies

with higher selectivity and sensitivity are required to accomplish the target of fair sport. To achieve the anti-doping laboratories should essentially utilize Mass Spectrometry based methods and technologies with a different combination of other hyphenated techniques. To deal with the challenge of newly added dopants, direct and indirect methods of screening and confirmation strategies may contribute to increasing the detection window to enhance result accuracy.

This review aims is to trace the chronology of PEDs since the sports came into existence at the Olympic platform and their pharmacological impacts which prompt sport persons to use them. The detailed description of the techniques that are in use for the individual category of prohibited substances and methods is critically analyzed.

II. History of Doping

Performance enhancing drugs (PED's) use from the last 100 years [8] creates a tarnished history of sports competition of Olympic games. Competitors doubtful with their capability and desire to become undisputed icons use them unlawfully [9]. The first used PED in 1904 was a plant-based alkaloid, Strychnine, found in many species of Strychnos plants[10]. Soon there were other PED's included in the list for their stimulant, anabolic, androgenic, growth enhancement, and metabolic modulator activities [11]. Up till the 1920s and 1930s, the use of these drugs had not drawn the attention of any medical and scientific community for their mysterious performance enhancement in competitors [8]. For the first time in 1948, the International Federation of Sports Medicine (FIMS) an International Olympic Committee (IOC) recognized international organizations took the responsibility to observe the use of drugs in sports [8]. The surveillance of the science and medicine aspects of sports was creeping. It was in the 1950s when the side-effects of amphetamine, one of the PEDs came in limelight and caused an uproar in the Olympic sports timeline. Testosterone as anabolic androgenic steroid was also added in the same decade in the list of PEDs in the Olympic weightlifting event [10]. In the 1960, a Danish cyclist Knut Jenson in Rome Summer Olympics died during the competition as he had taken beta-Pyridylcarbinol (Ronicol), a blood circulation stimulant, It was the first death in the record of Olympic timeline [12]. In 1967, methamphetamine was found in the dead body of Tom Simpson, an English cyclist [13]. In the 1960's many reports kept on coming on the use of Anabolic androgenic stimulant (AAS) by female and male athletes [7]. In 1967, the term 'DOPING' was coined for the abuse of natural or unnatural material and process to increase the performance of an athlete in competition [8]. In 1968 for the first time the list of substances decided to be banned was made and demand for testing of biological samples like urine for inclusion as drug testing policy in the Olympic game, came into being [8]. The sequence of abuse of drugs continued and on November 10, 1999, the World Anti-Doping Agency (WADA) was established to systematize and implement the anti-doping efforts in sports [8]. A summary of the timeline of the history of Doping in the Olympics is presented in Table 1. With time there has been a market developed for varieties of Doping agents that falls under different categories based on their effect from their natural products to synthetic ones [8]. WADA catalog all the agents into three categories i.e., substance prohibited always, substance prohibited in-competition, and substance inhibited in particular sports respectively [14]. Among all the categories, the substance and methods prohibited at all the times were the largest one. The Anabolic agents when administered exogenously as a copy or modified form of endogenous metabolite consist of the longest list of substances including natural, modified, and synthetic. Thus, it is not wrong to say that the anabolic agents are mainly fluffed out doping and their escapism from detection as their biological effect is the same with almost a similar chemical structure.

Table 1: Major milestones in the History of Doping in Olympics

Years	Events
1904	Use of Strychnine in Marathon
1920	Use of Sherry in Marathon
1927	Isolation of Testosterone by Fred Koch
1935	Synthesis of Testosterone in lab by a chemist Leopold Ruzicka
1948	Federation of Sports Medicine take charge for close observation of Olympics
1952	Ill effects of Amphetamine in Skaters in Olympic sports
1954	Use of Testosterone was revealed in weightlifting in Olympics
1961	Female athlete using male hormone and its analog Dianabol
1962	President of IOC declares the investigation of Doping as an official event
1965	Agerman Pharmaceutical company synthesize anabolic steroid oral-Turinabol
1967	DOPING term was given by IOC
1968	The random urine drug test was done in Olympics
1968	International Olympic Committee Medical Commission was created
1969	Use of Anabolic steroids come in light in a number of games in Olympic including decathletes, discus throw, shot put, weight lifting, running, jumping etc.
1980's	Use of Anabolic steroids was at peak along with the expansion of list of PEDs and Human Growth Hormone has become established PED
1999	World Anti-Doping Agency was established

III. Overview of the Performance Enhancing Drugs

Doping by using Performance enhancing drugs is an issue of sports scandals worldwide [15]. These PEDs are classified as per their pharmacological moiety that imparts their effect on the human body [16] and is cataloged as substance or methods prohibited all time; prohibited in-competition and prohibited in specific sports [14]. Under the domain substances or methods prohibited all time, the first category is of anabolic agents that comprise AAS and other anabolic agents that have a similar impact on physiology of human [14]. AAS is the huge category of > 60 agents with compounds of natural origin, a few with synthetic, as pro-hormone, intermediate and derivative of testosterone or estrogen [14]. Supplemental anabolic agents include Selective Androgen Receptor Modulators (SARMs), tibolone, zeranol, and clenbuterol [14]. These agents show anabolic effect and effectively raise the protein concentration in striated muscles [17, 18]. These agents enhance the size but do not affect the number [14]. SARMs attach to androgen receptors and alter their structure followed by their functioning [17]. Erythropoietins, Peptide hormones, Growth factors, and Growth factor modulator falls under the second category of WADA prohibited doping agents list [14]. Enhance in red blood cell production, testosterone secretion, muscle growth, and speedy recovery from sports injury are some manifestations or results of using these doping agents [19]. The third category covers β2 agonists - the agents that stimulate β2 androgenic receptors to achieve bronchodilation effect and enables one to avoid palpitation, arrhythmia, muscle cramps, and electrolytic imbalance. They are also associated with some anabolic effects like muscle-building [20, 21]. Group four including those agents that help in building muscles and burn fat but without any exercise [14]. Insulin and other drugs which are used for treating diabetes [22] are considered to belong to this group as well. The fifth category of substances includes the agents that help in masking the use of other doping agents that increases urine output resulting in removal of salts and fluids from the body. These are called as Diuretics or masking agents [23]. Though they are also used to lose weight in specific sports competition requires lower weight competitors [23]. Now some methods have also been developed under the umbrella of doping that involves M1: Manipulation of Blood and Blood components to accomplish the enhanced oxygen uptake capacity during competition [14]. M2: Chemical and Physical manipulation of biological samples to change the reliability of the biological sample [14].

M3: Gene and Cell doping is a recombinant DNA technology based biotechnology in which the cell's genome of the competitor's targeted cell is modified in terms of addition or deletion or gene transfer [14]. There are four groups of substances placed under the domain prohibited in-competition and were named as S6 including Stimulants, for example, epinephrine, cocaine, nikethamide, etc. [14]. Stimulants results in boosting vigor and lessening fatigue [24]. Common harmful effects of stimulants include trembling, palpitation, and increase in blood pressure [24]. High doses of stimulants, may lead to incoherence and paranoia, heatstroke, and severe cardiac arrhythmia [24]. A threshold concentration for stimulant is defined in a doping sample [14]. S7 Narcotics mainly use for pain-relieving action by manipulating the central nervous system, thus, improves athlete's performance in sports [14]. The sedative effect also helps in maintaining concentration in competition. Cannabinoids and their synthetic derivative are included in the S8 group [14]. They generally result in impaired athletic performance due to the impairment of coordination, reaction time, and memory resulting from CNS suppression [25]. S9 Glucocorticoids help in augmenting the body's ability to tolerate exertion [14]. Substance prohibited in particular sports includes P1. Beta-blockers that are used for treating hypertension and to avert a relapse of myocardial infarction, among other purposes [14, 26]. Their effect, which tranquilizes the CNS and reduces the heart rate and tremors, can improve athlete's performance in terms of concentration, steadiness of extremities and relaxing [26]. Table 2 depicts the pharmacologically based categorization of PEDs and Doping methods use in sport doping.

Table 2: Cataloguing of PEDs category and Doping Method based on their Pharmacology

S.No.	Pharmacological effects	Substances or Methods use in doping	Examples
1	Anabolic	S1, S2, S4,M3	Estrogen, Testosterone, Human Growth Hormone, Insulin, etc.
2	Androgenic	S1,M3	Testosterone, Dihydrotestosterone (DHEA), Dehydroepiandrosterone, DHEA sulfate (DHEA-S), etc.
3	Erythropoietic	S2, M1,M3	Erythropoietins
4	Nonsteroidal anti-inflammatory drugs (NSAIDs)	S2	Fibroblast Growth Factor, Thrombopoietin, Myostatin, etc.
5	Bronchodilators	β2 agonist	Albuterol sulfate, Metaproterenol, etc.
6	Antiarrhythmic	β2 agonist	Amiodarone, Flecainide, Procainamide, Sotalol, etc.
7	Anti-obesity	S4,M3	Insulin
8	Diuretic	S5, P1, M1	Cisplatin, Lasix,

			Bumetanide, Demadex, Edecrin, Acebutolol, etc.
9	Central Nervous System Stimulants	S6	Epinephrine, cocaine, nikethamide, etc.
10	Analgesic	S7	Opium, Heroin, Oxycodone, etc.
11	Sedative	S7	Isoflurane, diethyl ether, propofol, etomidate, ketamine, pentobarbital, lorazepam, midazolam, etc.
12	Psychoactive drug	S8	Cocaine, LSD, alcohol, tobacco, codeine, and morphine
13	Corticosteroids	S9	Beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisoneetc.
14	CNS depressants	P1	Benzodiazepines, barbiturates, etc.
15	Tranquilizer	P1	Valium, Ativan, etc.

IV. Antidoping Analysis

The evolution of doping and sports development goes hand in hand if we look at the timeline of the Olympic Games [8]. This evolution of dopants stressed the analytical field for the development of much more sensitive methods for antidoping analysis. The WADA established international guidelines for the testing of dopants at certified national laboratories to achieve the detection of PEDs and prevention of their abuse [3]. Also, Athlete Biological Passport (ABP) is a method to detect doping by implementing two modules of investigation including Haematological module in which blood manipulation in terms of RBCs number in blood, blood transfusion is detected by using Erythropoiesis-Stimulating agents(ESAs) and Homologous Blood Transfusion test while in Steroidal module all urine samples are analyzed by using Isotope Ratio Mass Spectrometry(IRMS) for endogenous metabolite profile that is manipulated exogenously [7]. WADA is engaged with experts and stakeholders to advance build up the ABP and are functioning on an endocrine module which seeks to identify the abuse of growth factors such as growth hormone [3].

The synthetic agents or drugs or biochemicals that are used deliberately by sports person and athlete support personnel to violate the 'spirit of sport' are included in the list of dopants[3]. The doping is identified by the detection of the doping agents within the biological samples like saliva, hair, urine, and blood [27]. In 1972, first time Gas chromatographic testing of >2000 urine samples was done to detect the presence of stimulants at the Olympic Games in Munich. In 1976 GC/MS was used again to confirm the presence of AAS at Montreal Olympic Games [28]. Later the advancement in the technique remains continue for a fair mass resolution to screen all of the urine specimens for the detection of maximum count of banned substances [28].

Anti-doping analysis is a very difficult area of forensic science, designed to identify the abuse of prohibited substances and methods by the athletes [29]. The analysis is mainly performed using mass spectrometry (MS) techniques and, employing the hyphenated technologies like chromatography and mass spectrometry [30]. Highly sensitive detection methods employing chromatographic/mass spectrometric techniques including Liquid Chromatography–Mass Spectrometry (LCMS), Gas Chromatography–Mass Spectrometry (GCMS), High Resolution Mass Spectrometry (HRMS) and their combination are being in use for the screening procedures for the detection of exogenous AAS [31]. Gas and liquid chromatography united with mass spectrometric detectors are being in use intensively for small molecules type dopants like steroids and their derivatives, diuretics, and some hormones [6]. The AAS group dopants require a pretreatment procedure including hydrolysis via the enzymatic or chemical method for the derivatization of the compounds present in the specimen to yield thermally stable and volatile derivatives to give a precise detection of AAS in urine sample [6]. Almost all of AAS, are excreted in the urine as gluco-conjugates or sulfo-conjugates [30]. In the case of investigation of abuse of testosterone(T), the direct detection became very difficult because of the structural similarities with of the synthetic steroids and the endogenous hormone [6, 30, 32]. Since the urinary concentration of the endogenous hormone is not constant so to imply a threshold value based detection is not a successful approach [6, 30, 32]. Therefore, the measurement of the concentration ratio between T and epitestosterone (E) is being implemented as a preliminary investigation which should support more study [6, 30, 32]. T/E ratio>6 is considered as T abuse and to get clear out from the detection the cheater in games use 'masking agents' these incorporate E, and peptide hormones like the gonadotropins (primarily human chorionic gonadotropin - HCG) [30]. The WADA changes this value by 4 and mandates further with Gas Chromatography coupled to combustion (C) isotopic ratio MS (GC-C-IRMS). The solution for the detection of such a shrewd method of doping was found in gas chromatography, combustion, and IRMS (GC-C-IRMS) [32]. The isotopic profiling of the sample is measured to determine the subtle variation in the isotopic composition of the substance of endogenous and exogenous origin. The IRMS method mainly measures the amount of stable isotope in a sample. In carbon-IRMS, the isotope of carbon i.e., 12C and 13C in an organic compound are measured in the sample [30, 33, 34]. By coupling GC with IRMS the endogenous and synthetic

homolog of naturally produced steroids can be easily discriminated by using the same principle of isotope analysis. Since the synthetic compound has less ration of 13C than their endogenous analogous and this discrimination is the convention utilized in GC coupled to IRMS[30, 33, 34]. These combinations of different techniques with high mass accuracy are in use for the identification of anabolic agents in this series one more is sequestered in which Chromatography is coupled with Time of Flight/Mass Spectrometry especially the liquid chromatography to yield (LC-TOF-MS) that requires no prior derivatization [35].

PEDs falls under the second group of prohibited substances are peptidic and their presence in very less concentration in biological sample necessitates the testing to be very peculiar [36]. Thus the approaches make use of chromatographic–mass spectrometric, electrophoretic, immunological, and combined test methods [37]. Doping with peptidic substances for example growth hormone (GH) poses challenges in front of forensic science due to similarity between the recombinant peptide hormone and naturally derived hormone from pituitary and the short half-life [38]. Thus following two strategies have been developed:

(i) the marker approach, which is an indirect way of detection as in this the measurement of the concentrations of hormone-dependent parameters in serum is performed

(ii) isoform approach detection of exogenous recombinant GH is detected by observing any changes in GH isoform [39].

Both the approaches are based on immunoassays; therefore, the availability and maintenance of the precise antibodies involved are essential [39].

The β-2 agonists possess the muscle relaxing feature by mimicking the actions of endogenous catecholamines, epinephrine, and nor-epinephrine that helps an individual to breathe more easily by relaxing the pulmonary muscles while participating in any sport [40]. Since their origin is exogenous they can be detected by using Immunoassay like ELISA and Mass spectrometry coupled with chromatography techniques in blood and urine biological fluids as well as in hairs due to their very good incorporation into hair matrix [41-43].

The Diuretics are mainly used by an athlete to promote the urine excretion to achieve the desired weight loss [44]. The hypotonic urine excretion leads to the release of more water out from the kidney with retention of solutes more within the body thus indirectly causes urine a hypotonic specimen which provides a shield for the metabolic waste [44]. This effect of diuretics makes them useful as masking agent for other dopants [44,45]. Osmotic diuretics extract more water from intracellular compartments. increase the extracellular fluid volume, thus viscosity of blood is reduced. The urinary excretion of electrolytes (like sodium, potassium, calcium, magnesium, chloride, biocarbanate and phosphate) increases [45]. As the diuretics are banned, they are regularly tested for by anti-doping laboratories [45]. There is a huge list of chemical agents present in diuretics and hydrochlorothiazide is the most common diuretic used. Numerous techniques like HPLC-UV-DAD, GC/MS, LC/MS and LC/MS-MS, micellar electrokinetic chromatography, and capillary electrophoresis, are available for the analysis of diuretics [45].

Flow cytometry, Isoelectric focusing, and omics (genomics/proteomics/metabolomics) technologies are used to detect blood doping in athletes [46]. Genomics applied to mRNA or miRNA is a hopeful analytical tool useful for the blood doping method in which the changes in transcriptome are measured in young cells [47]. Proteomics changes related to RBC membranes integrity which divulge the presence of cells stored for a timeframe, as an abnormal pattern of cell's morphology [48]. Manipulation of blood and blood components is done either by the administration of blood and red blood cells of any origin or by chemical stimulant means [49]. To get a hold on these various approaches have been developed and being exploited with different techniques. The detection of exogenous manipulating substances including erythropoietic stimulants and homologous transfusion comes under the direct detection approach while detection of certain biomarkers lying in an indirect approach [49]. The autologous blood transfusion is also a method of blood doping and to detect this doping storage lesion that includes changes in red blood cells during storage, glucose concentration in stored blood, diminished levels of 2,3-diphosphoglycerate (DPG) and ATP, while the increase in potassium levels are measured [50]. Another indicator in the urine sample of an athlete undergo blood transfusion is the presence of plasticizers which is used in the manufacture of blood bags to increase their flexibility and durability [51]. These markers can be detected with the help of chromatography coupled with mass spectrometry analytical techniques [51]. Table 3 presents the diagnostics methods available for different PEDs.

Table 3: Classification of Diagnostic Methods in Sports Doping Analysis

S.No.	Dopant	Biological Sample	Analytical method	Reference
1	Exogenous AAS	Urine	LCMS, GCMS, HRMS, GC-IRMS, LC-TOF-MS	6, 30-35
2	Peptidic harmone	Blood Urine	Chromatographic–mass spectrometric, Electrophoretic, immunological & combined test methods	36-39
3	β-2 agonists	Blood Urine Hairs	ELISA and Mass spectrometry coupled with chromatography techniques	40-43
4	Diuretics	Urine	HPLC-UV-DAD, GC-MS, LC-MS and LC-MS-MS, micellar electrokinetic chromatography & capillary electrophoresis	44,45
5	Blood doping, Gene doping	Blood Urine	Flow cytometry, Isoelectric focusing and Omics (genomics/proteomics/metabolomics) technologies	46-51
6	Stimulants	Urine	GC-MS	52
7	Narcotics	Blood Urine Hair	GC-MS LC-MS, LC-QTRAP	52
8	Cannabinoids	Blood Urine Hair	GC-MS LC-MS LC-QTRAP	53, 54
9	Glucocorticoids	Urine	GC-MS, LC-MS/MS	55
10	β Blocker agents	Urine	GC-MS	56

V. Confront and Possible Solution of Anti-Doping Analysis

Advancement in bioinstrumentation, their sensitivity, and in-depth knowledge of dopants are the main verticals contributing to anti-doping analysis [57]. The anti-doping analysis should be a part of each major and minor sport [57]. But due to the high costs of analytical methods, specimen collection, and pretreatment procedure for available methods the anti-doping remains limited to a very small fraction of sport community [58]. The major confront for the anti-doping community is to develop trustworthy, faster, and cheaper analytical practices. Major expenses are related to the specimen treatment, also the minimal size of the sample is another big reason for high costs [59]. Miniaturization of testing and microsampling can be a way to deduct the cost up to some extent. Microsampling allows us to find out analyte in the same sample with a range of analytical methods [51]. Also, the non-targeted analytical approach with MS techniques can be a possibility to find yet unknown compounds [60]. By generating the methods to deal with a biological sample like hair besides blood and urine may also help in decreasing the cost of testing as the maintenance of hair sample is less sensitive as compared to blood and urine [61].

VI. Conclusion

Cataloging of PEDs based on their pharmacological efficacy and the methods of antidoping analysis for each category provides a basis for employing advancement in the techniques for the analysis of dopants. There is an acute need to increase the window of analysis with the inclusion of new dopants in the existing list that mimics the endogenous metabolites. Antidoping and Dope testing laboratories should apply techniques that are more sensitive and precise [62, 63]. IRMS coupled with chromatography is a very important technique today due to its capacity to produce reliable results. There is a need to carry out in depth analysis and focused research to develop more sensitive and specific Dope Testing Technologies.

VII. Reference

[1]. World Anti-doping Agency (WADA). Athlete Biological Passport operating guidelines, Montreal, Canada (2018). www.wada-ama.org/sites/default/files/resources/files/guidelines abp v61 2018 jul en.pdf

[2]. WADA Independent Commission Report #1. Chapter 11 (2015). http://www.wada-ama.org/sites/def ault/files/resources/files/wada independent commission report 1 en.pdf

[3]. World Anti-doping Code 2015 with 2018 Amendments(2018). https://www.wada-ama.org/sites/default/files/resources/files/wada_anti-doping_code_2018_english_final.pdf

[4]. Duntas LH, Parisis C. Doping: A challenge to the endocrinologist: A reappraisal in view of the Olympic games of 2004. Hormones 2(1), 35-42 (2003).

[5]. Aikin R, Baume N, Equey T et al., Biomarkers of doping: uses, discovery and validation. Bioanalysis. 2020;10.4155/bio-2020-0035. doi:10.4155/bio-2020-0035

[6]. Carey K. The detection of Doping in Sport and the role of Forensic Science(2018), Undergraduate Honors College Theses 2016-201.

https://digitalcommons.liu.edu/post_honors_theses/19

[7]. Schumacher YO, d'Onofrio G. Scientific expertise and the Athlete Biological Passport: 3 years of experience. Clin. Chem. 58(6), 979–985 (2012).

[8]. Kremenik M, Onodera S, Nagao M, Yuzuki O, Yonetani S. A historical timeline of Doping in the Olympics(Part 1 1896-1968). Kawasaki Journal of Medical Welfare. 12, 19-18(2006).

[9]. Nieschlag E, Vorona E. Medical consequences of doping with anabolic androgenic steroids: effects on reproductive functions. European Journal of Endocrinology. 173, 47-58(2015).

[10]. Nieschlag E &Nieschlag S. Testosterone deficiency: a historical perspective. Asian Journal of Andrology 16, 161–168(2014).

[11]. Dirix A. The doping problem at the Tokyo and Mexico City Olympics Games. Journal of Sports Medicine and Physical fitness 6, ….-185(1966).

[12]. Holt RIG, Erotokritou-Mulligan I, Sonksen PH. The history of doping and growth hormone abuse in sport. GrowthHarmone and IGF research. 19, 320-326 (2009).

[13]. Lee Yu-H. Performance Enhancing Drugs:History, Medical Effects & Policy. http://nrs.harvard.edu/urn-3:HUL.InstRepos:8848241

[14]. The World Anti-Doping Code International Standard Prohibited List (2020) https://www.wada-ama.org/en/resources/science-medicine/prohibited-list-documents

[15]. Baron DA, Martin DM, Abol Magd S. Doping in sports and its spread to at-risk populations: an international review. World Psychiatry. 6(2),118–123(2007).

[16]. Pope HG, Jr.,Wood RI, Rogol A, et al. Adverse Health Consequences of Performance-Enhancing Drugs: An Endocrine Society Scientific Statement. Endocr Rev. 35(3), 341–375, (2014).

[17]. Solomon ZJ, Mirabal JR, Mazur DJ et al. Selective Androgen Receptor Modulators (SARMs) - Current Knowledge and Clinical Applications. Sex Med Rev. 7(1), 84–94 (2019).

[18]. Burniston JG, WA C, Tan LB, et al. Dose-dependent separation of the hypertrophic and myotoxic effects of the β2-adrenergic receptor agonist clenbuterol in rat striated muscles. Muscle Nerve. 33(5), 655–663(2006).

[19]. Kelland K. Substances and methods used in doping (2012). https://www.reuters.com/article/us-oly-dop-day1/substances-and-methods-used-in-doping-idUSBRE86R0DA20120728.

[20]. Billington CK, Penn RB, Hall IP. β2-agonists. Handb Exp Pharmacol. 237: 23–40(2017).

[21]. Daubert GP, Mabasa VH, Leung VWY et al. Acute clenbuterol overdose resulting in supraventricular tachycardia and atrial fibrillation. J Medical Toxicol: official journal of the American College of Medical Toxicology 3(2), 56-60(2007).

[22]. Home P, Riddle M, Cefalu WT, et al. Insulin Therapy in People With Type 2 Diabetes: Opportunities and Challenges? Diabetes Care. 37(6), 1499–1508 (2014).

[23]. Cadwallader AB, Torre X de la, Tieri A, et. The abuse of Diuretics as performance enhancing drugs and masking agents in sport doping: pharmacology, toxicology and analysis. British Journal of Pharmacology 161, 1–16(2010).

[24]. Avois L, Robinson N, Saudan C, et al. Central nervous system stimulants and sport practice. Br J Sports Med. 40(1), 16–20, (2006).

[25]. Huestis MA, Mazzoni I, Rabin O. Cannabis in Sport Anti-Doping Perspective. Sports Med. 41(11), 949–966(2011).

[26]. Dezsi CA and Szentes V. The Real Role of β-Blockers in Daily Cardiovascular Therapy. Am J Cardiovasc Drugs. 17(5), 361–373,(2017).

[27]. Harrison CR. Role of Capillary Electrophoresis in the Fight against Doping in Sports. Anal. Chem. 85, 6982−6987,(2013).

[28]. Bowers LD. Analytical advances in detection of performance enhancing compounds. Clin. Chem. 43(7), 1299-1304,(1997).

[29]. Jan N, Marclay F, Schmutz N. Use of Forensic investigation in Anti-Doping. Forensic Sci Int.213, 109-113, 2011.

[30]. Botre F. Mass spectrometry and illicit drug testing: analytical challenges of the anti-doping laboratories. Expert. Rev. Proteopmics. 5(4), 535-539(2008).

[31]. Geyer H, Shanzer W, Thevis M. Anabolic agents: recent strategies for their detection and protection

from inadvertent doping. Br J Sports Med. 48,820–826(2014).

[32]. Anderson JM. Evaluating the Athlete's Claim of an Unintentional Positive Urine Drug Test. Curr Sports Med Rep. 10(4), 191-196,(2011).

[33]. Cawley AT, Hine ER, Trout GJ, et al. Searching for new marker of endogenous steroid administration in athletes: "looking outside the metabolic box". Forensic Sci. Intern. 143, 103-114(2004).

[34]. Flenker U, Guentner U, Schaenzer W. δ13 C-values of endogenous urinary steroids. Steroids. 73, 408-416(2008).

[35]. Kioussi MK, Lyris E, Angelis YS, et al. A generic screening methodology for horse doping control by LC-TOF-MS, GC-HRMS and GC-MS. J Chromat.B. 941, 69-80, (2013).

[36]. Saugy M, Robinson N, Saudan C. Human growth hormone doping in sport. British J Sports Med. 40(1), 35-39, (2006).

[37]. Thevis M, Thomas A, Schanzer W. Detecting peptidic drugs, drug candidates and analogs in sports doping: current status and future directions. Expert Rev Proteomics. 11(6), 663-673, (2014).

[38]. Bidlingmaier M,Wu Z, Strasburger CJ. Problems With GH Doping in Sports. J Endocrinol Invest. 26(9),924-931, (2003).

[39]. He C, Wu M. Detection of doping with recombinant human growth hormone. Bioanalysis. 1(5):953-965(2009).

[40]. Hackney AC. Chapter 6 - Beta-2 Agonists. Doping, Performance Enhancing Drugs, and Hormones in Sport. Mechanisms of Action and Methods of Detection Emerging Issues in Analytical Chemistry. 65-76(2018).

[41]. Pleadin J, Gojmerac T, Lipej Z, et al. Accumulation of the beta(2)-adrenergic Agonist Clenbuterol in Mouse Dark Hair. Arch Toxicol. 83(11),979-983,(2009).

[42]. Kintz P, Dumestre-Toulet V, Jamey C, et al. Doping Control for Beta-Adrenergic Compounds Through Hair Analysis. J Forensic Sci. 45(1),170-174,(2000).

[43]. Di Corcia D, Morra V, Pazzi M, Vincenti M. Simultaneous determination of beta2-agonists in human urine by fast-gas chromatography/mass spectrometry: method validation and clinical application. Biomed Chromatogr. 24(4),358-366,(2010).

[44]. Thevis M and Schanzer W. Examples of Doping control analysis by liquid chromatography-Tandem mass spectrometry: Ephedrines, β-receptor blocking agents, Diuretics, Sympathomimetics, and Cross-linked Hemoglobins. J Chromatographic Sci. 43, 22-31, (2005).

[45]. Cadwallader AB, de la Torre X, Tieri A, et al. The abuse of Diuretics as performance enhancing drugs and masking agents in sport doping:pharmacology, toxicology and analysis. British Journal of Pharmacology, 161, 1–16, (2010).

[46]. Jelkmann W and Lundby C. Blood doping and its detection. Blood. 118 (9), 2395–2404, (2011).

[47]. Segura J, Lundby C. Blood doping: potential of blood and urine sampling to detect autologous transfusion. British Journal of Sports Medicine 48,837-841(2014).

[48]. Marrocco C, Pallotta V, D'alessandro A, et al. Red blood cell populations and membrane levels of peroxiredoxin 2 as candidate biomarkers to reveal blood doping. Blood Transfus. 10 (2),71-77, (2012).

[49]. Pottgiesser T, Schumacher YO. Current strategies of blood doping detection. Anal Bioanal Chem. 405(30),9625-9639,(2013).

[50]. Kor DJ, M Van Buskirk C, Gajic O. Red Blood Cell Storage Lesion. Bosn J Basic Med Sci. 9(1), 21–27, (2009).

[51]. Segura J, Monfort N, Ventura R. Detection methods for autologous blood doping. Drug Test Anal. 4(11),876-881(2012).

[52]. Ahrens BD, Kucherova Y, Butch AW. Detection of Stimulants and Narcotics by Liquid Chromatography-Tandem Mass Spectrometry and Gas Chromatography-Mass Spectrometry for Sports Doping Control. Methods Mol Biol. 1383(10), 247-263(2016).

[53]. Protti M, Rudge J, Sberna AE, Gerra G, Mercolini L. Dried haematic microsamples and LC–MS/MS for the analysis of natural and synthetic cannabinoids. J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 1044(1045), 77–86 (2017).

[54]. Tiscione NB, Miller R, Shan X, et al. An Efficient, Robust Method for the Determination of

Cannabinoids in Whole Blood by LC–MS-MS. J Analyt Toxicol 40(8), 639-648(2016).

[55]. Methlie P, Hustad SS, Kellmann R, et al. Multisteroid LC-MS/MS assay for glucocorticoids and androgens, and its application in Addison's disease. Endocr Connect. 2013;2(3):125-136. doi:10.1530/EC-13-0023

[56]. Amendola L, Molaioni F, Botrè F. Detection of beta-blockers in human urine by GC-MS-MS-EI: perspectives for the antidoping control. J Pharm Biomed Anal. 23(1),211-221(2000).

[57]. Protti M, Mandrioli R, Mercolini L. Perspectives and strategies for anti-doping analysis. Bioanalysis. 11(03)149-152(2019).

[58]. Outram SM, Stewart B. Condemning and condoning: elite amateur cyclists' perspectives on drug use and professional cycling. Int. J. Drug Policy 26(7), 682–687 (2015).

[59]. Aikin R, Baume N, Equey T, et al. Biomarkers of doping: uses, discovery and validation. Bioanalysis. 12(11) 791-800(2020).

[60]. de Albuquerque Cavalcanti G, Rodrigues LM, dos Santos L et al. Non-targeted acquisition strategy for screening doping compounds based on GC-EI-hybrid quadrupole-Orbitrap mass spectrometry: a focus on exogenous anabolic steroids. Drug Test. Anal. 10(3), 507–517 (2018).

[61]. Haller DL, Acosta MC, Lewis D, et al. Hair Analysis Versus Conventional Methods of Drug Testing in Substance Abusers Seeking Organ Transplantation. Am J Transplant. 10(10), 1305-1311(2010).

[62]. Boye E, Skotland T, Østerud B, Nissen-Meyer J. Doping and drug testing: Anti-doping work must be transparent and adhere to good scientific practices to ensure public trust. EMBO Rep.18(3),351-354 (2017).

[63]. Sharma B. A Critical Analysis of the Impact of Doping in Sports Domain International Journal of Law Management & Humanities. 4(2), 129-152 (2021)

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