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REVIEW PAPER

Anabolic Steroid use in Sports and in Physical Activity: Overview and Analysis

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Abstract

Anabolic steroids,commonly referred to as anabolic androgenic steroids (AAS), are a family of hormones that comprises testosterone. Exposure to these substances can result in damage to human health, such as liver cancer, and to the environment. This class of doping substances cause an extensive increase in the muscular massandis being used to improve athletic performance. Athletes are still using them to increase physical performance and bodybuilders are using them to improve size and cosmetic appearance. For performance enhancing use, these substances generally used without interruption and during several weeks preceding a competition. The preferred method is "piling up" oral ingestion and injections.This type of treatment has been used in sport medicine to manage a variety of joint, tendon and soft tissue injuries.The long-term side effects of anabolic steroids are severe and will depend on dosage and duration. In particular, early death from cardiovascular disease, sterility in men and, in women, masculinization and possible irreversible effects constitute the most serious dangers. More recently, studies have suggested that psychological and behavioral changes and addiction may result from chronic anabolic steroid abuse. AAS were the first identified doping agents that have ergogenic effects and are on the International Olympic Committee's list of banned substances. This paper identify a) AAS increasing represent only one of many different classes of agents it is important to used by recreational bodybuilders and by athletes in the 21st century b) their side effects c) their effects on sports performance c) phenomenon of polypharmacy.

Key words: *anabolic androgenic steroid, sport, testosterone, doping, educational programme*

Introduction

Generality information about physical activity, doping and sport

Sports and physical activity are a considerable importance both for the physiological end ethic benefits, not only by improving the performance conditions of an athlete but also for the positive influence on the character and personality of an individual (Mazzeo, 2016; Mazzeo et al., 2016). Research may foster understanding about how and what sport to can help promote energy balance and healthy body weight (Mazzeo, 2016).

The role of sport and physical activity in adult and children, for optimizing bone mass and reducing obesity and insulin resistance, people with cardiac disease and older people, merit special attention. Effective strategies exist for managing obesity yet are rarelyused by physicians and researcher (Mazzeo, 2016). Furthermore a new pharmacological target to fight obesity and its associated diseases are represented for example, by study on adiponectin, a collagen-like plasma protein secreted by adipocytes, has been suggested to play a causal role in the development of obesity, insulin resistance and cardiovascular disease (Illiano et al., 2017).

Physical activity describe all movement produced by skeletal muscles which increases energy expenditure, whether it's exercise or sport. At present daily participation in moderate and vigorous physical activities is low, and activity decreases with increasing age (Mazzeo et al., 2016; Montesano et al., 2013a). In addition, sports activity, at any level, remains a competition and emulation in respect of the other competitors and towards ourselves (Raiola, 2011).

Experts on performance sport define performance sports as

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the result from a specific action, usually competitions designated by a number or a rating scale value. Since the ancient times, were researched illicit systems that could artificially improve the athletic performance, in addition to training and physical preparation; in ancient Greece for example, during the carrying out of the Olympic Games, the athletes used to assume an infusion of herbs and mushrooms in order to increase their performance (Mazzeo et al., 2016). Man has always tried to improve his physical performance (Mazzeo, 2016). The restive evolution and multiplication of doping methods and substances, the fear by athletes of harsh sports and legal sanctions as well as the inadequacy of the identification techniques for illegal substances, contribute to make a not accurate evaluation of the prevalence of the Doping phenomenon (Lippi & Guidi, 1999).

The consumption of banned and potentially harmful substances in sports has become a problem for the public health. Current estimations of the prevalence of doping in sports are relatively uncertain, as most investigative tools do not reflect an absolute statistical power (Mazzeo et al., 2016). Exist not only doping in professional sport, but also affects amateur athletes (Mazzeo et al., 2016). Furthermore, the desire to enhance their physical abilities did not even spare the disabled athletes (Mazzeo, Santamaria, & Iavarone, 2015; Montesano, Tafuri, & Mazzeo, 2013b). Therefore, dopingis the assumption of substances or the recourse at particular methods which are able to artificially increase an athlete's performance during a sports competition, contrary to sports morals and despite physical and psychological health (Mazzeo, 2016; Lippi et al., 1999).

To estimate the use of prohibited drugs and other forms of doping in sports fields, in 1998 the National Italian Olympic Committee (CONI) and the National Research Council (CNR), appointed an independent committee designed to conduct a survey to ascertain the knowledge and opinions of the Italian athletes on doping practices (Scarpino et al., 1990). 1015 athletes and 216 sports professionals where interviewed during the survey. In total, 30% of athletes, coaches and sports managers and 21% of doctors stated that the athletic performance can be improved by using drugs or other doping techniques. In particular, more than 10% of athletes expressed the opinion that amphetamines and anabolic steroids are frequently used in national and international level. Moreover, the percentage of athletes and sports professionals that retain harmful the use of doping methods and prohibited drugs was higher than the percentage that considered their use effective (Scarpino et al., 1990; Mazzeo, 2016).

Drugs, substances biologically and pharmacologically active and medical practices, which their application is considered doping; are divided, in compliance with the provisions of the Strasbourg Convention and under the indications of the International Olympic Committee (IOC) and other international organizations responsible in the sports sector, in classes, according to their chemical and pharmacological character and their corresponding effect (Mazzeo et al., 2016; Mazzoni et al., 2011).WADA, significantly modified the Prohibited List of the IOC Medical Commission, binding from the end of 2003 and updates every year (Table 1).

Table 1. 2017 WADA prohibited substances and methods

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 (sativa, indica and derivates)
S9 Glucocorticosteroids
Substances prohibited in particular sport
P1 Alcohol
P2 Beta-blockers

Over time, doping has shown a great ability to discover and always use new substances and appropriated the new scientific discoveries (Anti Doping Convention 1989). Botrè (2008) distinguishes three main periods about the evolution of substances to identify (Table 2).

The first one–the early age-includes "in competition drugs"; the second period–the androgenic anabolic steroids age–includes "in and out competition drugs". The third age-protein chemistry and molecular biology age-includes the newly discovered in genetic engineering used for the treatment of diseases too. Now, in the "gene doping age", the new frontier of doping is the use ofcells,genes, genetic elements, or the modulation ofgene expression with the aim to increase the performance and not easy to detect (Botrè, 2008). This last period includes the blood doping. Indeed, the blood transfusion and administration can boost the capacity to transport the oxygen to the muscles. Therefore, before 1980, AAS were used primarily by elite athletes. After 1980, AAS used by elite athletics and by general population to enhance personal appearance (Kanayama & Pope, 2017).

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 (Calatayu, Alcaide, Zurian, & Benavent, 2007). For this reason, in 1928 the International Association of Athletics Federations became the first International Sport

Table 2. Evolution of substances to identify

	Period	Substances to identify
Origin early 1970s	1970	Stimulants, narcotics, drugs of abuse
Synthetic anabolic androgenic steroids (AAS)	Mid 1970–2000	Synthetic anabolic androgenic steroids, beta-blockers, diuretic, cannabinoids, glucocorticoids, human chorionic gonadotropin, endogenous testosterone and/or precursor, erythropoietin and analogs
Protein Chemistry and Molecular biology Age	2000-present	Designer steroids, hormone and hormone receptors modulators
	2003-present	Blood doping
	2005-present	Peptide hormones
Gene Doping Age	2008-present	No substances but cells, genes, genetics elements, modulation of gene expression

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.

It should be noted that the use of these "doping" products used to improve performance may not only not result in an advantage in terms of sports performance but, on the contrary, entails serious damage to the health of the athlete. Among the most frequently "abused" substances in the world of sports, anabolic steroids (AAS) and peptide hormones must certainly be considered (Mazzeo, 2016; Anawalt, 2018).

Anabolic steroids

Anabolic-androgenic steroids (AAS) are synthetic derivatives of testosterone and are a class of compounds studied and synthesized to stimulate body and muscular growth (anabolic effect) (Vasic & Jakonic, 2007). In men, testosterone is the principal secreted androgenand the Leydig cells synthesize the majority of testosterone.In women, testosterone also is probably the principal androgen and is synthesized both in the corpus luteum and the adrenal cortex by similar pathway (Celotti & Negri Cesi, 1992). Some authors use the term "steroids" to refer both to androgens and to anabolic steroids, since both have the same basic chemical structure. Since years anabolic agents are the most frequently detected doping substances in sports (Mazzeo et al., 2016). The testicular principle, we now know, is the male sex hormone testosterone, which was first synthesized in 1935. Experimental studies in both animals and humans showed that testosterone possessed both anabolic and androgenic action (Fragkaki et al., 2009). The androgenic actions of testosterone are those actions involving the development and maintenance of primary and secondary sexual characteristics, at the same time the anabolic actions consist of the positive effects of testosterone in inhibiting urinary nitrogen loss and stimulating protein synthesis, particularly in skeletal muscle (Goldman & Basaria, 2018).

Moreover, anabolic steroids, technically known as anabolic-androgenic steroids, are synthetic derivatives of testosterone, modified to enhance its anabolic actions (promotion of protein synthesis and muscle growth). The testosterone precursorsandrostenedione and dehydroepiandrosterone are weak androgens that can be converted peripherally to testosterone. However, natural testosterone is rapidly degraded by the liver so the plasmatic level required for the accomplishment of his anabolic effect, are not reached. AAS exert their pharmacological effects by binding to a cytoplasmatic receptor and moving into the nucleus incrementing RNA polymerase activity and synthesis of RNA and specific proteins (Goodman & Gilman's, 1990). AAS are used to increase muscle mass and are being used to improve athletic performance. Consequently, athletes are still using them to increase physical performance and bodybuilders are using them to improve size and cosmetic appearance. AAS were the first identified doping agents that have ergogenic effects and are on the International Olympic Committee's list of banned substances (Mazzeo et al., 2016).

About, 60 different AAS are available that vary in their chemical structure and thus in their metabolic fate and physiological effects (Celotti et al., 1992; Modlinski & Fields, 2006; Hakansson, Mickelsson, Wallin, & Berglund, 2012). The most popular AAS used as doping substances are: *oximetolone, oxandrolone, testosterone undecanoate, nandrolonedecanoate, nandroloneundercanoate, methandrostenolone, metiltestosterone, stanazolo.* To reach high dosages and rapid effects, steroid users practice a method known as "staking" which consist in the intake of two or more steroids in high dosages. Another method, called "pyramiding" provides a progressive increase of steroids dosage. The pyramid protocol is alternated with drug-free, process defined as "cycle" (Huang & Basaria, 2018). Screening procedures for AAS in World Anti-Doping Agency accredited laboratories are based mainly on gas chromatography-mass spectrometry, although liquid chromatography-mass spectrometry is becoming increasingly more valuable. The use of carbon isotope mass spectrometry is also of increasing importance in the detection of natural androgen administration, particularly to detect testosterone administration (Ahrens, Starcevic, & Butch, 2012).

Drugs bases on the AAS effects have been listed by the IOC (International Olympic Committee) as substances assumed for doping purpose (Mazzoni et al., 2011). More specifically, a extensive use of AS is registered in sports in which is required a significant muscle mass (weight lifting, box, fight, gymnastics, shot put) as well as in sports where the increment of muscle mass allows an increase in speed potential of an athlete (American football, speed races and high jump) (Celotti et al., 1992). Furthermore, other categories of athletes using AAS are Bodybuilders (man and a very small number of women), which not participate in elite athletic competition, but their target is to reach a particular physical appearance (Anawalt, 2018). In addition to their ability to promote the muscular growth and strength, AAS are able to reduce the time of physical recovery after intense and protracted physical activity and to stimulate aggressive and determined attitude, basic requisites in sports where is required physical contact with the opponent (Modlinski & Fields, 2006). The public has access to AAS through the internet and illicit sites and there is no monitoring program to detect AAS use by non-elite athletes.

AAS are frequently used by men even if since 1990 the use of AAS by women has undergone a significant increase. In 1997, in fact, according to the American statistics, about 175,000 female adolescences have admitted to assume AS with a 100% increase since 1991. As for male adolescences, according to current American, there are 325,000 consumers with over one million of adolescences who have not used AAS at the age 12 to 17. The percentage of youth assuming these drugs without medical prescription rises above the 6% according to an American estimation for the year 1993 (Modlinski & Fields, 2006). This percentage rises to over 50% if only adult male bodybuilders are assessed.

The declaration of the *American College of Sport Medicine* related to the use of AAS is the following: 1) the use of anabolic steroids during training in association with an adequate diet may contribute to increase body weight, especially on behalf of lean body mass; 2) in some individuals the use of anabolic steroids develop the effects induced by training in muscular strength if associated with an high-protein diet; 3) anabolic steroids are not able to modify the aerobic power and ability; 4) the use of AS can cause serious damage at liver and cardiovascular level, reproductive system and psychological disorders even on therapeutic doses; 5) the use of AS among athletes is against the rules and the ethical principles of sports.

Pharmacokinetic of as

AS are administered orally or by injection. Those ingested orally (danazol, fluoximesterone, methyl testosterone, oxandrolone, stanazolol) are absorbed from the stomach and, considering their short half-life are rapidly eliminated; in the liver they result more toxic than steroid administered by injection, and they are more effective. Inject able steroids (testosterone propionate, testosterone enanthate, testosterone cypionate) are characterized by: a) a delayed metabolism, reduced elimination and a longer permanence in the organism (a characteristic that increases the chances of detection with the anti-doping test); b) they imply less liver toxicity; c) a lower activity than orally administered steroids. The injections can be determined up to one month after administration, whereas oral only up to a maximum of two weeks when administered intermittently (Goodman & Gilman's, 2011).

Way of administration

AAS can be administrated orally or parenterally. When steroid injections are performed, Kenacort (triamcinolone) or Celestone (betamethasone) are the most commonly used preparations. The steroid is often mixed with local anaesthetic. For assumption of AAS, typically, to achieve high doses and rapid effects is used a method called "stacking," which involves the concurrent use of two or more steroids in high doses (Mottarm & Gorge, 2000). The use of such association is based on the assumption that each steroid has a different physiological action. The assumption involves the gradual increase in dose ("pyramiding"); athletes, begin with low-doses, reach the peak and then slowly decrease the dose for a period of time which can range from 4 to 18 weeks. The "pyramid" protocol consists in alternating steroid assumption with periods of suspension, process defined as "cycling". The dose (50-200 mg daily) used in this procedure is 200 times higher than the recommended dosage employed for therapeutic reasons (5-20 mg/day) (Mottarm & Gorge, 2000). The dose is reduced gradually during the months preceding the competition, to reduce the chances of failing the anti-doping test before the race (Table 3).

Table 3. The main AS used as doping substances and their dosage

STEROID- ChemicalName	TERAPEUTIC dosage	DOPING dosage*
oxymetholone	25-50 mg/die per os.	50-150 mg/die os.
Oxandrolone	2.5-5 mg/die per os.	15-20 mg/die os.
Testosterone Undecanoato	40-60 mg/die per os.	200 mg/die os.
Nandrolone decanoate	50 mg/ settimana i.m.	200-400 mg/week i.m.
Nandrolone Undecanoate	80.5 mg/settimana i.m.	170-340 mg/week i.m.
Methandrostenolone	15-30 mg/die per os.	50-250 mg/die os.

*Assay valuesare onlyindicative, derivedfromplasma assaysperformedduringdoping controlson the self-declaredoroccasional. Some expertsare extremelyunderestimated

The most commonly used antidoping tests, consist in measurement of serum testosterone, FSH and LH. The exogenous testosterone, non testosterone AAS or hCG suppress circulating FSH and LH concentrations, measurement of serum testosterone, FSH and LH concentrations are functional for determining the likelihood of AAS use (Anawalt, 2018). The ratio measure is not only urinary testosterone and luteinizing hormone (T/LH), but also the relationship between testosterone and epitestosterone (T/E). Recently, it was determined that a ratio T/LH greater than or equal to 30 represents a more sensitive marker of the use of AS compared to a T/E ratio greater than or equal to 6 (Takahashi, Tatsugi, & Kohno, 2004).

Side effects

AAS have been associated with a diversity of adverse effects that take in many organ systems (Table 4). The anabolic effect is determined by a local nitrogen (azotes) increment with an increase of new formed proteins, by the rise in glycogen, phosphorus content and phosphorus compounds of high energy potential, by an accentuated oxygen consumption on muscular level and by an increased water content in muscle mass (Goodman & Gilman's, 1990).AAS abuse causes significant side effect. In men, the abuse of this substances may cause infertility, azoospermia, testicular atrophy, and gynecomastia. Women may develop excessive body hair growth, menstrual irregularity, hypertrophy of sebaceous glands, acne. Other side effects are: 1) Prostatic Hypertrophy; 2) premature cease of growth caused by premature epiphysis closure; 3) Alteration of cardiovascular function; 4) increase of platelet aggregation and plasmatic levels of low density lipoproteins (LDL). Moreover, AAS cause liver damage; euphoria, aggressiveness, psychosis. Their action in central neuron system involves the dopaminergic neurotransmission and produces amphetamine-like activity. They induct a sensation of euphoria which may result in

increased aggressiveness. Sometimes, AAS abuse may lead to withdrawal syndrome, like alcohol or other drug abuse (Stella et al., 2005; Stella et al., 2003). A study conducted on 160 athletes including 88 AAS users and 68 control athletes, showed that the prime difference between the two groups concerned the incidence of psychiatric effects; in fact, 23% of users manifested maniacal symptoms, hypomania and depression (Pope & Katz, 1994).

Table 4. The mainside effects of AAS

Proven Effects
Increase in fat-free mass Increase in body weight Increase in arm girth Increase in leg girth Increase in bench press and squat scores Increase in libido
Side Effects
Hepatocellular damage Cardiovascular disease (stroke, MI) Psychological disturbance LH, FSH, SHBG sperm count and fertility index
Men
gynecomasty (development of breasts), atrophy of the testicles, diminished libido, reduced fertility and impotence, interrupted growth in adolescent
Women
hirsutism (excessive hair growth, especially on the face), masculinization of the voice and the body, alopecia (hair loss), atrophy of the breasts and uterus, hypertrophy of the clitoris, menstrual irregularities, amenorrhea (lack of menstruation), and oligomenorrhea (light menstruation)
Effects common to males and females
severe acne musculoskeletal injuries: ruptured tendons, torn muscles liver problems: development of bloody cysts in the liver, jaundice, liver cancer cardiovascular problems: increased risks of arteriosclerosis, thromboembolisms, myocardial infarctions, strokes, edema, hypertension mental problems: anxiety, irritability, aggressiveness, loss of perception of certain realities and values, insomnia, nightmares, depression, suicidal thoughts, mental confusion, hallucinations, delusions of grandeur, paranoid personality disorder, schizophrenia, and other psychoses physical and psychological dependence

Prolonged use of high doses of AAS, especially if taken orally, it causes significant side effects leading to serious health risks. There are a few reports on the endocrinological and pathological changers in AAS abusers (Takahashi et al., 2004).

Other side effects

AS are extremely toxic for liver. One of the most grave consequence is certainly peliosishepatis (Broeder et al., 2000), a disease characterized by the formation of hemorrhagic cysts (sometimes at splenic level), which can break and cause intra-abdominal haemorrhage, and death of the patient. Regarding the effects on glucose metabolism, AAS reduce glucose tolerance and increase insulin resistance (Pärssinen et al. 2000). In addition, AAS a use cause immune system suppression. Many studies have shown that immunoglobulin levels (IgG, IgM and IgA) were significantly lower steroid users compared to control groups (Saygin et al., 2006; Goldman & Basaria, 2018). These studies suggest that high doses of anabolic steroids alter the immune mechanism and that the suppression of the immune system for a long period could lead to higher risks of infection or certain malignant cancers. Last but not least, studies conducted on animals and humans suggest that AAS use, associated with an intense training period, may cause severe damage on connective tissue, which reduce the mechanical and elastic properties of tendon (tendon rupture) (Liow & Tavares, 1995; Laure, 1997). Therefore, there are a very important and negative effects derivate by use of these drugs, on various organ systems in men and women (Goldman & Basaria, 2018). Some of these side effects are mild and reversible but others are irreversible and consequently fatal.

Conclusions

Though the number of positive steroid tests at Olympic events appears to be decreasing, the high level of anabolic steroid usage by body-builders and weightlifters and the disturbing level of abuse by the young in the community shows that much remains to be make to deactivate the anabolic steroid problem.In the USA, the problem has been tackled by utilizing educational programmes in colleges, schools and gymnasia and encouraging medical practitioners to adopt a sympathetic attitude towards steroid abusers, particularly by advising on and treating side-effects of anabolic steroids (Mazzeo, 2016). Therefore, the use of AAS should be banned from the sport, making a work of supervision and accountability of the sports centers and authorities in this field. AS use for doping purposes is a dangerous practice, that exposes who uses them to considerable risks. Preventing and treating the hormonal pathologies and instructing athletes to a healthy "health of sport" are two necessities not only for the physicians, but for every operator involved in the sport competition and more generally

of motor activity (Mazzeo, 2016; Dobs, 1999).

In conclusion, this practice must be discouraged not only for social and moral reasons but also for toxicological reasons; Doping substances must be banned from sports, making a work of vigilance and authority accountability of sports nucleus and authorities in this field. More studies need be carried out and immediate educational programme centred on schools should be instigated.

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Conflict of Interest
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