THE USE OF ANABOLIC ANDROGENIC STEROIDS: A FOCUS ON POLYPHARMACY

**UPOTREBA ANABOLIČKIH ANDROGENIH STEROIDA SA FOKUSOM NA POLIFARMACIJU**

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**Summary**

**Introduction.** Anabolic androgenic steroids, such as testosterone and its synthetic analogue, nandrolone, have clear clinical indications. However, their abuse is practiced to enhance physical performance in professional, recreational and non-professional athletes; outside of sports, their nonmedical use is associated with different social groups (criminal activities, substance abuse). **Polypharmacy.** Testosterone and its synthetic analogues are also used for nonmedical purposes, mainly administered in supraphysiological doses in cycles lasting a few weeks. In order to potentiate the anabolic properties and control the adverse effects, the users also administer other pharmacological agents. Thus, growth hormone and insulin are complement to anabolic steroids; clenbuterol, amphetamine and thyroid hormones stimulate body fat loss; diuretics reduce the body weight and improve muscle definition; and erythropoietin increases the training capacity and accelerates the recovery after hard competitions. To control adverse effects, cardiovascular drugs, central nervous system depressants, central nervous system stimulants, human chorionic gonadotropin, sexual enhancement drugs, estrogen antagonists, analgesics/opioids, nonsteroidal anti-inflammatory drugs and others, are administered. Probenecid, finasterid and diuretics mask the administration of other doping agents. Additionally, during the last two decades, attention has increasingly been focused on the relationship between the use of anabolic androgenic steroids and psychoactive substances (alcohol, cannabis, amphetamines, cocaine, hallucinogens). **Conclusion.** Supraphysiological doses and polypharmacy additionally increase the risk of adverse effects, including withdrawal syndrome; therefore, prevention of nonmedical use of anabolic androgenic steroids should be a public health priority.

**Key words:** Anabolic Agents; Androgens; Drug Users; Polypharmacy; Substance-Related Disorders

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**Sažetak**

**Uvod.** Anabolički androjeni teroidi kao što su testosteron i njegov sintetski analog nandronol imaju jasne kliničke indikacije. Međutim, zloupotreba u svrhu poboljšanja fizičkih performansi u vruškom, ali i u rekreativnom i neprofesionalnom sportu se praktikuje; izvan sporta, nemedicinska upotreba teroida se dovodi u vezu sa različitim socijalnim grupama (fizički aktivnost, zavisnost od lekova i drugih sustacija). **Polifarmacija.** U nemedicinske svrhe testosteron i njegovi sintetski analozi se uglavnom primenjuju u suprafiziološkim dozama u ciklusima koji traju nekoliko nedelja, a kako bi potencirali anaboličke efekte i kontrolisali neželjene reakcije, korisnici primenjuju i druge farmakološke agense. Tako se u kombinacijama sa anaboličkim steroidima nalaze hormon rasta i insulin; klenbuterol, amfetamin i tiroidi hormon koji podstiču sagostavljanje telesnih masti; diuretici koji redukuju telesnu težinu i doprinose boljoj definiciji mišića; eritropoetin koji povećava mogućnosti treninga i ubrzava oporavak nakon napornih takmičenja. Za kontrolu neželjenih reakcija koriste se kardiovaskularni lekovi, depresori centralnog nervnog sustava, stimulansi centralnog nervnog sustava, humani horionski gonadotropin, lekovi u terapiji seksualne disfunkcije, antagonisti estrogena, analgetici/opioidi, nesteroidni antiinflamatorni lekovi i drugi. Probenecid, finasterid i diuretici maskiraju pozitivne rezultate u doping kontroli. Dodatno, tokom poslednje dve decenije pažnja se sve više usmerava na vezu između upotrebe anaboličkih teroida i psihoaktivnih sustacija (alkohol, kanabis, amfetamin, kokain, halucinogeni). **Zaključak.** Suprafiziološke doze i polifarmacija dodatno uvećavaju rizik od neželjenih reakcija, uključujući i apstinencijalni sindrom; stoga, prevencija nemedicinske upotrebe anaboličkih teroida treba da bude javnozdravstveni prioritet.

**Ključne reči:** anabolic; androgeni; narkomani; polifarmacija; bolesti zavisnosti

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Anabolic androgens are used to improve physical performance in elite athletes (e.g., sprint, shot, discus, hammer, javelin) as well as in recreational and non-professional sport (e.g., fitness, bodybuilding); outside the world of sports, the nonmedical use is practiced in different social groups (criminal activities, abuse of drugs and other substances).

The estimated prevalence of nonmedical use is between 1.27 and 4% in young adults, and there are significant differences at the level of some subpopulations [3, 4]. For example, approximately 20% of body-builders and 11% of prisoners use anabolic steroids [5, 6].

Polypharmacy

For nonmedical purposes, testosterone and its synthetic analogues are ingested orally, injected intramuscularly, or applied to the skin. The doses are 5 – 29 times higher than doses for conventional hormone replacement [7, 8]. Users typically combine different AAS (“steroid stacking”), injectable and oral ones. Oral formulations have a short half-life and are used daily; intramuscular formulations are generally administered weekly or biweekly. Nandrolone, testosterone, trenbolone, boldenone, methandrostenolone and stanozolol are some of the most popular (Table 1) [3]. After administration in cyclic manner, generally lasting 6 – 18 weeks, a period of abstinence follows [7]. It should enable the recovery of the hypothalamic-pituitary-gonadal axis and return the endogenous testosterone to the normal level.

To potentiate anabolic properties, control adverse health effects, or avoid a positive result in doping-control, other pharmacological agents are also administered [3]. Indeed, polypharmacy is widespread and between 50 and 95% users practice it [6, 9, 10]. The most commonly reported adjunct substances are growth hormone, insulin, thyroxine, clenbuterol, human chorionic gonadotropin (hCG), analgesics/opioids, dietary supplements, diuretics, alcohol and some illicit pharmacological agents [11].

Enhancement of anabolic effects

There are multiple mechanisms by which anabolic steroids can increase physical performance (Table 2); undoubtedly, they increase muscle mass and strength in dose-dependent manner; in case of action on the blood vessels, erythropoiesis and central nervous system, the evidence is less well established [12].

In order to complement anabolic effects, approximately one-fourth of AAS users administer human growth hormone (hGH), insulin-like growth factor-1 (IGF-1) or insulin [10, 13]; however, these extensive pharmacological regimens increase the risk of adverse effects [3]. Furthermore, several other performance enhancing agents are combined with steroids; clenbuterol, amphetamine, and some hormones as thyroxine, to stimulate body fat burning; diuretics (e.g., furosemide, thiazides) to improve muscle definition or to reduce body weight, erythropoietins to increase the ability of training and accelerate the recovery after hard competitions. Finally, a relationship between the use of AAS and dietary supplements has been documented [5, 14]; besides performance enhancing properties, simultaneous administration for long periods and/or in high doses increases the risk of synergistic adverse effects as acute renal insufficiency and cardiovascular events [9].

Adverse effects control

A wide range and a high prevalence of AAS adverse effects have been reported (nearly 100%) by illicit AAS users [3, 10]. Cardiovascular (dyslipidemia, atherosclerosis, cardiomyopathy, hypertension), neuropsychiatric (mood disorders, addiction, aggression, cognitive deficits), and neuroendocrine (infertility, gynecomastia) adverse effects are of particular interest. There are also well-recognized, but either less serious or less common, effects on other

| Table 1. Commonly used anabolic androgenic steroids |
|------------------------------------------------------|
| **Tabela 1. Često korišteni anabolički androgeni steroidi** |
| **PO Formulations/per os formulacije** | **IM Formulations/i. m. formulacije** |
| Methandrostenolone/Metandrotistenol | Testosterone enanthate/Testosteron enantat |
| Stanozolol/Stanzolol | Nandrolo dekanot/Nandrolon dekanaot |
| Oxandrolone/Oksandrolon | Boldenone/Boldenon |
| Oxymetholone/Oksimetolon | Trenbolone/Trenbolon |

Legend: PO - per os; IM - intramuskular/Legenda: i. m. – intramuskularno
organ systems (Table 3) [3]. Hence, in control of undesirable clinical outcomes, the use of medications such as captopril, carvedilol, digoxin, central nervous system depressants, central nervous system stimulants, gonadotropins, sexual enhancement agents, estrogen antagonists, aromatase inhibitors, is being practiced [11]. In addition, analgesics and non-steroidal anti-inflammatory drugs (NSAID) are frequently used in the treatment as well as in pain prophylaxis [15]; however, the latter mask the pain and additionally increase the risk of muscle injury.

Masking agents
The use of AAS in sports has been recognized as a common practice [16]. Maintaining safety and fairness in sports, the International Olympic Committee tests athletes for these prohibited substances, but athletes and their teams use different strategies to avoid doping violations. Among others, manipulations are based on pharmacological, biochemical, and genetic characteristics of testosterone and its synthetic analogues’ metabolism [16].

Testosterone undergoes hepatic and extrahepatic metabolism. The inactivation pathway occurs mainly in the liver via conjugation into testosterone conjugates (glucuronides and to a lesser extent sulfates) and in equal proportions into the 17-ketosteroids (androsterone and etiocholanolone). The conjugates of testosterone and its hepatic metabolites are excreted in the urine and bile. A small proportion of steroid is converted to biologically active metabolites, estradiol and dihydrotestosterone. In addition to the metabolites, approximately 1% of daily synthesized testosterone is excreted into the urine unchanged (Figure 2) [1, 17].

Epitestosterone is a 17α epimer of testosterone with unknown biological activity. Biosynthesis of these steroid molecules in human beings is constant, and in the urine the normal testosterone glucuronide and epitesterone glucuronide ratio (T/E) ranges between 0.4 and 2 (bimodal variation is in line with genetic polymorphism). T/E > 4 is considered to be a doping violation. In case of a simultaneous administration of testosterone and epitestosterone in a ratio of 30 to 1, the T/E is not changed and the doping result is false-negative [18]. Therefore, epitestosterone has been added to the list of banned substances as a masking agent for illicit testosterone use.

The World Anti-Doping Agency list also includes probenecid, 5α reductase inhibitors, diuretics and ketoconazole [19]. These drugs have different mechanisms of action and masking effects (AAS is mainly detected in a urine sample). Probenecid, uricosuric drug in the treatment of gout, interferes with renal excretion of steroid glucuronides. Inhibitors of 5α reductase, the class of pharmacological agents in the treatment of benign prostatic hyperplasia, alter metabolism of anabolic steroids reducing excretion of dihydrotestosterone and androsterone. Diuretics increase the volume of urine and subsequently decrease the concentration of AAS and their metabolites to undetectable levels. Ketoconazole, antifungal drug, inhibits synthesis of endogenous testosterone [16, 18].

Table 2. Ergogenic effects of anabolic androgenic steroids
Tabela 2. Ergogeni efekti anaboličkih androgenih steroida

| Organ system/Organski sistem | Effects/Efekti |
|-----------------------------|----------------|
| Muscles/Mišići              | Increased muscle mass/Urvećana mišićna masa |
| GH, IGF-1 secretion stimulation/Stimulacija sekrecije HR, IGF-1 |
| Decreased recovery time/Redukovano vreme oporavka |
| Blood vessels/Krvi sudovi   | Vasodilatation/Vazodilatacija |
| Erythropoiesis/Eritropoeza  | Erythropoiesis stimulation/Stimulacija eritropoeze |
| Increased motivation/Urvećana motivacija |
| CNS/CNS                     | Increased aggression/Urvećana agresivnost |
| Increased competitiveness/Urvećana kompetitivnost |

Legend: GH, growth hormone; IGF-1, insulin-like growth factor 1; CNS, central nervous system
Legenda: HR, hormon rasta; IGF-1, insulinu sličan faktor rasta 1; CNS, centralni nervni sistem
AAS, psychoactive substances and addiction

Over the last two decades, attention has increasingly focused on the relationship between the use of AAS and other psychoactive substances (e.g., alcohol, heroin, amphetamine, cocaine, hallucinogens) [14, 20]. At first sight, testosterone and the above-mentioned substances are an extremely heterogeneous pharmacological group; however, there is a link at molecular and cellular level. All of these substances, with certain quantitative differences, activate the mesolimbic dopaminergic pathway (reward pathway) and precipitate hedonic effects [21]; an inherent characteristic of the activation of pathway is the desire to repeat activity that leads to feeling of pleasure. Whether and when the loss of control over substance intake is experienced, it depends on the substance being used, the dose and route of administration as well as genetic makeup of the user.

Furthermore, AAS may accelerate addiction via anabolic and androgenic mechanisms [21]. Anabolic effect is mainly the motivation to begin using illicit AAS; in some cases, when the use is discontinued, due to a little reduction in muscularity, users become anxious and continuously administer steroids despite harmful consequences. In line with androgenic mechanisms, breaking the cycle (particularly a long cycle) often results in suppression of hypothalamic-pituitary-gonadal axis and consequently in hypogonadism related symptoms (fatigue, loss of libido, depression) that may prompt some users to quickly resume using AAS.

Using the criteria of the Diagnostic and Statistical Manual of Mental Disorders, it was estimated that 30% of AAS users develop an addictive disorder [21]. However, in case of its manifestation, therapeutic interventions have been insufficiently studied [20, 21]. Clinical experiences suggest that serotonergic antidepressants as well as cognitive-behavioral therapy may be useful in the treatment of muscle dysmorphia and depressive symptoms [21]. In association with hypogonadism, hCG can accelerate the synthesis of testosterone in the testes; clomiphene can stimulate pituitary function; phosphodiesterase inhibitors (e.g., sildenafil) may be used in the treatment of sexual dysfunction; and collective administration of hCG, clomiphene, and tamoxifen in varying time courses is also possible [21]. Finally, in animal studies, naltrexone, an opioid antagonist, blocked self-administration of testosterone (Hedonic effects of AAS are likely modulated by opioidergic mechanisms) [22]. Therefore, it is speculated that it could be used to treat AAS addiction [20, 21]; precipitated withdrawal syndrome may be treated by clonidine, benzodiazepines, non-opioid analgesics and antidepressants as well as cognitive-behavioral therapy may be useful in the treatment of muscle dysmorphia and depressive symptoms [21].

Conclusion

Nonmedical use of anabolic androgenic steroids is practiced among professional and non-professional athletes as well as non-athletes. Steroids are administered in supraphysiological doses and usually in combination with other licit and illicit substances. These patterns of use additionally increase the risk of adverse effects, including withdrawal syndrome. Therefore, prevention of nonmedical anabolic androgenic steroids use should be a public health priority.

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