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Anabolic agents in elite sport: accent on side effects (review)

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Summary

Under current conditions with noticeably increased competition between the leading sports countries on the global stage, the greatest success is achieved, as a rule, by representatives of the country, in which the latest achievements of science and technology are best used. The level of modern sport development, those overloads that the athletes experience are so high that any attempts to stop using medicinal preparations reflect the views of not even yesterday, but the day before yesterday. Over the past 15–20 years, the volume and intensity of training and competitive loads have increased by 2–3 times, and representatives of many sports events have almost reached the limit of the human body physiological capacities. That having been said, the nutritional inadequacy of athletes' diets, the need for recovery and preventive measures, body adaptation to intensive physical and psychoemotional loads as well as frequent climate and time zone changes necessitate the usage of pharmacological preparations contributing to work capacity increase and accelerating the recovery processes after significant loads. Unfortunately, this has led to widespread usage of doping in general and anabolic steroids, in particular.

Anabolic means are the substances the action of which is aimed at intensification of anabolic (synthetic) processes in the body, i.e. substances accelerating formation and regeneration of structural parts of cells, tissues and muscular structures. Non-Olympic sports events representatives and the youth not engaged in professional sport tend to use steroid doping as well. The prevalence of usage of banned substances and methods remains high, reliable high-precision methods for the detection of many of them are absent, and athletes, not knowing the pitfalls of taking anabolic agents, continue to use them on a mass scale, which can cause both immediate and remote negative effects on health and quality of life. Therefore, every new attempt to explain potential health and life quality hazards is a step forward in the fight against doping.

This review presents modern classification of anabolic agents, headlines their action mechanism and details side effects of using representatives of all three groups of banned drugs including those recently synthesized. It is emphasized that the use of anabolics may not only lead to deprivation of medals won illegally, but cause immediate and delayed negative influences on the athlete's body further resulting in deterioration of social adaptation, loss of health and, possibly, life itself.

Keywords: *sport, doping, WADA Prohibited List, anabolic agents, androgenic anabolic steroids, athlete health.*

Problem statement

The level of modern sport development, those overloads that the athletes experience are so high that attempts to refuse to use allowed pharmacological ergogenic aids at all reflect the views of not even yesterday, but the day before yesterday. It is known that over the past 15–20 years, the volume and intensity of training and competitive loads have increased significantly, and representatives of many sports events have come close to the limit of the human body physiological capacities (Maravelias et al., 2005). According to Julian Savulescu, Professor of Oxford University (Great Britain), "... *humanity has exhausted nature inherent capacities of the*

body. After Ben Johnson only nine athletes managed to run 100 m faster than 9.8 seconds, and he set his record back in 1988. Only two of them are still doping unspotted." (Savulescu et al., 2013). The above necessitates application of allowed pharmacological preparations of ergogenic character, however, in many cases the process of elite athletes' preparation is not without the use of WADA banned anabolic means.

Anabolic means are the substances the action of which is focused on intensification of anabolic (synthetic) processes in the body, i.e. substances accelerating formation and regeneration of structural parts of cells, tissues and muscular structures (Frati

et al., 2015). The use of steroids or more precisely androgenic anabolic steroids (AAS) was widely spread among the Olympic athletes in 70–80s of the last century. In November 1990, all anabolic steroids were ranged to a class of controlled dangerous substances (CDS) by American legislation (Gosetti et al., 2013). As of today, the prevalence of usage of banned substances and methods remains high, reliable high-precision methods for the detection of many of them are absent, and athletes, not knowing the pitfalls of taking anabolic agents, continue to use them on a mass scale, which can cause both immediate and remote negative effects on health and quality of life (Geyer et al., 2014).

In view of the aforesaid, the **objective** of the given review of scientific and methodological literature was the formation of ideas about anabolics as a prohibited means, mechanism of their biological action and side effects that occur during their usage and produce negative impacts on the health of athletes.

Structure and mechanism of anabolic steroids action

Anabolics traditionally top the WADA list of prohibited substances. In WADA list 2015 it is Class S1. “Anabolic agents”, which includes three groups of prohibited substances: AAS proper, endogenous anabolic steroids when administered exogenously and “other anabolic agents”. Despite stringent prohibition by the International Olympic Committee, elite athletes in their zeal to gain victories quite frequently resort to anabolic steroids use during preparation, thus making a choice between health and the Olympic gold in favour of the latter.

All anabolic steroids (AS) are based on a tetracyclic hydrocarbon that has a radical methylation $-\text{CH}_3$ in position 13, sometimes in position 1, 7, 10; of crucial importance is the presence of different length radical in position 17 determining the duration of action of this or that anabolic steroid, to a great extent. Direct correlation between radical length and duration of action is explained by the fact that its elongation results in increased lipid solubility and intensity of depot formation in subcutaneous tissue. It is just availability of radical methylation $-\text{CH}_3$ in position 17 that confers hepatotoxic properties to anabolic steroids (Busardò et al., 2015).

AS usage is associated with drastic increase of body ability to absorb proteins – protein requirement

may increase more than threefold, up to 300 g per day. Accordingly, the proportion of fats and carbohydrates decreases leading to impairment of metabolic processes (Grandys et al., 2012). Increase of anabolic steroids dose above therapeutic one provides only slight enhancement of anabolic action along with sharp rise in side effects manifestation (Hajimoradi, Kazerani, 2013).

The influence of anabolic steroids on protein metabolism is related, above all, to the impact on cell genetic apparatus. Anabolic steroids penetrate directly into the cell nucleus through cell membranes and inhibit protein synthesis gene depressor. This leads to protein synthesis intensification in the cell: the synthesis of both matrix protein and RNA and DNA enhances (Marqueti et al., 2012; Pomara et al., 2015). Besides, permeability of cell membranes to amino acids, micronutrients and carbohydrates tends to increase along with elevation of glycogen synthesis rate. Use of AS intensifies the activity of pentose phosphate cycle where the parts of protein molecules are synthesized from carbohydrates. Anabolic steroids improve carbohydrate metabolism, increase insulin action as well as reduce blood sugar content. Besides, they may potentiate the action of endogenous somatotropin (growth hormone) that further enhances the anabolic effect.

All researchers note an increase of liver protein synthesis as a consequence of AS usage, however, in 5% of the followed up patients treated with these drugs, jaundice has developed as a result of cholestatic hepatitis, which disappeared after steroid hormones withdrawal. Practitioners note liver pains in almost 70% of cases of AS usage caused by biliary retention in bile ducts (Ross, 2014). While using prohibited anabolics the observed body mass gain occurs at the expense of not only muscular tissue but the increase of viscera mass – liver, heart, kidneys, etc. (Luciano et al., 2014; Maravelias et al., 2005) as well, which produces adverse effects on health, although being expressed to a lesser extent than the body mass increase.

Classification of anabolic androgenic steroids

Anabolic androgenic steroids (AAS) are subdivided into *endogenous*, i.e. inherent in the body, but administered exogenously, and *exogenous*, not inherent in it initially. This subdivision is pretty speculative as far as even Professor Charles Kochakian, a world renowned expert in this field

and the pioneer in the creation of synthetic steroids has never been able to clearly divide AAS into exogenous and endogenous during the period of 25 years (Kochakian, Yesalis, 2008), and here is why. The term “anabolic steroids” is commonly used to denote synthetic androgenic steroids, other than testosterone derivatives, however both names are used alternately. It is known that the main male sex hormone testosterone and its analogs possess anabolic activity. Anabolic activity of this or that preparation is determined in relation to anabolic activity of testosterone, which is taken as a unit. Androgenic activity is expressed in a similar way relative to androgen activity of testosterone, whereas the ratio of anabolic to androgenic activity is called the anabolic index (Gunina, 2015). Pronounced androgenic action of these compounds prevents their usage as health anabolic aids. In this respect, new steroid compounds close in structure to androgens but possessing a selective anabolic activity along with simultaneously less evident androgenic action were synthesized. These compounds were called anabolic steroids. A widely recognized review published under authorship of Dr. C. R. Braun of the Columbia Hospital of Ohio State University (USA) discusses numerous effects of the natural steroids – anabolic that are necessary for tissue construction and androgenic leading to masculinization (Braun, 2013), which corresponds to findings of other American scientists (Shahidi, 2001).

It should be noted that scientists have invested great efforts in order to obtain a purely anabolic preparation without side effect of androgens. The molecules of steroids were subjected to a wide variety of changes, which led to the creation of a number of new AAS. Substances were obtained with either increased or decreased androgenic and anabolic activity. Structural changes of some steroids resulted in even higher androgenicity and reduced anabolic activity (Robles-Diaz et al., 2015). Despite all efforts the scientists failed to create a “pure anabolic” with dissociated anabolic and androgenic features.

The main representative of AAS is a male sex hormone testosterone that has a direct influence on most tissues acting through specific androgen receptor. In muscle cells, it probably acts directly on androgen receptors, the density of which there is much lower as compared to other, more androgen sensitive tissues. Anabolic effect of most modern anabolic preparations significantly exceeds that of testosterone (Mhillaj et al., 2015). Consequently, all these preparations produce side effects peculiar for testosterone to a greater extent: retention of sodium, potassium, sulphates, phosphates and water, increased muscle growth in response to physical load, increased aggressiveness and libido, etc. (Isidori et al., 2005).

Synthetic derivatives of testosterone entering the body affect hypothalamus and hypophysis inhibiting hormone release and terminating testosterone production by testes, which influences seminal fluid production and thus, destroys the natural closed system of internal regulation. After cessation of synthetic steroid use, even in case of therapeutic usage, the body natural functions may not recover (Srinath, Dobs, 2014), especially when high doses of anabolic steroids were used as is the case with the athletes (Gunina, 2015).

Side effects of anabolic steroids

The mechanism of AS impact on the body is multifaceted, and the range of side effects during their long-term and even short-term usage is extremely wide (Table). For instance, it has been demonstrated that anabolic steroid use may contribute to disorders of thyroid gland function, activity of gastrointestinal tract up to the development of the hemorrhages (Vanberg, Atar, 2010). AS usage is associated with the decrease of sexual activity and progressive mental changes with unpredictable mood fluctuations, increased excitability, irritation, development of aggressive behaviour or depression (Ahrens et al., 2012).

Table

Mechanism of action, efficiency and side effects of anabolic steroids

Characteristics	Mechanism of action	Efficiency	Side effects
A group of different in structure and origin means able to enhance the processes of protein and other substances synthesis in the body. Anabolic steroids are synthetic derivatives of testosterone with reduced androgenic and preserved anabolic activity. In addition to anabolic steroids proper, this class includes "other anabolic agents" (zeranol, zilpaterol, clenbuterol), selective androgen receptor modulators (andarine and ostarine) that have been synthesized recently, and whose negative effects and long-term side effects have been insufficiently studied.	The most peculiar feature of anabolic steroids is their ability to enhance the synthesis of nucleic acids and protein, as well as structural elements of body cells; stimulation of amino acids absorption in the small intestine. Activate the production of insulin-like growth factor I and erythropoietin, as well as anabolic processes in the bone marrow (antianemic action). Increase appetite and weight gain. Positively affect nitrogen metabolism; inhibit the removal of potassium, sulfur and phosphorus required for protein synthesis; promote calcium fixation in the bones.	Activation of repair processes in bone and muscle tissue. Increase of strength indices, muscle volume, decrease of body fat content, breathing stimulation, increase of endurance and muscle capillarization. Work capacity increase, intensification of regenerative reactions and regeneration processes after traumas.	Synthetic derivatives of testosterone entering the body affect hypothalamus and hypophysis inhibiting hormone release and terminating testosterone production by testes. Lead to ligament damage (Achilles tendon rupture); tissue fluid retention, cardiovascular system dysfunction, mental disorders, liver damage, virilisation (in women), development of gynecomastia, decrease in testicle volume and quantity of sperm, infertility (in men), premature growth cessation in children and adolescents, manifested in cessation of epiphyseal plate growth in the bones; development of malignant tumours. After cessation of synthetic steroid preparation use the body natural functions may not recover.

Marked shifts in character and behavior often lead to serious consequences: break up with friends, family breakdown, appearance of prerequisites for making socially negative and even dangerous actions ("steroid rage"). According to some observations, complete discontinuation of AS is often accompanied by depression, which is considered as a manifestation of mental dependence on anabolics, similar to dependence on narcotic drugs (Mhillaj et al., 2015).

Anabolic steroids cause disorders of carbohydrate and fat metabolism, reducing resistance to glucose and increasing that to insulin, which is accompanied by drop in blood sugar, sometimes being of a critical nature. Usage of tableted forms of AS increases insulin secretion, which contributes to the onset of type II diabetes mellitus (Srinath, Dobs, 2014.). In addition, the development and/or rapid progression of atherosclerosis and other cardiovascular system diseases may occur (Thomas et al., 2012).

AS usage promotes intensive growth of muscle mass, which significantly exceeds the growth and development of respective tendons, ligaments and other connective tissues. This leads to ruptures of ligaments during heavy physical loads, the occurrence of inflammatory diseases and joint capsule, the development of tendon degeneration. Reduced viscosity of muscle tissue, due to water and sodium retention, causes a decrease of muscle elasticity (subjectively evaluated as "delayed onset muscle soreness" or "stiffness"), leads to inability

to develop full-fledged muscular efforts. All this causes a predisposition to injuries of the muscular system and ligamentous apparatus during training and competitions.

It is also known that the use of AAS can lead to neoplasm development in the athletes – liver cancer (hepatocellular carcinoma) and gynecomastia (Rahnema et al., 2014, Teng et al., 2015). Less important for the prognosis and quality of life are such negative effects of steroids as virilization (hirsutism in women), the appearance of acne, fluid retention in tissues (Hajimoradi, Kazerani, 2013). Women should also be mindful of the potential virilizing effects of AAS (coarsening of the voice, irregular periods, changes in skin structure, trichauxis and enlargement of the external genitalia). However, up to now, the side effects of all the numerous, known to date, AAS have not been fully studied.

Anabolic steroids in adolescents may induce irreversible changes: cessation of long bone growth (closure of growth zones), followed by the development of short stature, precocious sexual development, the phenomenon of virilization and gynecomastia (Hajimoradi, Kazerani, 2013), which indicates absolute inadmissibility of steroids usage by young athletes.

In addition to the AAS proper, "other anabolic agents" also belong to the class S1 of prohibited anabolic agents: zeranol, zilpaterol, clenbuterol, selective androgen receptor modulators; the latter include, in particular, andarine and ostarine,

recently synthesized and insufficiently studied in terms of their acute and remote negative effects on the body (Thevis et al., 2015), as well as tibolone. It is noteworthy that tibolone, which is mainly used for treatment of postmenopausal symptoms in women, can be successfully replaced with a nontoxic herbal preparation (based on the extract of *Actaeoracemosa*, the rattleweed, better known as *cimicifuga*), since the action of the active components of the latter has quite comparable direction and efficiency with chemical substance tibolone (Ross SM, 2014).

The most common representative of “other anabolic agents” group in sport is clenbuterol. This substance does not belong to the steroid hormones proper, but the mechanisms of its influence on the body are compared with those of steroids. First of all, clenbuterol has a powerful anti-catabolic effect, i.e. it reduces the percentage of protein degrading in muscle cells and promotes an increase in the number and volume of muscle cells. Clenbuterol has a number of side effects, ranging from the occurrence of tremor, sweating, insomnia, anxious feelings to the appearance of tachycardia and seizures, which substantiates its ban for unauthorized use in sport according to the criterion of “harm/benefit” (Thieme, Hemmersbach, 2010). As concerns andarine, first included in the Prohibited List in 2015, it is a preparation developed by “GTX.Inc” company for treatment of such diseases as muscle atrophy, osteoporosis and benign prostatic hypertrophy. Andarine prevents the occurrence of side effects of antiandrogen drugs and prevents the development of prostatic hyperplasia. This property of local blocking of dihydrotestosterone binding to the receptors deprives the andarine of such negative side effects as premature hair loss or prostate enlargement, which are so characteristic of other anabolic drugs of steroid nature. Ostarine is a new representative of this group of AAS class (Enobosarm, GTx-024, MK-2866). This active substance, now undergoing clinical trials, belongs to the class of selective androgen receptor modulators (Thevis et al., 2015). Ostarine was developed by “Merck & Company” and “GTX Inc.” pharmacological giants for treatment of muscular atrophy and osteoporosis. In the course of clinical trials it has been found that the level of testosterone in men not only fails to increase, but tends to decrease. Besides, a decrease in the level of high-density lipoproteins has been shown with an invariable level of low-density lipoproteins, which

is indicative of increased risk of cardiovascular pathology development. Increased level of liver marker enzymes has been also noted, which may indicate the impairment of liver function.

Conclusion

Therefore, numerous data of modern scientific literature demonstrate that despite an obvious increase of sports results as a consequence of anabolic agents usage, their acute and especially long-term negative effects on athlete body are extremely high. The widest range of side effects of these pharmacological substances does not stand up to analysis according to “harm/benefit” ratio as the most important criterion for their inclusion in the WADA Prohibited List. It is the side effects, which develop during the use of anabolic agents by both young and skilled athletes that should become the object of focused attention of coaches, sports physicians and officials as well as mass media for the purpose of maintaining athletes’ health, quality of life and the life itself. In this light, a number of new initiatives have been recently implemented to coordinate the anti-doping strategy in sport at the international level, including the development of new analytical methods for studying the steroid profile of athletes.

The widest range of anabolic steroids side effects according to “harm/ benefit” criterion fully justifies their inclusion in the WADA Prohibited List and requires close attention on the part of sports and medical community to prevent the use of steroids by athletes, and especially the young, due to the threat of quality life deterioration and the risk of fatal outcomes.

One should bear in mind that the correct way of life, the competent use of training and permitted extra-training ergogenic aids, balanced rational nutrition, adequate to load intensity, sports event specifics and the period of preparation application of recovery means will help athletes to succeed honestly without the use of anabolic steroids.

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ANABOLINĖS MEDŽIAGOS ELITINIAME SPORTE: ŠALUTINIO POVEIKIO EFEKTAS (APŽVALGA)

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SANTRAUKA

Tarptautinėje sporto arenoje, nuolat didėjant konkurencijai tarp didžiųjų valstybių, dažniausiai sėkmingai pasirodo tų šalių sportininkai, kuriuose daugiau taikomi naujausi mokslo ir technologijų laimėjimai. Šiuolaikinio sporto išvystymo lygis, dideli krūviai, kuriuos patiria sportininkai, neįmanomi be farmakologijos preparatų, medicininio aprūpinimo. Per pastaruosius 15–20 metų treniruočių ir varžybų krūvių apimtis ir intensyvumas padidėjo 2–3 kartus ir daugumos sporto šakų atstovų jis pasiekė kritinę žmogaus organizmo fiziologinių galimybių ribą. Be to, esant neracionaliai mitybai, nepakankamam atsigavimo ir reabilitacijos procedūrų kiekiui, dideliems psichoemociniams krūviams, dažnai klimatinių ir laiko juostų kaitai kelionės metu vis labiau didėja farmakologinių preparatų, didinančių darbingumą ir skatinančių atsigavimo procesus po krūvių, poveikis. Todėl šiuo aspektu dopingas ir anaboliniai steroidai, deja, labai paplito.

Anaboliniai preparatai – tai medžiagos, kurių veikla nukreipta į anabolinių (sintetinių) procesų stiprinimą organizme. Šios medžiagos skatina ląstelių, audinių, raumenų struktūros susidarymą ir atsinaujinimą. Neolimpinių jėgos sporto šakų sportininkai ir jaunimas, lankantis treniruočių sales, taip pat vartoja steroidinį dopingą. Draudžiamų preparatų vartojimas ir metodų taikymas pakankamai paplitęs, o sportininkai, nežinantys anabolinių medžiagų vartojimo pavojaus, masiškai juos vartoja ir tai gali turėti neigiamų pasekmių sveikatai ir gyvenimo kokybei tiek artimiausiu metu, tiek ir tolesnėje ateityje. Todėl kiekvienas bandymas išsiaiškinti galimą žalą sportininko sveikatai ir jo gyvenimui yra žingsnis pirmyn kovojant su dopingo vartojimu.

Apžvalginiame straipsnyje pateikta naujausia anabolinių preparatų klasifikacija, nušviestas jų veikimo šalutinis efektas.

Darbe akcentuojama, kad anabolinių preparatų vartojimas gali nutraukti sportininko karjerą, taip pat gali tapti negatyvios įtakos organizmui priežastimi tiek tuo metu, tiek ir tolesnėje ateityje, sukelti sportininko socialinės adaptacijos problemų, pavojų sveikatai bei gyvybei.

Raktažodžiai: sportas, dopingas, WADA draudžiami preparatai, anaboliniai preparatai, anaboliniai steroidai, sportininko sveikata.

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