

Prescribing medication for athletes: guidelines for general practitioners

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ABSTRACT

The number of persons taking part in organized sports in our islands is increasing every year. Many of these athletes and the events that they participate in are subject to doping control tests by the National Anti-Doping Organisation (NADO) or the national federation or association of their particular sport. A small number of these tests record a prohibited substance present in the athlete's sample, which may have serious consequences on the sporting career of the athlete. Many athletes consult their general practitioner (GP) or team doctor regularly for advice when they develop a medical condition. This article is intended to provide the GP with background information regarding drugs that may be used safely and without consequences for the athlete, the procedure to follow when the athlete needs to be treated with drugs which are prohibited to athletes, and the pitfalls of accidental doping.

Key words

Doping, sports, athlete, supplements, prohibited list

INTRODUCTION

The sanctioning of star tennis player Maria Sharapova in 2016, following alleged medical use of the drug meldonium, resulted in a spate of media activity which brought to the attention of the world the possibility of athletes being sanctioned when using drugs prescribed legitimately. The drug was declared a prohibited drug on 1st January 2016 and resulted in a total of 283 positive tests worldwide during that year. It is prudent to bring the issue of safe prescribing to athletes to the attention of the family doctor / general practitioner (GP), and provide the necessary tools to make an informed decision when treating athletes. Contrary to normal patients, athletes are not allowed to use certain medications as this may result in a positive doping control test, which could lead to a sanction.

The World Anti-Doping Agency (WADA) was established in 1999 as an international, independent agency composed and funded equally by the sport movement and governments of the world. Its key activities include scientific research, education, development of anti-doping capacities, and monitoring of the World Anti-Doping Code (WADC/Code) – the document harmonizing anti-doping policies in all sports and all countries. The first Code was drawn up in 2004 and revised in 2015.

Malta ratified the Anti-Doping Convention of the Council of Europe and the UNESCO Convention against Doping in Sport in 2011. The first Anti-Doping Regulations were passed in 2011 (LN 281 of 2011) and the Maltese National Anti-Doping Organisation (NADO) started operation in February 2012 in line with the WADC. Since then the Anti-Doping regulations were changed in 2015 (LN 17 of 2015) to be in line with the new WADC, which, in a nutshell, lays down the rules on what constitutes an Anti-Doping Rule Violation (ADRV) and how the NADO should conduct its operation (Anti-Doping Regulations of Malta, 2015). This involves testing, results management and sanctioning. Since its inception, Maltese NADO has carried out 441 doping control tests and sanctioned 18 athletes.

There are 10 ADRVs in our law and the WADC. These are summarised in Table 1. The most common ADRV by far is finding the presence of a prohibited substance or its metabolites in an athlete's sample. This is what constitutes a positive doping control test.

THE PROHIBITED LIST

The WADA Prohibited List (List) is the comprehensive document serving as the international standard in identifying substances and methods prohibited in all sports (World Anti-Doping Agency, 2017). The List is revised every year after months of review by experts and stakeholders and comes into force on 1st January of every year. The Maltese Anti-Doping Regulations refer to this

Table 1: Antidoping rule violations

1	The presence of a prohibited substance or its metabolites or markers in the athlete's sample.
2	The use or attempted use of a prohibited substance or prohibited method.
3	Evading sample collection or refusing or failing to submit to sample collection.
4	Any combination of three missed tests or filing failures in one calendar year.
5	Tampering or attempted tampering with the doping control process.
6	Possession by an athlete support personnel of any prohibited substance or method in and out of competition.
7	Trafficking or attempted trafficking of a prohibited substance or method.
8	Administration or attempted administration to an athlete of any prohibited substance or method.
9	Assisting, encouraging, aiding, abetting, conspiring, covering up involving an ADRV.
10	Prohibited association.

document and a copy is published in the Government Gazette in January of every year and it is also available online. It is very important that athletes and their medical providers are aware that changes may occur from year to year according to new evidence which would have emerged regarding performance enhancing drugs.

A substance or method is considered by WADA for inclusion in the prohibited list if it meets two of the following three criteria:

- Medical or scientific evidence, pharmacological effect, or experience that it has the potential to enhance or enhances sport performance.
- Medical or scientific evidence, pharmacological effect, or experience that the substance represents an actual or potential health risk to the athlete.
- Use of the substance is considered to violate the spirit of sport.

All athletes participating in organized sports are subject to doping control testing at all times. The definition of athlete in the Maltese legislation is as follows: “*athlete*” means any person who competes in sport at the international level as defined by each international federation or at the national level as defined by each national anti-doping organisation.” This means that any person registered with a local sporting association or federation, or who participates in a competition organized by the same, is bound to abide by the anti-doping regulations. These athletes may be tested not only during a competition but also at other times (out of competition).

The Maltese Anti-Doping Regulations and the WADC stipulate athlete ‘strict liability’. This principle is applied in situations where urine or blood samples collected from an athlete have produced adverse analytical results, and means that the athlete is held responsible for the substances found in his or her bodily specimen. An anti-doping rule violation occurs whenever a prohibited substance (or its metabolites or markers) is found in the specimen, whether or not the athlete intentionally or unintentionally used a prohibited substance (even if it was legitimately prescribed by a doctor) or was negligent or otherwise at fault. This means that the athlete is solely responsible for any prohibited substance found in his sample and needs to be very vigilant about which medications or substances he or she might be consuming at all times, not just around the time of competition.

The substances and methods included in the List are divided into 4 sections as follows:

- Substances prohibited at all times (Table 2). These drugs cannot be used by athletes in and out of competition. This section includes anabolic steroids, beta 2 agonists, diuretics and growth hormone among others.
- Substances prohibited in-competition only (Table 3). This section includes stimulants, narcotics, glucocorticoids and cannabinoids. The athlete must pay attention to stop any medication containing any of these drugs early enough for the all of the drug to be metabolized and cleared by the

Table 2: Substances prohibited at all times

Class			Examples of substances
S0. Non approved substances	Any pharmacological substance not addressed by the other subsections and not approved for human therapeutic use	Drugs under clinical or pre-clinical development or discontinued, designer drugs, drugs approved only for veterinary use	GW501516
S1. Anabolic agents	1. Anabolic androgenic steroids (AAS)	Exogenous AAS	Bodenone, nandrolone, stanozolol
		Endogenous AAS, when administered exogenously	Testosterone, DHEA, androsterone, epitestosterone
	2. Other anabolic agents		Clenbuterol, selective androgen receptor modulators (SARM's), tibolone, zilpaterol
S2. Peptide hormones, growth factors, related substances and mimetics	1. Erythropoietin-receptor agonists	1.1 Erythropoiesis stimulating agents (ESA's)	EPO, dEPO, CERA
		1.2 Non erythropoietic EPO-receptor agonists	ARA-290, asialo EPO, carbamylated EPO
	2. Hypoxia inducible factor (HIF)	HIF stabilisers	HIF stabilisers e.g. cobalt, HIF activators e.g. argon, xenon
		3. Chorionic gonadotrophin (CG) & luteinising hormone (LH) & their releasing factors in MALES	
	4. Corticotrophins and their releasing factors		<ul style="list-style-type: none"> • Corticorelin
	5. Growth hormone (GH) and its releasing factors	Growth hormone releasing hormone (GHRH) and its analogues, secretagogues (GHS) and releasing peptides (GHRP's)	<ul style="list-style-type: none"> • CJC-1295, sermorelin, ghrelin, GHRP-6, hexarelin

Class			Examples of substances
	Additional prohibited growth factors		<ul style="list-style-type: none"> IGF-1, FGF, HGF, VEGF, PDGF
S3. Beta2 agonists	All beta2 agonists including optical isomers EXCEPT INHALED salbutamol, salmeterol, formoterol in therapeutic doses		Terbutaline, albuterol
S.4 Hormone and metabolic modulators	1. Aromatase inhibitors		Aminoglutethimide, anastrozole, formestane
	2. Selective estrogen receptors modulators (SERM's)		Tamoxifen, raloxifen, toremifen
	3. Other anti-estrogenic substances		Clomiphene, cyclofenil, fluestrant
	4. Agents modifying myostatin function		Myostatin inhibitors
	5. Metabolic modulators		Meldonium, insulin and insulin-mimetics, trimetazine
S.5 Diuretics and masking agents	All diuretics & masking agents	EXCEPT drosperinone, pamabrom, ophthalmic use of carbonic anhydrase inhibitors, local use of fenylpressin in dental anasesthesia	Probenicid, acetazolamide, bumetanide, furosemide, indapamide, thiazides, spironolactone

body in time for competition. Different substances have got different rates for elimination and this also varies from person to person.

- Substances which are prohibited in particular sports only (Table 4). This section includes alcohol, and beta blockers, which are prohibited in certain sports.
- Prohibited methods (Table 5). Examples of this category include blood transfusions, intravenous infusions and genetic manipulation.

The List provides a long list of examples of drugs in each category. However it needs to be emphasized that all drugs belonging to the particular categories are prohibited even if they are not mentioned in the List.

THERAPEUTIC USE EXEMPTIONS (TUE'S)

When an athlete has a health condition, which demands treatment or medication, it is extremely important for the athlete and/or the doctor to check the status of the substance or method to be used with the Prohibited

List. If the substance or treatment method is prohibited, the athlete must apply for and obtain a Therapeutic use Exemption (TUE) from the NADO (available from <http://nadomalta.org/tue-form>), and treatment must not start until this confirmation is received. Only in acute medical emergencies is an athlete allowed to start treatment before the TUE is approved. There is no guarantee that, in every case, an approval will be granted retrospectively. Although the doctor completes much of the TUE application form for the athlete, it remains the athlete's responsibility to ensure that they have a valid TUE when they are taking, or have taken, a prohibited substance, or used a prohibited method.

The evaluation of TUEs by the NADO is governed by a mandatory International Standard for Therapeutic Use Exemptions (ISTUE). This standard first came into effect in January 2005 with several revisions since then, the latest one came into effect on 1 January 2016.

According to the ISTUE, an athlete may be granted a TUE if, (and only if), he/she can show, by a balance of probability, that each of the following conditions is met:

1. The prohibited substance or prohibited method in question is needed to treat an acute or chronic medical condition, such that the athlete would experience a *significant* impairment to health if the prohibited substance or prohibited method were to be withheld.
2. The therapeutic use of the prohibited substance or prohibited method is highly unlikely to produce any additional enhancement of performance beyond what might be anticipated by a return to the athlete's normal state of health following the treatment of the acute or chronic medical condition.
3. There is no reasonable therapeutic alternative to the use of the prohibited substance or prohibited method.
4. The necessity for the use of the prohibited substance or prohibited method is not a consequence, wholly or in part, of the prior use (without a TUE) of a substance or method which was prohibited at the time of such use.

Table 3: Substances prohibited in competition: all substances prohibited out of competition and the following

Class			Examples of substances
S.6 Stimulants	a. Non-specified		Amphetamine, bromantan, cocaine, fenfluramine, mesocarb
	b. Specified	Note: cathine, ephedrine, pseudoephedrine subject to urinary levels.	Cathine, ephedrine, adrenalin, seleginine, pseudoephedrine, methylhexanamine, dimethylbutylamine
S.7 Narcotics			Morphine, pethidine, fentanyl, mathadone
S.8 Cannabinoids	a. Natural		Marijuana, hashish, cannabis, THC
	b. Cannabimimetics		"Spice", JWH-018, JWH-073, HU-210
S.8 Glucocorticoids	All prohibited when administered by oral, intra-muscular, intra-venous, rectal route	Allowed when administered by inhalation, nasal, dermal, ophthalmological applications	

Table 4: Substances prohibited in particular sports

Class	Comments	Sports	Examples of substances
P.1 Alcohol (ethanol)	Blood concentration threshold of 0.10 g/L	Air sports, archery, automobile, powerboating	
P.2 Beta-blockers	Prohibited in competition	Archery, automobile, billiards, darts, golf, shooting, skiing, snowboarding, ski jumping, underwater sports	Atenolol, carvedilol, labetalol, propranolol, sotalol, timolol etc.
	Prohibited in-competition and out-of-competition	Archery, shooting	

Table 5: Prohibited methods

Class	Comments
M1. Manipulation of blood and blood components	<ol style="list-style-type: none"> 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. Artificially enhancing the uptake, transport or delivery of oxygen. Including, but not limited to: perfluorochemicals, efaproxiral (RSR13) and modified haemoglobin products e.g. haemoglobin-based blood substitutes and microencapsulated haemoglobin products, excluding supplemental oxygen. Any form of intravascular manipulation of the blood or blood components by physical or chemical means.
M2. Chemical and physical manipulations	<ol style="list-style-type: none"> 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, e.g. proteases. 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	<ol style="list-style-type: none"> The transfer of polymers of nucleic acids or nucleic acids analogies. The use of normal or genetically modified cells.

One of the basic principles for treating athletes is to prescribe medication or treatments that are not prohibited. For example a hypertensive athlete who needs treatment can be prescribed several classes of allowed drugs, but not diuretics and beta-blockers (the latter in certain sports only, Table 4). The only situation where these drugs may be considered for a TUE is when

the athlete can provide sound medical evidence that all allowed drugs were not effective in controlling his blood pressure and he responds only to the prohibited ones. The TUE application needs to be accompanied by medical evidence to prove this.

There is a belief among the local sports community that as long as a TUE application form is filled in and

submitted, it will be accepted automatically and TUE granted. This is not the case. The TUE Committee needs to be convinced that the condition that requires the prohibited drug exists and there is no other alternative treatment. Comprehensive medical evidence needs to accompany the application. This includes a detailed medical report, any laboratory and test results and imaging studies. The TUE panel takes all the evidence into consideration and reaches a decision whether to grant or refuse the TUE. This decision has to be in line with ISTUE standards. There have been instances where doctors have insisted on their right to decide how and when to treat patients. This can be understandable for the non-athletic population. However, with regards to athletes that have to abide by the WADA code, prescription must be guided by the relevant anti-doping regulations.

RETROACTIVE TUE's

There are infrequent situations for which TUE's may be granted retroactively. These cases are evaluated in the same way as standard TUE applications i.e. the TUE Committee evaluates the application and issues its decision. The ISTUE stipulates which situations may result in the granting of a retroactive TUE, as follows:

1. Emergency treatment or treatment of an acute medical condition was necessary (a medical emergency or acute medical situation is one which justifies immediate administration of a prohibited substance or method and failure to treat immediately could significantly put the athlete's health at risk). It is always preferable to address a TUE application prospectively rather than retrospectively; or
2. Due to other exceptional circumstances, there was insufficient time or opportunity for the athlete to submit, or the TUEC to consider, an application for the TUE prior to sample collection; or
3. Applicable rules for the particular sport required the athlete or permitted the athlete to apply for a retroactive TUE.
4. It is agreed, by WADA and by the NADO to whom the application for a retroactive TUE is or would be made, that fairness requires the grant of a retroactive TUE.

Once a TUE is granted, this would be for a specific method or substance, with a defined dosage and route of administration. It would also be for a specific period

of time and would, therefore, have an expiry date. The TUE approval certificate should, ideally, be presented to doping control officials at the time of any eventual doping controls. When the doping control authority receives a report of an adverse analytical finding from the laboratory, an initial evaluation will take place to verify that the TUE is still in effect and that the results of the analysis are consistent with the TUE granted (nature of substance, route of administration, dose, time frame of administration, etc.). If the review is satisfactory, the result of the test will be recorded as negative. It is important to note that rejected TUE's can be appealed to WADA under the rules of International Federations and NADOs. However, one may always reapply to the NADO to have a new TUE application considered, especially if new compelling medical information is presented.

PITFALLS FOR THE ATHLETE AND THE GP

As explained above, the athlete is always responsible for what goes into his body. Therefore he needs to discuss both the need and the choice of medication with the doctor, pointing out that he may be subject to doping control. There are online applications that may be accessed to check whether medications are prohibited or not. A useful one is a website maintained by the United Kingdom, Canadian, Japanese, Swiss, Australian and United States authorities called Global DRO which can be accessed at <http://www.globaldro.com/UK/search>.

The commonest situations where accidental doping may occur are when using:

1. 'Cold & flu' and cough preparations. Many times these contain drugs from the stimulant class, which would help to relieve the nasal congestion e.g. ephedrine, pseudo-ephedrine. Both these drugs are prohibited in-competition up to a certain urine concentration. The athlete and doctor must make sure that they are not consumed within a week of competition to allow time for the drug and its metabolites to be cleared from the body. A better solution would be to avoid these preparations altogether and use alternative medications like intranasal decongestants, e.g. xylometazoline, which are allowed.
2. Supplements. The majority of athletes make use of different kinds of dietary supplements to enhance their nutrition and optimise performance. The most widely used are protein, creatine, amino acids and various combinations of vitamins. Several studies have reported that prohibited substances

were found in a number of supplements on the market varying from 3-19% of the total number of supplements tested (Geyer et al., 2014; Judkins, Hall and Hoffman, 2007; Judkins, 2008; Kamber et al., 2001). These drugs would not be declared on the list of ingredients and athletes would think that the supplements are safe to consume. Classes of drugs most commonly found in these studies were anabolic steroids and stimulants. Contamination of these supplements may occur either as a deliberate, undeclared inclusion by the manufacturer to increase the effect of the supplement, or cross contamination during manufacture from poorly maintained machinery. In 2013, Jamaican athletes Asafa Powell and Sharon Simpson tested positive after making use of a supplement called Epiphany D3 which was spiked with an undeclared stimulant oxilofrine. (Drayton, 2014), and were eventually sanctioned.

- Herbal medication or supplements. Such products are usually labeled as “natural”, and athletes mistakenly believe that they are safe. Plants may contain metabolically active substances which are prohibited. For example, the Chinese herb ma huang is the equivalent of ephedra and contains ephedrine. ‘Geranium oil’ product labeling is often associated with the banned stimulant methylhexaneamine (DMAA). In actual fact geranium oils do not contain methylhexaneamine but these herbal supplements are spiked with the synthetic drug. (Lisi et al, 2011).

WADA and the International Olympic Committee advise athletes not to make use of dietary supplements as that is the only way to make sure that no prohibited substances are consumed inadvertently. Otherwise athletes need to scrutinize in detail the contents of supplements and only consume those which have been batch tested by the manufacturer. There are several websites which list supplements that are batch tested, and therefore safer for consumption by athletes than those which are not. The following are the most useful lists:

- <http://www.informed-sport.com/certified-product-brands>
- <http://www.koelnerliste.com/en/product-database.html>
- <http://www.nsf.org>
- <http://info.nsf.org/Certified/Dietary/>

CONCLUSION

Athletes need to be vigilant about what they are consuming. Their health care providers must be aware that certain drugs may not be used by athletes as they may result in serious consequences for the athletes and their sporting careers. TUE requests must be filled in correctly and comprehensively and always backed by sound medical evidence. There are several online tools to help both athlete and doctor to arrive at an informed decision. It is also important to keep in mind that the Prohibited List is subject to change every year from the 1st of January.

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