

## Development of Doping in sports: overview and analysis

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### Abstract:

Doping is a public health issue and not simply a problem inside the professional sports community. It is a complex and ancient phenomenon considering the vast variety of substances, supplied through both legal and illegal trading routes. It occurs in elite athletes but also affects amateur athletes and was generally considered as dangerous and unhealthy. Furthermore, it involves athletes' friends and relatives, medical staff, managers, chemists, biologists and pharmacists, pharmaceutical industries, clandestine laboratories and criminal organizations. Over time, doping has shown a great ability to discover and always use new substances and appropriated the new scientific discoveries. Unfortunately, new discoveries for the human health are being used in a distorted way by the athletes. In fact, the athletes may be able to use gene therapy to re-engineer their bodies for better performances. Drug dependence depends on several factors: the socio-environmental context of the subject and what effects have the substance in the body. We will agree that sport is essentially under the current anti-doping campaign executed by a coordinated alliance between the World Anti-Doping Agency (WADA), law enforcement authorities, sports organizers and the media. This paper explores a comprehensive description of the state of doping and its regulation in the modern Olympic Movement.

**Key words:** doping, drugs, sport, education, WADA, ethical

### Introduction

The desire to increase their own physical performances in order to obtain better results in sports led athletes to seek alternative methods to train hard (Mazzeo, 2016). For a long time individuals have tried to improve in an artificial way their physical performances. Man has always tried to improve his physical performance by any method: legal or illegal, healthy or harmful to health (Mazzeo et al., 2016; Santamaria et al., 2013; Sjöqvist et al., 2008; Calatayud et al., 2007). The reasons of these attempts are various and they are changed over time: from to get best results in the hunting to obtain profit. In fact, best performances mean, great earnings (Lippi et al., 2009). Furthermore, it involves athletes' friends and relatives, medical staff, managers, chemists, biologists and pharmacists, pharmaceutical industries, clandestine laboratories and criminal organizations (Marclay et al., 2013; Esseiva et al., 2007).

Therefore, drug abuse is one of the biggest problems in sports. In elite athletes, it involves the repeated and excessive use of substances to realize a certain effect (Mazzeo, 2017; Sjöqvist et al., 2008). Furthermore, the desire to enhance their physical abilities did not even spare the disabled athletes (Mazzeo et al., 2015; Montesano et al. 2013). Doping has ancient origins, probably it would have the same age of sport phenomenon as from the moment in which individuals began to practice physical activity in competition with others, in fact, they have sought to improve their own performance by taking mixtures of various types of plants. Indeed, it seems that the term "doping" is derived from an ancient African dialect "doop" as meaning "a mixture or a potion". Doping is an ancient phenomenon. Probably would have the same age of sport as from the moment when the man began to practice physical activity in competition with other men, he sought to improve own performance by taking mixtures of various types of plant origin (Calatayud et al., 2007). In fact, it seems that the term doping is derived from an ancient African dialect "doop" as meaning a mixture or a potion. Greek wrestlers and the Roman gladiators attempted to improve their own performance by eating specific part of animal's meat (Dilger et al., 2007). Doping exists not only in professional sport, but also affects amateur athletes who are making increasing use of performance-enhancing drugs (Mazzeo, 2017). Doping is thus increasingly a matter that concerns the whole society (Lippi et al., 2008; Anti Doping Convention 1989). The World Anti-Doping Agency (WADA) was established on November 10, 1999. In 2004, the World Anti-Doping Code has harmonized the rules and regulations governing anti-doping across all sports and countries for the first time. If we consider all substances included in the WADA Prohibited List, we conservatively estimate 253,700 users of doping products in Italy for specific use.

In the beginning of the 20th century, in the search for substances able to make it stronger than others, the athlete was matched and complicity in different professionals: coaches, managers, doctors and pharmacists, nutritionist, equally interested in increasing their power, in a general and economic perspective. In the last quarter of the twentieth century, the use of doping in sport activities has become massive and systematic (Mazzeo et al. 2015). With the advent of sponsors and mass media, the success in major sports competitions (Olympics, World Championships, and so on) has been playing an increasingly significant social and economic goal, such as to encourage the use of all means, legal and illegal to catch up.

Doping poses a threat to sport worldwide. It undermines the principle of open and fair competition (Mottram, 2005). It is a factor that discourages the practice of sport in general and puts the professional under unreasonable pressure. It seriously affects the image of the industry and represents a serious threat to individual health (Anti Doping Convention 1989; Mazzeo et al., 2016). Unfortunately, in the past and for a long time, doping was underestimated and public institutions considered it as a problem exclusively of sports organizations that alone had to vanquish a phenomenon in continuous expansion (Møller e Di Meo, 2014).

In accordance to the WADA Code, doping is conceived in different ways including different specific meanings. That is: *“the presence of a prohibited substance or its metabolites or markers’ banned; the possession, use or attempted use of prohibited substances or methods; the refusing or the failing, without compelling justification, to submit to sample collection; the violation of applicable requirements regarding athlete availability for out-of-competition testing; the tampering or the attempting to tamper with any part of doping control; the trafficking or the attempted trafficking in any prohibited substance or methods; the administration or the attempted administration to any athlete of any prohibited methods or substances, or the assisting, encouraging, aiding, abetting, covering up or any other type of complicity involving an anti-doping rules violation or any attempted anti-doping rule violation”*( WADA ,2015).

### **A brief policy analysis**

In the beginning of the 20th century, in the search for substances able to make it stronger than others, the athlete was matched and complicity in different professionals: coaches, managers, doctors and pharmacists, nutritionist, equally interested in increasing their power, in a general and economic perspective. In the last quarter of the twentieth century, the use of doping in sport activities has become massive and systematic. With the advent of sponsors and mass media, the success in major sports competitions (Olympics, World Championships, and so on) has been playing an increasingly significant social and economic goal, such as to encourage the use of all means, legal and illegal to catch up. The economic factor plays an important function, but certainly not the only one: doping cases have also been discovered in amateur athletes and, even if specific economic benefits are not achieved, this aspect indicates the existence of motivations more complex and sometimes not easily understood. About doping phenomenon, as already evidenced, several definitions have been developed over time, and sometimes partially conflicting. Doping is also known as follows: *“The intentional use by the athletes of drugs or methods aimed at obtaining an improved sports performance beyond the limits possible only with the training”*. However, although this definition is very easy to understand might bring a wide debate: it does not take into account, for example, any medical needs of athletes and, conversely, lead to an improper use of nutritional supplements, vitamins, minerals and more. In the ethical perspective, the athletes resort to doping contravening the fairness rules that characterize the sport and competition whatever they might be. In addition, there is no doubt that the substances and methods used to artificially enhance the body posing a risk to the health of those who use it. More specifically, the problem is much more nuanced and articulated. In the elite sport, for example, doping phenomenon is complicated from some factors that must be taken into account to avoid unnecessary, often counterproductive, legal disputes. First, it is necessary remind that sport means work for an elite athlete. Any disqualification for doping automatically involve the loss of job for a certain period of time (months or years), with understandable economic damage. For this reason, it is necessary that the anti-doping procedures and results of the tests have the character of absolute certainty. The athlete is deprived of his/her right to work that is, a measure against which it will try to fight with all the weapons at his disposal and, for that reason, must be conclusive in technical terms (fairness of the procedures used in the doping control), and legal. Secondly, the athlete can have common diseases (e.g. asthma) or troubles caused by sporting activities (e.g. tendonitis) and, like all the citizens, this can rely on the right to heal in the best way possible, using virtually any drugs if available, including those that may be included in the list of forbidden substances.

Moreover, many aspects are involved in the prevention and fight of doping (as damage to the health of the athlete). In this scenario, also we need to pay attention to the adequacy of sporting rules against doping, the adequacy of state regulations doping (Law 376/2000), the harmonization of regulatory system doping, including sport and state at national and international level. Furthermore, the desire to enhance their physical abilities did not even spare the disabled athletes. The International Paralympics Committee (IPC), a non-profit international organization for the Paralympics Movement, organizes the Summer and Winter Paralympics Games, and serves as the International Federation for 12 sports, which supervises and coordinates the organization of the World Championships and other competitions. The mission of the International Paralympics Committee is to allow disabled athletes to achieve sporting excellence and to create opportunities for everyone at any level. In addition, the IPC sets as its aim the promotion of the Paralympics values, which include courage, determination,

inspiration and equality. The information stored in an athlete's biological passport may be then sufficient to launch a disciplinary procedure against the athlete but the rationale for doping control is based on the need to respect and maintain both ethical and medical principles.

Already in the early 1900s it was realized that the use of substances to increase physical performance, not only falsified the results of competitive sport but it was also very dangerous for the health (Calatayud et al., 2007). For this reason, in 1928 the International Association of Athletics Federations became the first International Sport Federation (IF) to ban the use of stimulating substances. Only after the death of a cyclist at the Olympic Games in Rome in 1960 urged the relevant authorities to introduce the first anti-doping test.

After eight years, during the Olympic Games of Mexico City, there was a pilot project with the aim to analyze the efficacy of anti-doping tests and thanks to their success, the first official anti-doping screening started in 1972 during the Summer Olympic Games of Munich (Botrè, 2008). At beginning, the tests were sporadic and not completely reliable. But in 1999, thanks to the creation of the World Anti Doping Agency (WADA), it finally created an organization with the sole purpose to fight this "cancer" of sport and consequently the situation of tests is changed (Dvorak et al. 2014; Valkenburg et al., 2014). One of most important WADA function was to harmonize the Olympic anti-doping code and develop a single and complete code applicable and acceptable for all the stakeholders. The world anti-doping code developed by WADA introduced several international standards (ISs) with the main goal to harmonize the anti-doping disciplines from each country (Mazzeo et al., 2016). The Agency has compiled a list of banned substances and practices that is constantly updated. Now, WADA, for example, has identified more than two hundred banned substances currently divided into 10 classes (including the class S0) and three methods (Strano Rossi 2011; Badoud 2011) (Table 1).

Table 1 Wada 2017 Prohibited List

Substances and methods prohibited (in and out competition)
S1 Anabolic agents
S2 Peptide hormones, growth factors, related substances and mimetics
S3 Beta- 2 agonists
S4 Hormone and metabolic modulators
S5 Diuretics and masking agents
M1 Manipulation of blood and blood components
M2 Chemical and physical manipulation
M3 Gene doping
Substances and methods prohibited in competition
In addition to the categories S1 to S5 and M1 to M3,
S6 Stimulants
S7 Narcotics
S8 Cannabinoids
S9 Glucocorticosteroids
Substances prohibited in particular sport
P1 Alcohol
P2 Beta-blockers

### Gene doping: the physical limits of human strength and endurance.

The discovery of the complete human genome with approximately 30.000 different genes leads to new possibilities for diagnosis and prevention of a wide variety of diseases. In addition, this knowledge may be used for the design of a new therapeutics use, including gene therapy, based on the DNA sequence informations (Doessing et al., 2005; Mazzeo, 2017). Gene therapy may be defined as the transfer of genetic material to human cells for the treatment or prevention of a disease or disorders. Its principle is based on the delivery to a cell, of a therapeutic gene which may compensate an absent or abnormal gene (Unal et al., Mazzeo e Volpe, 2017). This material can be encapsulated into a virus, such as adenovirus or retrovirus, or into a lipid, such as a liposome. The viruses are crippled so that they are no longer pathogenic. The encapsulated genetic material is mostly referred to as a vector and is introduced into the body by direct injection into the target organ or administered by aerosol for lung delivery (Lippi et al, 2009; Doessing et al., 2005). Also, it is possible to isolate cells from a patient and treat these cells with the vector in the laboratory and then re-implant these into the patient. Gene therapy is currently an experimental therapy and its use is strictly regulated (Gaffney et al., 2007; Beerens et al., 2003).

Unfortunately these new important discoveries for the human health are been used in distorted way by the athletes. In fact, the athletes may be able to use gene therapy to re-engineer their bodies for better performances. They know that any physiologic process involved in producing a motor action or assisting the implementation of a motor movement could be a candidate for gene doping (Oliveira et al., 2011).

The World Anti-Doping Agency (WADA," defines gene doping as the "nontherapeutic use of cells, genes, genetic elements, or modulation of gene expression, having the capacity to enhance performance" (World Anti-Doping Agency, 200; Santamaria et al. 2013; Gaffney et al., 2007).

The goals of gene doping include the injection of novel genes of the modulation of existing genes too; however, the gene doper introduces the gene products for the enhancement of physiologic parameters expedient to the athlete's competitive tasks, rather than the treatment of a medical illness [Gaffney 2007; Keying 2008; Doessing 2005].

Now, in the 2013 WADA Prohibited List, gene doping, is "the transfer of polymers or nucleic acid analogues" and "the use of normal or genetically modified cells" (World Anti- Doping Agency 2013).

Growth hormone (GH) has a multitude of effects on the body associated with growth. It has a well-documented stimulatory effect on carbohydrate and fatty acid metabolism, and a possible anabolic effect on muscle proteins (Doessing et al., 2005).

Doessing and Kjaer (2005) also suggest a role for GH as an anabolic agent in connective tissue in human skeletal muscle and tendon (Gaffney et al., 2007). Recombinant GH, is already being used as a doping agent in sports. Insulin-like growth factor 1 is a protein that stimulates cellular proliferation, somatic growth and differentiation (Doessing et al., 2005) (Table 2)

Table 2- Genes for sports doping and physiologic response.(Santamaria et al., 2013)

Gene/Product	System/ target tissue	Gene product properties	Physiologic response	Sport
ACE	Skeletal muscles	Peptidyl dipeptidase	ACE-I seems to correlate with endurance ACE-D involved in sprint and powers	Endurance
ACTN2,3	Muscular system	Actin-binding proteins related to dystrophin	Involved in fast twitch muscles	Endurance and sprint
Endorphins, Enkephalins	Central and peripheral nervous systems	Widely active peptides	Pain modulation. Increases risk of overuse of musculoskeletal and cardiovascular system. Increase stress and pressure on heart	Endurance
EPO	Hematopoietic system	Glycoprotein hormone	Increases RBC mass and oxygen delivery	Endurance
HGH	Endocrine and muscular system	191–amino acid protein	Increases muscle size, power, and recovery	Entrengh
HIF	Hematologic and immune systems	Multisubunit protein	Regulates transcription at hypoxia response element	Endurance aerobic
IGF-1	Endocrine/metaboli c/skeletal muscle	70–amino acid protein	Increases muscle size, power, and recovery	Entrengh
Interleukin-15	Skeletal muscle	cytokine with strong antitumor properties	Myoblast proliferation and muscle-specific myosin heavy chain (MCH) expression	Strength
Myostatin.	Muscular system	2-subunit protein	A negative muscle mass regulator. Damage of tendons ligament and bone	Entrengh
PPAR-δ	Skeletal muscle and adipose tissue	Nuclear hormone receptor protein	Promotes fat metabolism and increases number of slow twitch fibers	Speed and endurance
VEGF	Vascular endothelium and angiogenesis	Glycosylated disulfide-bonded homodimers	Induces development of new blood vessels	Endurance

Abbreviation: ACE, angiotensin-converting enzyme; ACTN3, actinin binding protein 3; EPO, erythropoetin; HGH, human growth factor; HIF, hypoxia inducible factor; IGF-I, insulin-like growth factor; PPAR-delta, peroxisome proliferators-activated receptor (delta); VEGF, vascular endothelial growth factor. (Gaffney, Parisotto, 2007)

The field of gene therapy, and by extension, gene doping, is full of unpredictable and dangerous results like this, which is why Sweeney, Evans, and other researchers who have identified DNA targets that could potentially be exploited for gene doping are the first to emphasize that the research is still at only an

experimental stage. More important than the ethical implications of gene doping, some experts say, is the fact that gene doping could be dangerous, and even fatal in the spirit of sport (Pray, 2008; Mazzeo, 20016)

**Results**

The athlete using drugs or nutritional supplements practice mainly sport where appearance is a significant aspect as in body building (Mazzeo et al., 2013). These substances are more and more used by athletes not only in competitive sports, but also in fitness and recreational sports. It is important to ask why athletes dope. In advance, it is important to know that the prohibited substances and / or the amount of substance prohibited constantly change: some of them have been eliminated over time while others have been added. For example, pseudoephedrine and norephedrine were removed from the list in 2003 but in 2013, the first substance was reintroduced with a different dosage. Local anesthetics and caffeine were eliminated in 2004 (Strano Rossi S. and Botrè F. 2011), even if the substance has been included in the monitoring program of WADA in 2015 (Table 3) (World Anti-Doping Agency, 2015).

Table 1. 2015 WADA List of monitored substances

Category	Moment	Substances
Stimulants	In-Competition only	Bupropion, caffeine, nicotine, phenylephrine, phenylpropanolamine, pipradrol and synephrine
Narcotics	In-Competition only	Hydrocodone, mitragynine, morphine/codeine ratio, tapentadol and tramadol.
Glucocorticoids	In and Out-of-Competition	
Others	In and Out-of-Competition	Telmisartan, Meldonium

One thing is certain the substances that give pleasant sensations or help the subject in his activity will bring him to repeat the consumption. But, not all people develop drug dependence. It depends on several factors: the socio-environmental context of the subject and what effects have the substance in the body. Moreover, the drug dependence could be connected to the indirect gratification. It consists in all situations in which the person has a social, economical or psychological benefit thanks to use drugs. For example: we can see direct gratification in the winning of a competition and indirect gratification in the money that the athlete receives after. If all the gratifications are connected to use of drug, maybe he will use drug in the future.

A lots of researches focused their attention on subject's personality. It is demonstrate that people with an ego orientation have a low self-esteem, are aware that only with their own abilities fail in their main purpose: to beat the others. They also hate the defeat and, therefore, looking for the victory in any way (Serpelloni et al., 2006). Perhaps, an ego oriented person probably will use drugs because he doesn't want to improve himself but only give the appearance of improvement; and this result will get it only through the use of performance-enhancing drugs (Duda et al., 1995; Duda & Nicholls 1992). Kahneman and Tversky (Tversky 1974; Kahneman 1979) give us others reasons that push people to resort to doping. Indeed, they identify four factors: the effect of formulation, the principle of utility, the heuristic of the accessibility and the representativeness heuristic.

Data showed that in Italy in 2010, the percentage of doped athletes is higher than other years with 4.8% (53 doped athletes on 1115 controlled - Figure 1) and from 2008 to 2012 did not fall below 3%. In 2013, the percentage is 2.8%.

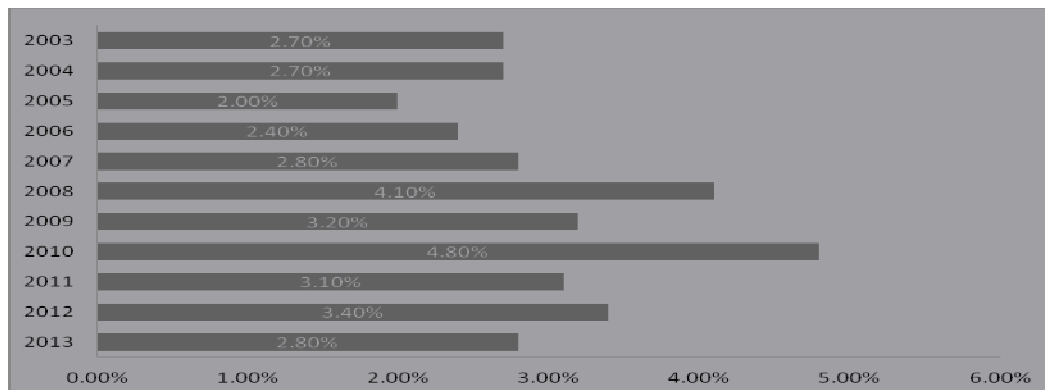


Fig. 1. Percentage of doped athletes over the years. Reference period: 2003-2013

Many of this substances taken, have various gratifications' effects, such as stimulants, anabolic, narcotics and cannabinoids Stimulants are used to increase the concentration, alertness and safety. They also increase the aggressiveness and the sense of competitiveness (Stella et al., 2005). To anabolic are recognized for

the following effects: euphoria, sense of wellbeing, glee, increased motivation and self-esteem. Moreover, the athlete doesn't get bored during the training (Mazzeo , 2016).

Narcotics have a calming effect on the psyche as well as beta-blockers reduce the anxiety and stress. Corticosteroids have, instead, a stimulating effect like alcohol. Moreover, other effects include euphoria, increased sociability and sense of wellbeing.

Cannabinoids, such as cannabis, hashish and marijuana, cause changes in mood and perception, euphoria, happiness, relaxation and deep sleep and reducing anxiety (Mazzeo, 2017). They are considered drugs to use social-recreational (Stella et al.,1999; Loffreda et al 2003).

Shifting the focus on the consumption of prohibited substances and considered that the control activities of the Anti-Doping Commission began in April 2003, in that year there was a high consumption of stimulants equal to 40%. The lower percentages were 10.3% in 2010 and 6.7% in 2013. Compared with the year 2012, consumption fell by 13 percentage points. The average consumption from 2003 to 2013 is 20.9%.

The cannabis derivatives have a peak of consumption in 2005 and 2007, respectively, with 42.6% and 42.3%. Their use, in any case, in the other years was characterize by ups and downs: it should be noted, indeed, that in 2012 the percentage is 31.8%, while in 2013 is 16.7%. Its lower consumption occurred in 2010 with the 7.2%. The average consumption is 26.3%.

Regarding diuretics and masking agents, they have had a trend almost constant over the years. The peak was reached in 2011 with 24.8% and 2013 is not recorded specifically changes compared to the normal course (10%).

Inhaled  $\beta_2$  agonists, which are among the drugs of choice for treatment of asthma, are prohibited for non-asthmatic athletes according to the most recent list of prohibited substances released by WADA (Mazzeo, 2016). This means that an athlete with asthma or EIA has to prove the presence of the disease to a medical committee of their national or an international ruling body and wait for grant of a therapeutic use exemption (TUE) before they can start  $\beta_2$  agonist treatment. The main reason for prohibition of the use of inhaled  $\beta_2$  agonists in non-asthmatic athletes is its claimed ergogenic potential (Perrotta et al.,2017). From 2003, the Commission carried out doping tests. The tests collected only urine samples.

15.396 athletes have been checked in these 10 years – 2003 to 2013 -: 10.347 (67.2%) men and 5.049 (32.8%) women

The current system of the fight against doping makes the assessment carried out by analytical laboratories accredited by WADA as a test not able to analyze the state of health of the athlete but as a real anti-fraud control: the goals are diametrically opposed (Mazzeo et al, 2016; Colucci A. P. and Gagliano-Candela R. 2004).

Moreover, the highest average age of those athletes is 36 in 2010, followed by 35 in 2010. In 2013, the average age is 33 years old and analysing that average during the last ten years, it is 31 years old. Furthermore, as you can see in the figure 2, the phenomenon mainly touches people over 45 years old and saves younger.

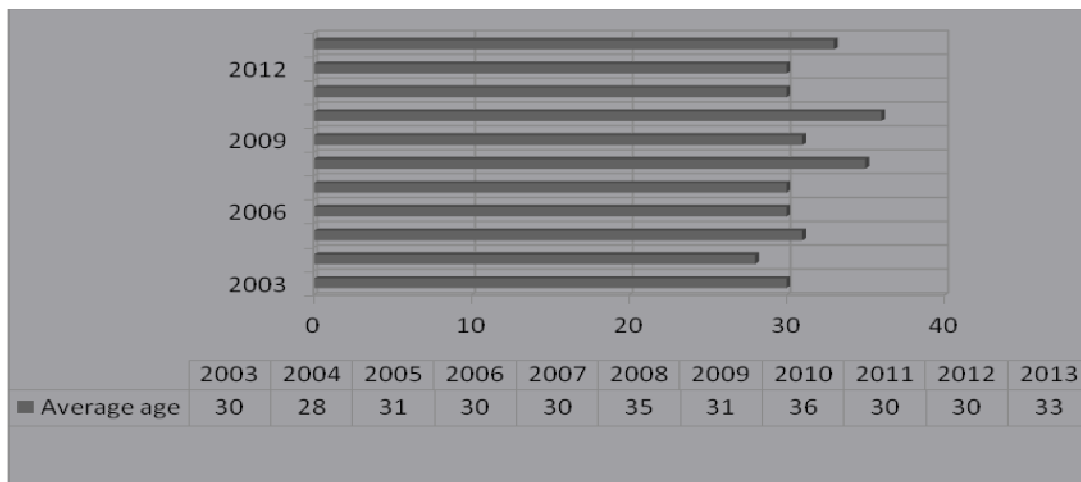


Fig. 2. Average age of doped athletes. Breakdown per years. Reference period: 2003-2013

**Conclusions**

The first step to do to prevent the recourse to the doping is to extend the knowledge on it and in particular on its dangerous effects on health (Thomas , 2011). The arrival of new sponsors led to the arrival of new professionals who brought a new performance approach (Brissonneau, 2010). Indeed, most athletes will not have enough knowledge to fully understand the potential health hazards caused by it. It is necessary, therefore, that public and sports institutions implement information and awareness campaigns aimed particularly at young people. This can be easily achieved only with strict collaboration between the two above-mentioned institutions. It's necessary to enhance the role of local institutions and the National Olympic Committee to give tools, especially economic, to carry out the work of education, training and control (de Mérode and Schamasch 1999).

It is important that campaigns be launched to a broad audience too. These awareness-promoting actions must involve mass media. In terms of training, about the doctors, they are at the forefront and, unfortunately, they often have a very sketchy understanding of the relationship between therapy and doping, particularly in terms of knowing which treatments are permitted and which are not ( de Mérode and Schamasch 1999).

From a scientific point of view, one of the most effective preventive measures can be considered the inclusion, by the Ministry of Health, in the class S0 - substances not approved - of doping substances of Law 376/2000, also drug for veterinary purposes in view of the spread of this type of medication for the purpose of doping (Ministero della Salute 2013).

The laboratories have an important role in the discovery of new substances; most of them are included in the WADA List. They also determine the quantitative of those substances, carry out anti-doping tests, and determine cases, criteria and methodologies of anti-doping tests too. Currently, there are 34 laboratories in the World (Table 4) (Valkenburg et al., 2014, Mazzeo, 2016).

The Biological Passport is a tool for indirect detection of the presence of a doping substance in biological samples of an athlete. With it, in fact, the changes of certain bio-markers of doping are recorded and monitored. If the data, combined with the personal data localization in a given period, exceeded a certain range, the athlete would assume the banned substances (WADA, 2015). The Anti-Doping Administration and Management System (ADAMS) is an on-line database system where are recorded all data: laboratory results, therapeutic use exemptions (TUEs) and information on anti-doping rule violations. It allows the sharing of information amongst the organizations and promotes efficiency, transparency and effectiveness in all anti-doping activities (Møller et al., 2014). Unfortunately, today, despite the technological advancement that characterizes the field of scientific research, the analytical methods are not sufficiently reliable for the search of the entire group of substances included in the antidoping lists. Professional athletes must serve as role models and spokesmen for drug-free sport and lifestyle (Baron et al., 2007; Gomez J 2005 ). In addition, professional athletes are frequently the role models of adolescent and young adult populations, who often mimic their behaviours, including the abuse of drugs. Continuing, updates educational programs developed for these at-risk populations by national Olympic organizations and athletic federations are important first steps to curb and to control these dangerous behaviours (Baron et al., 2007). Raising consciousness on the reality and involvement of the situation would help to legitimate the establishment of legal grounds necessary to the implementation of Anti-Doping Intelligence and this might prove efficient at a more proactive response to any potential or emerging doping phenomenon or to address existing problems with innovative actions or/and policies (Mazzeo et al., 2018).

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