

What every physician should know about doping and doping control

O QUE TODO MÉDICO DEVERIA CONHECER SOBRE *DOPING* E CONTROLE *ANTIDOPING*

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Probably the medical professional who is closer to the daily life of an athlete, who participates regularly in competitions, whether or not high-performance, is the expert in exercise and sports medicine. However, occasionally the athlete may need to resort to other medical professionals, for various reasons, such as a general practitioner, a dermatologist, a cardiologist, an orthopedist or a gastroenterologist. Therefore, every physician is subject to come across a patient who is an intermediate level or high-performance athlete, and will need to go through doping controls throughout his sporting life. The purpose of this article is to provide concepts and information to medical professionals so that they can properly treat their “athlete patients”, avoiding the use of substances that may harm them in a doping control situation.

HISTORY

In the past, the list of banned substances was drawn up by the Medical Commission of the International Olympic Committee (IOC) and usually revised in the year previous to an Olympic game. The IOC list was used by international federations of different sports, in many countries. However, over time, alternative lists slightly different from each other were created. This would compel the experts in exercise and sports medicine to know which authority was responsible for a given competition, and what the list of banned substances adopted would be. The problem was finally resolved with the creation in 1999 of the World Anti-Doping Agency, also known as WADA.

WADA annually updates the list of prohibited substances and methods. The list is valid from January 1 of each year and is usually updated and approved by WADA Executive Committee in the last quarter of the preceding year, then published on WADA’s website: www.wada-ama.org.

CONCEPT OF DOPING

The concept of doping by WADA is based on three criteria: enhancement of sports performance; risk to the health of the athlete; and that use of the substance or method violates the spirit of sport. When two of these three cri-

teria are present in a substance or a method, the theoretical possibility of listing occurs.

Examples of artificial performance enhancement include anabolic steroids, which also cause serious risks to the health of the athlete. This group of substances includes two of the three basic principles of the concept of doping, and therefore makes the list.

The concept of “violating the spirit of sport” can give rise to subjective interpretations, but these values are explained in WADA World Anti-Doping Code as follows: ethics, fair play and honesty; health; excellence in performance; character and education; fun and joy; team spirit; dedication and commitment; respect for rules and laws; self-respect and respect for the other athletes; courage; solidarity.

Cannabinoids, such as hashish and marijuana, are examples of substances considered doping because they are harmful to the health of the athlete and contrary to the fundamental values of sport, although they not enhance athletic performance.

DEFINITION OF DOPING

By resolution of the World Anti-Doping Code, doping is characterized when there is/are one or more anti-doping rule violations, which are as follows:

1. Presence of a prohibited substance or its metabolites or markers in the sample collected from an athlete;
2. Use or attempted use by an athlete of a prohibited substance or prohibited method;
3. Refusing or failing without compelling justification to submit to sample collection after notification, or otherwise evading doping control;
4. Violation of the requirements regarding athlete availability for out-of-competition testing;
5. Tampering or attempted tampering with any part of doping control;
6. Possession of prohibited substances and prohibited methods;
7. Trafficking or attempted trafficking of prohibited substances and prohibited methods;
8. Administration or attempted administration to any athlete in-competition of a prohibited substance or a prohi-

bited method; or administration or attempted administration to any athlete out-of-competition of a substance or method that is prohibited out-of-competition;

9. Assisting, encouraging, aiding, abetting, conspiring, covering up or any other type of intentional complicity involving an anti-doping rule violation;

TYPES OF DOPING CONTROL

In-competition control is performed in a specific competition, such as a soccer game or a swimming competition. In this type of control, all WADA-prohibited substances and methods are considered doping.

The out-of-competition control can be performed at the discretion of International Federations, National Olympic Committees or National Anti-doping Agencies, which have a database on the location of athletes, updated periodically. An athlete may receive a visit from an anti-doping control officer at any time, at home, at the training facilities, at the workplace or during holidays. In principle, this type of control can be performed up to 48 hours before a sporting competition.

WADA LIST OF PROHIBITED SUBSTANCES AND METHODS

As mentioned above, the list of prohibited substances and methods is annually updated by WADA, always in the last quarter of the year, coming into force on January 1 of the following year and being valid until December 31 of that year.

The following tables show the prohibited substances and methods, as updated by WADA for the year of 2016. Table 1 shows the list of prohibited substances and methods in any in- and out-of-competition testing. Table 2 shows the list of prohibited substances and methods for in-competition testing only. Table 3 shows the list of prohibited substances in particular sports. The Tables display the most common substances in each category. The complete list can be found in English on WADA website (www.wada-ama.org) or in Portuguese, on the website of the Brazilian Doping Control Authority (*Autoridade Brasileira de Controle de Dopagem* – ABCD): www.abcd.gov.br.

AUTHORIZATION FOR THERAPEUTIC USE

An athlete can use any substance that is part of WADA list for medical treatment, after requesting and being granted a therapeutic use exemption (TUE) to/by the competent body. It is also necessary that each of the following situations is covered:

- a. That the prohibited substance is necessary to treat an acute or chronic medical condition, so that the suspension or non-use of the substance significantly worsens the symptoms;
- b. The prohibited substance being claimed for use cannot enhance the physical performance beyond what would be expected with the simple treatment and reestablishment of the normal state of the athlete's health;
- c. There are no other evidence-based alternatives to the use of the prohibited substance, or – in other words – that the prohibited substance is considered irreplaceable in the treatment of the athlete's medical condition;
- d. That the need for the use of the prohibited substance does not result from previous non-therapeutic use of any substance or method banned by WADA.

World-class athletes and athletes who participate in an international competition should apply for TUE directly from the international federation for their sport. Athletes who participate in national competitions, in turn, must request a TUE directly from the ABCD, as soon as possible and within a period not less than 30 days before the competition. In Brazil, applications should be completed by the athlete and his/her assisting physician (form available on the ABCD website). Assessment is made by the ABCD TUE Commission (CAUT-ABCD); if the CAUT-ABCD considers that the use of the substance meets the criteria defined by the International Standard for Therapeutic Use Exemptions, the TUE is granted. Evidently, the form must be accompanied by appropriate documentation confirming the diagnosis, including results and expert opinion reports of the relevant complementary tests.

If due to a medical emergency a medical doctor has to administer a prohibited substance, the case must be reported as soon as possible to the ABCD using the TUE request system, available from www.abcd.gov.br. Documents proving admission to the emergency room and a clinical report of the emergency should also be sent. The request for therapeutic use of a prohibited substance with retroactive approval is possible only in cases of emergency treatment due to acute medical conditions, or in exceptional situations where the sending of the request for therapeutic use prior to doping control is not possible.

CONCLUSION

One of the principles of doping control is to seek to ensure the maintenance of the athlete's health and fair play. We must remember that the athlete is responsible for all

substances that may be found in his or her body. For this reason, we consider that all medical professionals, regardless of their specialty, should have – as part of their medical knowledge wealth – the domain of basic con-

cepts of doping control, not only to provide the best therapeutic alternatives, but mostly to avoid iatrogenic events that can jeopardize the credibility and career of an athlete patient.

TABLE 1 Permanently prohibited substances and methods (in- and out-of-competition).

Class	Sub-classes, examples, comments
S0. Non-approved substances	Any pharmacological substance which is not addressed by any of the subsequent sections of the list and with no current approval by any governmental regulatory health authority for human therapeutic use (e.g. drugs under pre-clinical or clinical development or discontinued, designer drugs, substances approved only for veterinary use) is prohibited at all times
S1. Anabolic agents	<ol style="list-style-type: none"> Anabolic androgenic steroids (AAS) <ol style="list-style-type: none"> Exogenous AAS, including stanozolol and nandrolone Endogenous AAS, including androstenodione and dihydrotestosterone Other anabolic agents, such as clenbuterol and tibolone
S2. Peptide hormones, growth factors, related substances and mimetics	<p>The following substances are prohibited, as well as their releasing factors:</p> <ol style="list-style-type: none"> Erythropoiesis-stimulating agents, e.g. erythropoietins (EPO) and darbepoietin (dEPO) Hypoxia-inducible factor (HIF) stabilizers, e.g. cobalt; and HIF activators, e.g. argon and xenon Chorionic gonadotrophin (CG) and luteinizing hormone (LH), both prohibited in males Corticotrophins Growth hormone (GH) Additional prohibited growth factors, e.g. fibroblast growth factors (FGFs), insulin-like growth factor-1 (IGF-1) or mechano (MGFs), and more growth factors
S3. Beta-2 agonists	<p>All substances in this class are prohibited, except for:</p> <ul style="list-style-type: none"> Inhaled salbutamol (maximum 1,600 mcg over 24 hours) Inhaled formoterol (maximum delivered dose 54 mcg over 24 hours) Inhaled salmeterol in accordance with the manufacturers' recommended therapeutic regimen <p>The presence in urine of salbutamol in excess of 1,000 ng/mL or formoterol in excess of 40 ng/mL is presumed not to be an intended therapeutic use of the substance and will be considered as an Adverse Analytical Finding (AAF), unless the athlete proves, through a controlled pharmacokinetic study, that the abnormal result was the consequence of the use of the therapeutic inhaled dose up to the maximum indicated above</p>
S4. Hormone and metabolic modulators	<p>The following hormones and metabolic modulators are prohibited:</p> <ol style="list-style-type: none"> Aromatase inhibitors, e.g. aminoglutethimide Selective estrogen receptor modulators, e.g. tamoxifen and raloxifene Other anti-estrogenic substances, e.g. clomiphene Agents modifying myostatin function(s) Metabolic modulators <ul style="list-style-type: none"> Activators of the AMP-activated protein kinase (AMPK) and peroxisome proliferator activated receptor δ (PPARδ) agonists Insulins and insulin mimetics Meldonium Trimetazidine
S5. Diuretics and masking agents	<p>Thiazide diuretics, e.g. chlorthalidone, indapamide and hydrochlorothiazide</p> <p>Potassium-sparing diuretics, e.g. spironolactone and triamterene</p> <p>Loop diuretics, e.g. furosemide</p> <p>Masking agents, e.g. probenecid and plasma expanders</p>

(Continue)

TABLE 1 (Cont.) Permanently prohibited substances and methods (in- and out-of-competition).

Prohibited methods	
M1. Manipulation of blood and blood components	The following are prohibited: <ol style="list-style-type: none"> 1. The administration or reintroduction of any quantity of autologous, allogenic (homologous) or heterologous blood, or red blood cell products of any origin into the circulatory system 2. Artificially enhancing the uptake, transport or delivery of oxygen, including efaproxiral (RSR13) 3. Any form of intravascular manipulation of the blood or blood components by physical or chemical means
M2. Chemical and physical manipulation	The following are prohibited: <ol style="list-style-type: none"> 1. Tampering, or attempting to tamper, to alter the integrity and validity of samples collected during doping control, including, but not limited to urine substitution and/or adulteration 2. Intravenous infusions and/or injections of more than 50 mL per 6 hour period except for those legitimately received in the course of hospital admissions, surgical procedures or clinical investigations
M3. Gene doping	The following, with the potential to enhance sport performance, are prohibited: <ol style="list-style-type: none"> 1. The transfer of polymers of nucleic acids or nucleic acid analogues 2. The use of normal or genetically modified cells

Note: Only a few examples are cited; see the full list on WADA or ABCD websites.

TABLE 2 Substances and methods prohibited in-competition (In addition to the categories S0 to S5 and M1 to M3 defined above, the following categories are prohibited in-competition).

Class	Sub-classes, examples, comments
S6. Stimulants	All stimulants, including all optical isomers, are prohibited, including: <ol style="list-style-type: none"> a. Non-specified stimulants, e.g. amfepramone, amphetamine, fenproporex, methylamphetamine b. Specified stimulants, e.g. sibutramine Except for: <ul style="list-style-type: none"> • Clonidine • Imidazole derivatives for topical/ophthalmic use and those stimulants included in the 2016 Monitoring Program: <ul style="list-style-type: none"> * Bupropion, caffeine, nicotine, phenylephrine, phenylpropanolamine, pipradrol, and synephrine: These substances are included in the 2016 Monitoring Program, and are not considered prohibited substances ** Cathine: Prohibited when its concentration in urine is greater than 10 mcg/mL *** Ephedrine and methylephedrine: Prohibited when the concentration of either in urine is greater than 10 mcg/mL **** Epinephrine (adrenaline): Not prohibited in local administration, e.g. nasal, ophthalmologic, or co-administration with local anaesthetic agents ***** Pseudoephedrine: Prohibited when its concentration in urine is greater than 150 mcg/mL
S7. Narcotics	The following are prohibited: Buprenorphine, dextromoramide, diamorphine (heroin), fentanyl and its derivatives, hydromorphone, methadone, morphine, oxycodone, oxymorphone, pentazocine and pethidine
S8. Cannabinoids	The following are prohibited: <ul style="list-style-type: none"> • Natural, e.g., cannabis, hashish and marijuana, or synthetic delta 9-tetrahydrocannabinol (THC) • Cannabimimetics, e.g., "Spice", JWH-018, JWH-073, HU-210
S9. Glucocorticoids	All glucocorticoids are prohibited when administered by oral, intravenous, intramuscular or rectal routes

Note: Only a few examples are cited; see the full list on WADA or ABCD websites.

TABLE 3 Prohibited substances in particular sports.

Class	Examples and comments
P1. Alcohol	<p>Alcohol (ethanol) is prohibited in-competition only, in the following sports. Detection will be conducted by analysis of breath and/or blood. The doping violation threshold is equivalent to a blood alcohol concentration of 0,10 g/L</p> <ul style="list-style-type: none"> • Air sports (FAI) • Archery (WA) • Automobile (FIA) • Powerboating (UIM)
P2. Beta-blockers	<p>Beta-blockers are prohibited in-competition only, in the following sports, and also prohibited out-of-competition where indicated:</p> <ul style="list-style-type: none"> • Archery (WA) * • Automobile (FIA) • Billiards (all disciplines) (WCBS) • Darts (WDF) • Skiing/Snowboarding (FIS) in ski jumping, freestyle aerials/halfpipe; and snowboarding halfpipe/big air • Golf (IGF) • Shooting (ISSF, IPC) * • Underwater sports (CMAS) in constant-weight apnea with or without fins, dynamic apnea with and without fins, free immersion apnea, jump blue apnea, spearfishing, static apnea, target shooting and variable weight apnea <p>* Also prohibited out-of-competition</p> <p>Including, but not limited to: Acebutolol, atenolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, pindolol, propranolol and sotalol</p>

Note: Only a few examples are cited; see the full list on WADA or ABCD websites.