# Drug Abuse, Doping, and Extreme Sports

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## 9.1 Definition

Doping in sport is defined as voluntary or involuntary use of prohibited substances or methods. The World Anti-Doping Code is a set of rules that was created to harmonize anti-doping efforts. The Code has been accepted by all international Olympic sport federations, Olympic and paralympic committees, and many other sport organizations. It was implemented from 1 January 2004 (revised 1 January 2009). Among signatories are federations such as the World Triathlon Corporation, Confédération mondiale des activités subaquatiques, or International Mountaineering and Climbing Federation [1].

The Code is closely related to five international standards which set up rules in testing, laboratories, Therapeutic Use Exemptions, the List of Prohibited Substances and Methods, and privacy protection.

A substance/method is placed on the list when it has the potential to enhance or enhances sport performance, it poses a health risk for the athlete, or it is contrary to the spirit of the sport.

An updated List of Prohibited Substances and Methods is announced every year on the website of the World Anti-Doping Agency. It comprises substances prohibited at all times (in and out of competition): S0, non-approved substances; S1, anabolic agents; S2, peptide hormones, growth factors, and related substances; S3, beta-2 agonists; S4, hormone and metabolic modulators; and S5, diuretics and other masking agents.

Among methods forbidden at all times are M1, manipulation of blood and blood components; M2, chemical and physical manipulation; and M3, gene doping. To substances and methods prohibited in competition belong S6, stimulants; S7, narcotics; S8, cannabinoids; and S9, glucocorticosteroids. Alcohol (P.1) and beta-blockers (P.2) are banned in particular sports.

In the list of adverse analytical findings and atypical findings reported by WADA-accredited laboratories in 2012, the most frequent ones were as reported in Table 9.1 [2].

## 9.2 Substances Prohibited at All Times

### 9.2.1 Non-approved Substances

Athletes are warned against the use of any substances that are not registered (or with expired/lost registration) for human therapeutic use. This includes also agents under evaluation in clinical trials.

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**Table 9.1** List of adverse analytical findings and atypical findings reported by WADA accredited laboratories in 2012

| | | |
|---|---|---|
| AAS | 2279 | 50.6 % |
| Stimulants | 697 | 15.5 % |
| Cannabinoids | 406 | 9.0 % |
| Glucocorticosteroids | 365 | 8.1 % |
| Diuretics and other masking agents | 322 | 7.2 % |
| Peptide hormones, growth factors, and related substances | 181 | 4.0 % |
| Beta-2 agonists | 131 | 2.9 % |
| Hormone and metabolic modulators | 74 | 1.6 % |
| Narcotics | 26 | 0.6 % |
| Beta-blockers | 13 | 0.3 % |
| Alcohol | 5 | 0.1 % |
| Enhancement of oxygen transfer | 0 | 0.0 % |
| Chemical and physical manipulation | 1 | 0.02 % |
| Total | 4500 | |

## 9.2.2 Anabolic Agents

### 9.2.2.1 Anabolic-Androgenic Steroids (AAS)

AAS are probably the most common performance enhancers easily available all over the world. They are used by both elite and recreational athletes. There is no doubt that individuals keen on extreme disciplines may misuse AAS as well.

It is estimated that 2.4 % of Australian students report lifetime AAS use [3], while in Sweden between 10,000 and 100,000 subjects may be exposed to AAS every year [4]. Data from other countries and continents suggest that AAS users can be counted in millions [5–7]. The situation is emerging as a public health concern [8].

The most coveted by athletes effect of AAS is muscle hypertrophy. However, one cannot forget about side effects of these compounds. They are common and involve diverse body organs and systems [9–11]. One of the most prominent AAS effects in men is suppression of the hypothalamo-pituitary-gonadal (HPG) axis leading to decreased production of testosterone and spermatozoa. AAS abusers are at risk of acne, baldness, gynecomastia, cardiovascular diseases, lipid profile changes, liver tumors, and peliosis hepatis. Women may suffer from masculinization: decrease of the breasts size, changes in fat distribution and skin structure, hirsutism, losing scalp hair, deepening of the voice, and enlargement of the clitoris. Adolescents using ASS do not achieve the expected height due to premature epiphyseal closure.

AAS effects are not limited to the anabolic ones, but they exert also direct psychoactive actions. There is evidence that prone individuals may develop psychiatric dysfunction while using steroids. A number of studies link AAS abuse with increased risk of mania, anxiety, aggression, violence, or paranoia [12, 13].

Clinicians often observe AAS dependence in recreational or elite athletes. The long-term use of steroids, their higher doses, and greater dissatisfaction with body image are factors that increase such a risk. There are attempts to explain it by "myoactive" and psychoactive effects of steroid compounds [14]. Another important issue is depression or suicidal attempts following the withdrawal of AAS [15].

AAS may modulate neurotransmission in concert with other drugs of abuse. AAS are, e.g., used concomitantly with opioids. It is interesting that animal models show that AAS overdose induces changes similar to those observed after opioids [12]. Testosterone acts as a partial opioid agonist. AAS increase beta-endorphin levels in the ventral tegmental area and the thalamus. Nandrolone use is associated with decreased levels of kappa receptors in the nucleus accumbens and increased mu, delta, and kappa receptor binding in the hypothalamus, striatum, and midbrain periaqueductal gray [16, 17].

The classical pathways of AAS effects in the brain comprise androgen and estrogen receptors (alpha and beta) which are present in highest concentrations in basal telencephalon and diencephalon. The enzymes that play an important role here are 5α-reductase, aromatase, 3α-HSD, 3β-HSD, and 17β-HSD. AAS are thought to induce transcription and synthesis of new proteins [12].

Apart from genomic effects, AAS modulate kinase activity, ion channels, and G-protein

second messenger systems. Some of these actions are much quicker than those induced through transcription factors [12].

Aggression is indicated as one of the most prominent behavioral traits in AAS abusers. It is observed even after discontinuation of AAS use. Animal studies prove that it can be attenuated by application of, e.g., selective serotonin reuptake inhibitors [18]. AAS reduce the expression of serotonin receptors in the anterior hypothalamus (1A), globus pallidus (1B), or hippocampus [19, 20]. Anabolic-androgenic steroids decrease serotonin concentration in basal forebrain and dorsal striatum [21] but increase in the cerebral cortex [22]. For example, methyltestosterone injections associate with rise in energy, sexual arousal, and shorter sleep. It is probably caused by elevation of serotonin within the cerebral cortex what was monitored by an increase of 5-hydroxyindoleacetic acid in the cerebrospinal fluid [23].

AAS are also likely to modify the mesolimbic dopamine system by stimulation of dopamine release and synthesis [22]. It has been shown in human volunteers that nandrolone injections increase the serum levels of dopamine metabolite – homovanilic acid [24].

Another central neurotransmission system that is involved in AAS actions is GABA system. Androgen derivatives diminish concentration of GABA receptors and thus reduce fear in animals [25]. It stands in line with observations of, e.g., male users of AAS.

#### 9.2.2.2 Other Anabolic Agents

Clenbuterol is a beta-2 agonist used as a bronchodilator in asthma. It seems that dopers combine testosterone with clenbuterol more often than with GH, levothyroxine, EPO, or insulin [26]. Animal studies showed that clenbuterol increases muscle mass and decreases fat deposits. Catabolism is reduced up to 18 % what leads to a raise of the total protein content by 6 %.

Due to the use of clenbuterol in fattened animals (the procedure forbidden in EU and the USA), there is a risk of positive anti-doping testing after consumption of contaminated meat.

### 9.2.3 Peptide Hormones, Growth Factors, and Related Substances

#### 9.2.3.1 EPO

Erythropoietin (EPO) is responsible for the oxygen-carrying capacity of the blood. When it is used in therapeutic doses, it may increase red blood cells and hemoglobin by 6–11 % and lead to raises in $VO_{2max}$. Sportsmen use EPO to increase aerobic power and endurance. The substance is applied as subcutaneous, intravenous, or intraperitoneal injections.

Compared with the first-generation recombinant human EPO, the second-generation products (e.g., darbepoetin) have extended half-life. Continuous erythropoiesis receptor activators (CERAs) are called the third-generation agents. The second- and third-generation EPO can be applied less frequently as their half-life reaches 140 h. A disadvantage of the newer forms of EPO – from the point of view of a doper – is longer period in which they can be detected. Cheating athletes may undertake training at higher altitudes or use altitude tents to mask EPO doping. The latter forms of performance enhancement are not forbidden. Thus increases of hematocrit could be attributed to the latter "procedures" rather than to doping with EPO.

Another problem of the recent years is availability of products biosimilar to EPO. Their structures and properties are different to the medically approved form, and they might not be detected by standard anti-doping tests [27].

Side effects of EPO comprise arterial hypertension, increased risk of arterial thrombosis, and venous thromboembolism but also flu-like symptoms (fever, arthralgias, muscle pains, conjunctivitis), skin allergic reactions, seizures, changes of serum potassium, urea, and phosphorus concentrations. EPO doping poses a special risk for dehydrated athletes, e.g., triathlonist or ultramarathon runners (a rise in the hematocrit can be augmented and reach even 80 %). One cannot exclude mitogenic effects of EPO when used in supraphysiological doses.

The first suspected cases of EPO doping were several cyclists who died suddenly in the late

1980s. The first documented darbapoietin dopers were four medalists of Salt Lake City 2002 Winter Olympics. The winner of the 2004 Hawaii Ironman Triathlon (Triathlon World Championship) Nina Kraft was stripped of the title by World Triathlon Corporation being found positive for EPO.

#### 9.2.3.2 Gonadotropins

hCG stimulates synthesis of testosterone in the testes. It is not very popular, and it is used by male athletes only. The side effects are similar to those of AAS [28]. There is no scientific rationale for the use of gonadotrophins as "protection" for gonads during AAS doping.

#### 9.2.3.3 GH/IGF-1

Growth hormone (GH), GH secretagogues, IGF-I, and its analogues began to gain their reputation in the sport world from the Los Angeles 1984 Summer Olympic Games. GH is desired for its anabolic and lipolytic properties. It is often applied together with AAS. In an anonymous American survey, 25 % of AAS buyers reported concomitant use of GH [29].

Our knowledge on GH effects is based mainly on studies in subjects with GH deficiency. In such cases, positive effects of GH administration on body composition and performance are well documented. GH is to increase $VO_{2max}$ and exercise time. What stands in contrast – in patients with acromegaly (a model of GH excess) – one finds reduced aerobic fitness and reduced left ventricle ejection fraction.

GH decreases body fat, increases cardiac output, and enhances wound healing. Observed effects of GH in muscles comprise:

- ↑ diameter of muscle fibers
- ↑ muscle protein content
- ↑ number of muscle cell nuclei
- ↑ glucose uptake
- ↑ protein synthesis
- ↓ muscle protein degradation
- ↑ myoblast proliferation
- ↓ myoblast apoptosis

The scientifical evidence for effectiveness of GH as a performance-enhancing agent in healthy individuals is poor. Athletes administer 3–8 mg of GH/24 h on 3–4 days of every week (mean daily dose of GH is 1–2 mg). It is 2–3×higher than physiological pituitary secretion of GH [30]. In one double-blind, placebo-controlled study in the elderly testosterone combined with GH in a higher dose was less effective in changing muscle strength than testosterone with a lower dose of GH.

One must keep in mind that prolonged use of GH/IGF-1 in high doses is associated with a range of serious side effects. Among the most typical ones are edema, muscle and joint pain, arterial hypertension, headache, vertigo, tinnitus, nausea, vomitus, gynecomastia, insulin resistance, goiter, and mitogenesis (colon cancer).

Anti-doping laboratories developed techniques to detect GH/IGF-1 abuse; however, it still poses a challenge [31].

### 9.2.4 Beta-2 Agonists

Beta-2 agonists are the first-line therapeutics in bronchial asthma. The evidence seems to exclude their ergogenic effects (if inhaled). For example, there was no improvement in 5 km time-trial performance following the inhalation of up to 1600 μg of salbutamol in non-asthmatic athletes [32]. Nevertheless, it is intriguing that prevalence of asthma is several times higher in elite athletes (Olympic medalists) than in general population.

Dopers are supposed to use beta-2 agonists in doses exceeding recommended levels by several times. Agents such as salbutamol, salmeterol, and fenoterol applied in high doses increase glycogenolysis, lipolysis, and muscle contractility. They stimulate insulin and growth hormone secretion. Animal studies show that beta-2 agonists decrease degradation of proteins and stimulate muscle mass gain. Such effects have been not unequivocally confirmed in humans; however, it is suspected that beta-2 agonists may enhance muscle strength and endurance in mechanisms not elucidated yet. Typical signs of intoxication are headaches, vertigo, chest pain, dyspnoe, tremor, sweating, tachycardia, hypotonia, hyperglycemia, hypokalemia, and myocardial damage (leading to heart infarcts).

### 9.2.5 Hormone and Metabolic Modulators

The list includes aromatase inhibitors (e.g., anastrozole), selective estrogen receptor modulators (e.g., raloxifene), other anti-estrogenic substances (e.g., clomiphene), agents modifying myostatin function (e.g., myostatin inhibitors), and metabolic modulators (e.g., insulin).

Aromatase inhibitors (aminoglutethimide, anastrozole, letrozole, testolactone) inhibit the synthesis of estrogens from AAS or testosterone. They are registered for the treatment of breast cancer. They may stimulate LH secretion and further increase production of testosterone. Similar effects are observed during the application of clomiphene, which is used in ovulatory dysfunction in infertile women. Selective estrogen receptor modulators (SERMs) may behave as agonists or antagonists of the estrogen receptor (depending on the tissue). They oppose bone loss, and they are used to prevent osteoporosis in postmenopausal women.

Myostatin is a negative regulator of skeletal muscle mass. It is a member of transforming growth factor family. Animal and human observations indicate that mutations of the myostatin gene result in muscle hypertrophy. In the absence of myostatin, muscle fibers show hypertrophy, hyperplasia, changes of glucose, and fat metabolism. Myostatin inhibitors have a potential to be used by athletes to increase their muscle mass. Among such inhibitors one can find antibodies or proteins directed against myostatin. So far neither of these substances has been approved for the treatment of humans.

Insulin has potent anabolic properties. It acts synergistically with growth hormone and androgens. Insulin increases the uptake of glucose into adipose/muscle tissues and stimulates glycogenesis what improves postexercise recovery. Apart from the impact on glucose metabolism, insulin inhibits proteolysis and thus enables muscle mass gain. During the application of insulin, there are observed improvements of endurance. Tissue repair processes are facilitated as well. A dangerous side effect of insulin use is the risk of hypoglycemia. Athletes using insulin may experience hypoglycemia even long hours after its application. As a growing number of sportspersons use AAS, glucocorticosteroids, or GH, they may develop insulin resistance what in turn may require insulin therapy. There are some unanswered questions in regard to diagnosing and treating of diabetes in athletes (potential doping properties).

### 9.2.6 Diuretics and Other Masking Agents

Diuretics modify the body fluid balance through enhanced renal excretion of salt and water. Athletes use diuretics mainly to achieve rapid weight loss. It may be required for, e.g., meeting a weight category before competition. Diuretics are also applied to mask the presence of other illegal doping agents. They increase urine flow and thus decrease concentration of a specific substance in urine (dilution). They may also change urine acidity [33].

Recent WADA reports indicate that diuretics are present in more than 7 % of cases positive for doping.

## 9.3 Methods

### 9.3.1 Chemical and Physical Manipulation

Any attempts to change the status of samples taken during doping control are prohibited. There is also a warning against intravenous infusions and injections apart from these administered during legal, necessary medical procedures.

### 9.3.2 Manipulation of Blood and Blood Components

The administration of blood (autologous or heterologous) or red blood products and use of techniques to optimize oxygen delivery are prohibited. Blood manipulations increase the risk of life-threatening events such as cerebral and pulmonary embolism and stroke.

One of the first athletes who was known to use blood doping was Lasse Viren – 5000 and 10,000 m steeplechase gold medalist at the Munich Olympic Games in 1972. Nowadays the main procedure used by cheaters is autologous blood transfusion, as heterologous one is easy to detect and very risky.

"Operacion Puerto" led by Spanish authorities revealed systemic use of autologous blood transfusion by many athletes. Blood was withdrawn and stored refrigerated for several weeks before major competitions and then it was reinfused a few days before the event. Top sportsmen might use cryopreservation of blood which is a more expensive alternative of blood storage.

Another important problem is substances that modify expression of EPO or other genes. Some of them are comfortable to use (e.g., cobalt salt tablets that can be taken orally); however, this may be associated with serious health-hazards (cardiac and thyroid disturbances). There is, e.g., a potential to modify the expression of hypoxia-inducible genes by inhibiting hypoxia-inducible factor (HIF). One of the possible ways to achieve this goal is to inhibit HIF prolyl hydroxylase (enzyme that regulates HIF). It could lead to increased production of EPO [27].

Artificial ways of blood enhancement (e.g., hemoglobin-based blood substitutes or perfluorochemicals) are forbidden as well.

### 9.3.3 Gene Doping

Gene doping means the enhancement of performance by transfer or manipulation of genetic material. Genes may be derived from cells acquired from the organisms, which are modified out of the body and then transferred back into the organism, or the procedures that involve actions in vivo only (straight gene/nucleic acid transfer).

So far, the attempts to use gene therapy in treating specific diseases have not brought spectacular results. The greatest obstacle is unpredictable side effects of such manipulations which include fatal outcomes.

Genes that attract greatest attention in regard to sport performance are genes that encode erythropoietin (EPO), vascular endothelial growth factor (VEGF), peroxisome proliferator-activated receptors and co-activators, insulin-like growth factor 1(IGF-1), myostatin (MSTN), follistatin (FST), growth-hormone (GH), or GH-releasing hormone (GH-RH).

Genetic modifications are not easily detectable by anti-doping procedures, though there is a constant progress in this field. Researchers work on direct methods or combinations of indirect techniques to detect such an abuse in athletes [34]. Up till now no cases of gene doping in sports have been revealed.

## 9.4 Substances and Methods Prohibited In Competition

### 9.4.1 Stimulants

Drinking coffee and smoking cigarettes are cultivated in many parts of the world. They belong to the most common human addictions. There is evidence showing that caffeine and nicotine improve concentration, but effects can be expected also in other areas desired by extreme sport participants.

Caffeine ingestion may have positive influence on performance in both aerobic and anaerobic activities. There are observed increases of endurance and maximal cycling power. Caffeine positively impacts cognitive functions, motor skills, and the postexercise recovery time. Some role is attributed to mild analgesic properties of the substance.

Nicotine activates the sympathetic nervous system. It stimulates secretion of catecholamines and increases muscle blood flow and lipolysis. Athletes using nicotine revealed enhancements in learning, memory, attention, reaction time, and motor abilities. The time to exertion is lengthened, and similarly to caffeine sensibility to pain is reduced [35].

Caffeine was banned by WADA until 2003. Caffeine and nicotine are not included in the List of Prohibited Substances and Methods. Bupropion, phenylephrine, phenylpropanolamine, pipradol, and synephrine are not considered as banned substances either.

### 9.4.2 Narcotics

This group of psychoactive agents comprises diverse compounds. Among a broad range of actions, they may induce desirable analgesia. On the other hand, the use of, e.g., derivatives of morphine leads to frequent side effects: low blood pressure, dizziness, drowsiness, and constipation. Less frequently are noted: bradycardia, bronchospasm, rash, or blurred vision.

Authors of an anonymous survey of British recreational divers reported that 22 % of the respondents used illicit substances such as benzodiazepines, amphetamine, cocaine, ecstasy, LSD, heroin, or "magic mushrooms" [36].

The following are prohibited: buprenorphine, dextromoramide, diamorphine (heroin), fentanyl and its derivatives, hydromorphone, methadone, morphine, oxycodone, oxymorphone, pentazocine, and pethidine.

### 9.4.3 Cannabinoids

At present cannabis is an illegal substance in majority of the countries. Its use by athletes is forbidden in competition only. Cannabinoids are among the most common substances detected during anti-doping testing (after AAS).

Cannabis contains a range of chemical compounds including over 60 cannabinoids. Smoking of cannabis results in the formation of more than 2000 chemical agents. The psychoactive actions of the plant are attributed to tetrahydrocannabinol (THC) and to a much smaller extent – cannabinol. Other cannabinoids exert anxiolytic, antipsychotic, and alerting effects (e.g., cannabidiol).

Cannabis changes cognitive and behavioral functions. It affects perception and time reception, induces euphoria and relaxation, and enhances sensory experiences. Upon cannabis use, short-time memory, reaction time, and motor skills are impaired. Among the physiological effects are increased heart rate, alterations of blood pressure, bronchodilation, increased appetite, dry mouth/throat, analgesia, and sedation.

Athletes explain that cannabis eases stress and anxiety. It is to improve concentration and enhance creativity. It may reduce muscle tension and provide better sleep.

The side effects of cannabis comprise anxiety and panic reactions. Long-term users may develop chronic bronchitis, reproductive disturbances, impairments of attention/memory, and a dependence syndrome [37].

Cannabis is the most common drug, next to alcohol, in drivers involved in fatal accidents or stopped for impaired driving. It impairs piloting as well [38, 39].

The use of cannabis by athletes may influence technical skills and decision-making. It increases the risk of incidents and injuries.

### 9.4.4 Glucocorticosteroids

Glucocorticosteroids (GCSs) are used to treat various diseases of the skin, respiratory, alimentary, endocrine, and musculoskeletal systems. Athletes get familiar with this class of medications while suffering from musculotendinous inflammatory processes. Another common use is in the therapy of allergic rhinitis and bronchial asthma.

Anti-inflammatory properties of GCS can shorten the recovery period after contusions. It may be attractive in a whole range of sports.

On the other hand, the application of GCS is associated with the risk of serious side effects. Among the most characteristic are increased risk of infections (fungal ones if inhaled), acne, thin skin, bruising, delayed wound healing, gastritis, weight gain, myopathy, heart rate disturbances, increased blood pressure, diabetes mellitus, osteoporosis, glaucoma and cataracts, mood changes, aggression, and depression.

## 9.5 Substances Banned in Particular Sports

### 9.5.1 Alcohol

In many cultures, alcohol is an ingredient of everyday diet. Moderate alcohol consumption favorably influences the risk of cardiovascular disease. On

the other hand, alcohol abuse is linked to cardiomyopathy, arrhythmias, stroke, arterial hypertension, liver disease (steatosis, hepatitis, cirrhosis), pancreatitis, cancer (mouth, esophagus, throat, larynx, liver, breast), and immune disturbances.

Alcohol has ergolytic effects and its chronic use induces myopathy. It decreases utilization of glucose and reduces skeletal muscle capillarity [35].

Alcohol impairs psychomotor performance and increases the risk of injury. It has detrimental effects on endurance, and it may negatively affect recovery period.

Alcohol is banned in competition in sports such as aeronautics, archery, automobile, karate, motorcycling, and power boating.

### 9.5.2 Beta-Blockers

Beta-blockers oppose actions of catecholamines exerted through beta-receptors. They decrease heart rate and lower blood pressure. Agents such as bisoprolol, metoprolol, atenolol, or propranolol are widely used in conditions such as cardiac arrhythmias, ischemic heart disease, heart failure, arterial hypertension, and hyperthyreosis.

In sports, beta-blockers are used for their anxiolytic effects. They can positively influence performance in activities in which the lack of hand tremor and steadiness are required (sport shooting, archery). Beta-blockers impair endurance. They decrease maximum exercise load, lipolysis, and muscle glycogenolysis [40].

**Conclusion**

It is a common knowledge that a significant percentage of physically active people use banned substances to enhance their performance. The temptation seems to be similar for individuals engaging in popular and extreme sports, professional and recreational athletes.

At the moment, there are reliable laboratory methods to detect doping with EPO, GH, homologous blood transfusion, AAS, stimulants, SARMs, and other substances. Nevertheless, in spite of a significant increase of the number of anti-doping tests (from 150,000 to 250,000 annually), the efforts of the anti-doping community do not bring the expected results. The ratio of positive cases remains low (less than 1 %) and nearly constant from 1985.

It is especially disappointing in the context of affairs such as BALCO's, Festina's, Floyd Landis's, or Lance Armstrong's (to count just a few). It is assumed that this situation is not caused by technical or scientific insufficiency but is due to human and organizational failure.

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