

## TREND OF DRUG ABUSE IN 2011–2014 IN ITALY

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**Abstract** Doping, although was born as a medication and not with the purpose of enhancing performance, is a widespread practice in all sports, between amateur and gym-goers. The Italian sports federations were in second place worldwide for positive doping-test, after Russia.

This review focuses on the analysis of data collected by Italian National Olympic Committee (CONI) in the 2012–2014 period, showing that the most commonly used substances were anabolic androgenic agents, glucocorticoids, diuretics and stimulants.

Prevention in doping could be a key to limit the damage caused by this harmful practice both, for the physical health and the athlete's moral integrity and anti-doping campaigns should be direct as much as possible to young people, since about two-thirds of adolescents appear to be dissatisfied with their body. Even coordination between the various professionals that surround athletes could help fight doping by planning specific training and adapted to the individual athlete, taking into account the actual physical limitations and physical features of each.

**Key words** drug abuse, physical health, AAS, glucocorticoids, diuretics, stimulants

### Introduction

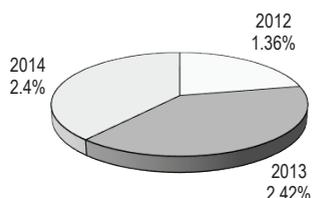
Doping, that is the uncontrolled intake of drugs or other substances in order to improve sports performance, is a widespread practice in all sports, not just among competitive athletes but also between amateur and gym-goers. It should be stressed that most of the doping agents are born as medications and not with the purpose of enhancing performance.

In Italy doping is rife, so much that in 2014 the Italian sports federations were in second place worldwide for positive doping-test, after Russia. Some people, however, argue that the finding of such a high number of positives is a direct result of marked controls than other countries of the world.

CONI, Italian National Olympic Committee, is a public institution that controls the associations in professional categories and annually publishes a statistical anti-doping report, normally detected by biological analyzes conducted

on samples of blood or urine, collected during or outside the competition. The analyzed sports federations are about 62, including the Italian Paralympic Committee.

Our report focuses on the analysis of data collected by CONI in the 2012–2014 period by which it was possible to analyze the Italian athletes' behaviour in relation to the use of prohibited substances in the WADA's list. Analyzing the data reported by anti-doping statistical report, it comes out that most of the Italian athletes' doping tests were negative. This trend is a good result because it means that, compared to the past, both athletes and athletic trainers have understood more consciously the risks for health derived from the use of these substances. Despite these encouraging data, we must not underestimate the presence of athletes who take doping substances. Although the percentage is small, an average of 2% of athletes subjected to the test was positive (Figure 1).



**Figure 1.** The percentage of positive samples for anti-doping tests

## CONI data for the 2012–2014 period

This study focuses on data collected in 2012–2014 to clarify the progress of unhealthy habits among Italian athletes.

Who determines which products are prohibited is the world anti-doping agency (WADA), an international independent agency founded in 1999, which annually draws up a list containing all the performance-enhancing drugs and has developed an anti-doping policy worldwide for all sports, also promoting campaigns of prevention and scientific research (Creado, Reardon, 2016).

Athletes positive to the analysis, are grouped in the CONI report in two categories:

1. Subjects with AAF (adverse outcome) in which the analysis of the biological samples has detected the presence of a prohibited substance or its metabolites.
2. Subjects with ATF (atypical outcome), where the biological analysis yielded results that require further investigations before to claim certainty adverse outcome.

In addition, although many athletes are positive to the investigation, the existence of certifications TEU, i.e. exemptions for therapeutic purposes, which allow athletes with a known disease, to take substances that normally fall into the WADA blacklist, also during the competitive period should be considered.

To be obtained, a TUE must respect some specific criteria, demonstrating the need to take that particular substance, normally prohibited, only for therapeutic purposes. It is important, therefore, that it is established that the non-administration of the drug should cause health problems and that its use, in compliance with the dosage, almost certainly will not make improvements to the sports performance; there must not exist a drug that can be prescribed

as an alternative to face the disease and eventually, the use of this substance should not be consequently “forced” by the use of another one banned previously assumed (Fitch, 2016).

In recent years, sport federations that have the highest number of positive athletes are: cycling, football, athletics and swimming (Figure 2).

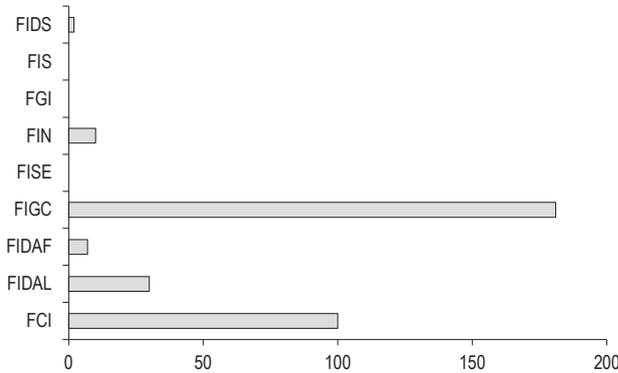


Figure 2. The number of positive individuals within some sports federations

### Enhancing drugs most commonly used by athletes

The reports published annually by CONI show that, under review, the most commonly used substances were (Figure 3):

- Anabolic Androgenic Agents,
- Glucocorticoids,
- Diuretics,
- Stimulants.

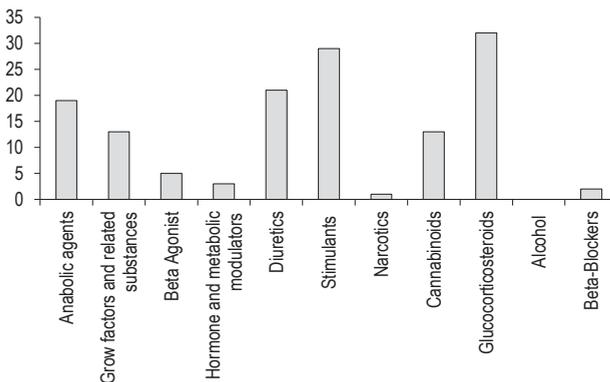


Figure 3. Substances identified in all sports

## Anabolic Androgenic Agents

The first category includes all agents that increase anabolism, i.e. protein synthesis in order to increase muscle mass. Anabolic Androgenic Steroid (AAS), included in the WADA blacklist, have anabolic effect and mimics the endogenous steroidal androgens effects associated with virilisation, increase in strength, voice deepening and growth of hair. Testosterone, the androgenic steroid hormone *par excellence*, and its synthetic derivatives accepted for the purpose of doping, have an effect to minimize the androgenic effects and increase anabolic ones. The clinical use of testosterone is exclusively limited to males with hypogonadism (Contrò, Bianco, Proia, 2012).

Among the most serious consequences of AAS use, there is hepatotoxicity which can induce the occurrence of peliosis, adenoma or the most severe form of hepatocellular carcinoma (Bond, Llewellyn, van Mol, 2016). Also it is known to cause dependence exerting several brain actions influencing the behaviour and causing aggression, anxiety, paranoia and manic-depressive states. Furthermore, it should induce cardiovascular system damages, causing for example myocardial infarction or thrombosis.

Some substances, passed as food supplements, may cause similar effects reported for AAS abuse. In 2010 a case was reported about a body builder of 31 years in whom the assumption of SUS 500, a pro hormone, induced liver problems and altered behaviour. In Italy the sale of pro-hormones is not allowed, as well as AAS and even if in some countries of the world they are legal, WADA has placed them among the banned substances since they alter the normal athletic ability (Wingert, Tavakoli, Yoder, 2010).

Doping seen more as a general phenomenon, it affects even women and, as collateral effects it causes alterations in the menstrual cycle and development of male secondary characteristics. A study conducted by the Karolinska Institute on 8 women that took anabolic androgenic steroids (AAS) and/or clenbuterol (beta 2 agonist) found particularly significant side effects; particularly identified in 5 of them, voice changes were observed, in addition to changes in the clitoris and growth of body hair. While in 2 of them tachycardia and depression were detected (Börjesson, Gårevik, Dahl, Rane, Ekström, 2016).

## Glucocorticoids

Glucocorticoids are a class of corticosteroids that are synthesized from cholesterol in the adrenal cortex in particular in the zona fasciculata. They modulate the activity of the cells of our body and are essential for life; however, when taken exogenously they may give rise to more or less severe side effects (Buckingham, 2006).

The blood levels of these substances are held constant by a negative feedback mechanism involving the hypothalamus-pituitary axis: in response to various stimuli, for example stress or hypoglycemia, the hypothalamus secretes the corticotrophin releasing hormone (CRH) that stimulates the release by the pituitary adrenocorticotrophic hormone (ACTH) into the systemic circulation, which acts in turn on the adrenal cortex resulting in the production of corticosteroids which are released into the systemic circulation. Through the bloodstream, glucocorticosteroids are sent to the target tissues where they will explicate their mechanism of action: it stimulates fundamental processes to maintain constant levels of glucose in the blood such as gluconeogenesis in the liver, transcription of enzymes involved in gluconeogenesis, mobilization of amino acids from extra-hepatic tissues (these serve as substrate for gluconeogenesis), stimulation of lipolysis in adipocytes (Hackney, Walz, 2013).

These substances modulate the blood pressure, act on bone tissue and are also involved in cell growth mechanisms; they play a role in the central nervous system both on neurons and on the glial cells.

These substances also have anti-inflammatory and immunomodulatory effect and in fact they are used in the pharmacological treatment of chronic inflammatory diseases and autoimmune diseases such as sclerosis multiple, eczema, rheumatoid arthritis, atherosclerosis (Coutinho, Chapman, 2011). They are also used in the treatment of severe allergies, adrenal problems, asthma, eye or vision problems, or ulcerative colitis (Matabosch et al., 2011). Chronic use of corticosteroids may lead to the onset of Cushing's disease that manifests as weight gain, fatigue, hirsutism, amenorrhea in women and impotence in men (Kirby, 1989).

Glucocorticoids are lipophilic substances which can cross the phospholipid bilayer of the cell membrane to bind their cytosolic receptor. The glucocorticoids receptor (GR) is a member of the superfamily of receptors that modulate gene transcription; in fact, this receptor mediates the transcription via transactivation of target genes by binding to glucocorticoid response element (GRE) (Yudt, Cidlowski 2002).

The GR receptor is found in the cytosol bound to heat shock proteins hsp90 that prevent translocation into the nucleus when is unbound to glucocorticoid (Hayashi, Wada, Ito, Adcock, 2004). When the glucocorticoid binds the receptor, the hsp90 proteins dissociate and the hormone-receptor complex migrates to the nucleus where it modulates gene transcription helped by cofactors, bind the promoter regions of anti-inflammatory genes, such as the inhibitor lipocortin-1 and suppresses phospholipase A2 (Karin, 1998; McNally, Muller, Walker, Wolford, Hager, 2000). The glucocorticoids decrease transcription of adhesion molecule, chemokines, cytokines and increase the transcription of secretory leukocyte inhibitory protein (SLPI) and  $\beta$ 2-adrenergic receptor (ADRB2).

The main target of glucocorticoids is the muscle tissue where they regulate the metabolism of glucose and protein. Under stress conditions, such as exercise, the levels of glucocorticoids rise and determine the reduction of protein synthesis and the increase of protein catabolism in order to provide aminoacids as substrate for gluconeogenesis; they are used to take advantage as anti-inflammatory and to increase the overall racing performance of the body's response to stress. Chronic use of these substances may determine muscle atrophy and muscle weakness (Kuo, Harris, Wang, 2013).

Large doses of glucocorticoids can alter muscle physiology and susceptibility to neuromuscular blocking drugs by mechanisms not clearly understood (Shin, Fink, Khiroya, Ibeunjo, Martyn, 2000).

Muscle atrophy is called "steroid myopathy" and causes weakness, especially in the muscles of the upper and lower limbs and neck. Different conditions that cause muscle atrophy are correlated with increased levels of glucocorticoids suggesting that these substances play an important role in this process (Cea et al., 2016).

Some athletes use glucocorticoids to improve their performance inducing mobilization of fatty acids, amino acids and stimulate gluconeogenesis, although many of them use it to reduce pain and fatigue, not knowing the side effects in the long term (Nikolopoulos, Spiliopoulou, Theocharis, 2010). For example, glucocorticoids are administered for the treatment of chronic tendinitis and tendon injuries.

Glucocorticoids are used by professional athletes since 1960 in which the chronic abuse was detected through hair analysis and urine (Nichols, 2005); corticosteroids are inserted in the list of prohibited substances that has been drawn up by WADA because they have an ergogenic effect and cause health risks (Matabosch et al., 2013).

## Diuretics

Diuretics are substances that cause a greater urine production through increased excretion of water and salt in the kidney but can also interfere with the excretion of other electrolytes such as potassium, calcium and uric acid. Their effect determines the decrease of the liquid in the circulation and, therefore, blood pressure.

There are various types of diuretics, but the most used are the loop diuretics and thiazide diuretics. Loop diuretics, such as furosemide, are organic anions, which act in the loop of Henle structure. In particular, they act on the Na/K/2Cl transporter blocking the reabsorption of sodium and chlorine resulting in a reduction of the concentration of urine. The thiazide diuretics are organic anions which act in the distal tubule and collecting duct by binding to Na/Cl cotransporters preventing sodium reabsorption (Brater, 1998; Brater, 2000; Ellison, 1994). Then both substances cause excretion of sodium and water but by different action mechanisms. Diuretics are used for treatment of cardiac disease, acute pulmonary edema and chronic congestive heart failure, for the treatment of the edema of nephrotic syndrome and for life-threatening hyponatremia. Hypovolemia, hypersensitivity, and ototoxicity are typical side effects, such as electrolyte imbalance which causes a reduction in blood levels of potassium, magnesium, calcium and uric acid. Furosemide can also result in acute interstitial nephritis and skin rash (Se Won Oh, Sang Youb Han, 2015).

Since 1988, the use of diuretics in sports is prohibited (Cadwallader, de la Torre, Tieri, Botrè, 2010), both during and out of competition. This is due to the fact that athletes use diuretics for many reasons: to reduce their body weight or to limit the excessive water retention caused by the abuse of anabolic steroids and to mask the presence of banned substances in urine. Therefore, when urine samples are taken to carry out the doping test, the research of these substances is always carried out (Thevis, Schänzer 2005). However, if the athlete is suffering from a disease that requires treatment with diuretics, the doctor may request the their use for therapeutic purposes (TUE) to WADA and therefore to be considered negative for anti-doping controls (Cadwallader et al. 2010).

Diuretics constitute a default and not advantageous final body weight in some sports such as wrestling, boxing, judo and among athletes who want to maintain a low body weight, such as gymnasts and dancers.

The analysis of the data collected by CONI found out that furosemide and hydrochlorothiazide are diuretics used by most athletes. They are very powerful diuretics that can also result in serious adverse effects if not administered properly.

The use of these substances in healthy subjects can lead to considerable loss of fluids and salts, which can lead to a significant reduction in blood pressure with consequent collapse in athletes which carry out an intense physical effort; hypokalemia can determine onset of severe arrhythmias and cardiac arrest.

## Stimulants

Stimulants are substances, which act at the level of the Central Nervous System increasing the responsiveness and concentration and reducing the feeling of fatigue and affect mood; some have anorexiatic effect for which they are taken to lose weight. They also act on the cardiovascular system causing, for example, even fatal arrhythmias.

Although many stimulants fall under WADA lists, some of them are prohibited only if they exceed certain concentrations in the urine; moreover their use is prohibited only during competition because they have a very short duration of action that does not cause long-term effects. The use of these substances is not limited to the above effects: in fact they are also hired to counteract the side effects due to AAS.

Are included in this category ephedrine and pseudoephedrine, amphetamine, cocaine and mildest caffeine. Pseudoephedrine, for example, when taken at therapeutic doses (60–120 mg) serves to relieve nasal and sinus congestion, but if taken in overdose (>180 mg) it may determine performance improvement, therefore it shows ergogenic effect carried out in a dose-dependent manner (Trinh, Kim, Ritsma, 2015). Even caffeine is among the stimulants. In concentrations >3–6 mg/kg it may cause ergogenic effects, although this dose ranges do not lead to

exceeding the allowable limit in the urine of 12 mg mL<sup>-1</sup>; so WADA was forced to remove it from the list of prohibited substances, even if it continues to monitor it (Deventer, Roels, Delbeke, Van Eenoo, 2011).

## Discussion

Prevention in doping could be a key to limit the damage caused by this harmful practice both for the physical health and the athlete's moral integrity. Therefore is good acting during adolescence, before puberty, conducting as much as possible anti-doping campaigns for young people (Wippert, Fließner, 2016).

Research conducted over the last 10 years on young people state which about two-thirds of adolescents appears to be dissatisfied with their body (Yager, O'Dea, 2014) and this dissatisfaction involves a perennial pursuit of physical perfection that leads young people to adopt harmful diets for weight loss and to practice strenuous exercise which they try to cope with initially by taking supplements, which can later open a direct route to the use of banned substances and thus doping.

Even coordination between the various professionals that surround athletes could help fight doping by planning specific training, adapted to the individual athlete taking into account the actual physical limitations and physical features of each.

To minimize the phenomenon of doping, information and prevention should be done with young athletes, trying to involve other subjects (e.g. sports physicians, coaches or family) in order to establish and maintain attitudes and behaviours correct. It is very important to involve sports organizations that provide greater resources to psychosocial projects in relation to anti-doping controls at all levels. It would also be desirable to test sport rules by event organizers and federations in order to avoid the potential benefits of using prohibited substances in competitions, trying to change attitudes towards doping and doping culture.

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