Androgens from physiology, through pharmacy and pharmacology to the status of lifestyle drugs - are we going in the right direction?

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Summary

The aim of this review was to evaluate the current cognition about androgens (A) physiology, their pharmaceutical development and place in modern medicine. Special aspect was to explore the reasons and consequences of A use as so-called "lifestyle drugs" (LD).

To write this review, we used the scientific papers in English of a recent date on PubMed, reference textbooks, books and monographs of different disciplines, as well as official documents and reports of some internationally recognized organizations (European Medicines Agency, World Anti-Doping Agency, Medicines and Healthcare products Regulatory Agency).

Endocrinological role of A is generally known, but their non-hormonal effects are still the subject of intensive investigation. For decades, testosterone (T) and its esters have been the substitution therapy of the first choice in clearly defined clinical conditions. When it comes to pharmaceutical development, there are large number of effective and safe T formulations on the market which provide a very good patients' compliance. Regarding clinical application of synthetic A with dominant anabolic activity, the only acceptable indication nowadays is severe burn injuries, while others have to be proven by high-quality clinical studies. Particularly worrying is the wide-spread use of anabolic steroids (AS) for non-medical purposes, as so-called LD. Although numerous and serious side-effects are well-documented, general impression is that both users of AS and clinicians should know more about the risks of their use.

This review points to the need of better information and more comprehensive education at different levels, as well as implementation of additional preventive strategies, especially in the youth population, in order to avoid potentially serious consequences of the AS use.

Key words:
Androgens. Physiology. Pharmacy. Pharmacology. Lifestyle drugs.

Andrógenos, de la fisiología, a través de la farmacia y la farmacología al estado de las drogas de vida, ¿vamos en la dirección correcta?

Resumen

El objetivo de esta revisión fue evaluar el conocimiento actual sobre la fisiología de los andrógenos (A), su desarrollo farmacéutico y su lugar en la medicina moderna. Un aspecto especial fue estudiar las razones y consecuencias del uso de llamadas "medicamentos de estilo de vida" (LD).

Para llevar a cabo esta revisión, se realizó una búsqueda de artículos científicos en inglés recientes en PubMed, libros y monografías de diferentes disciplinas, así como documentos oficiales e informes de algunas organizaciones reconocidas internacionalmente (Agencia Europea de Medicamentos, Agencia mundial Antidopaje, Agencia Reguladora de Medicamentos y Productos Sanitarios).

El papel endocrinológico de los A es generalmente conocido, pero sus efectos no hormonales siguen siendo objeto de una investigación intensiva. Durante décadas, la testosterona (T) y sus ésteres han sido la primera elección para terapia de sustitución en condiciones clínicas claramente definidas. Cuando se trata del desarrollo farmacéutico, hay una gran cantidad de formulaciones de T eficaces y seguras en el mercado que proporcionan un muy buen cumplimiento por parte de los pacientes. Con respecto a la aplicación clínica de A sintético con actividad anabólica dominante, la única indicación aceptable en la actualidad son las lesiones por quemaduras graves, mientras que otras deben ser probadas por estudios clínicos de alta calidad. Particularmente preocupante es el uso generalizado de los esteroides anabólicos (AS) para fines no médicos, como los llamados LD. Aunque los efectos secundarios son numerosos y graves, la impresión general es que tanto los usuarios de AS como los clínicos deberían saber más sobre los riesgos de su uso.

Esta revisión apunta a la necesidad de una mejor información y una educación más integral en diferentes niveles, así como la implementación de estrategias preventivas adicionales, especialmente en la población joven, para evitar consecuencias potencialmente graves del uso de AS.

Palabras clave:
Andrógenos. Fisiología. Farmacia. Farmacología. Medicamentos de estilo de vida.

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Introduction

Male sex hormones or androgens (A) and their role in the human body are being learnt from elementary school. Later, at schools and faculties of health care, students learn about diseases and conditions that result from their insufficient or excessive secretion. Medical doctors and pharmacists know most about A as medicines, while other professions, as well as the general public, know very superficially or to the extent of their own needs or interests. As with many other medicines, some indications for A use are unquestionable and generally accepted from both clinicians and regulatory bodies, while others are still waiting for valid evidence.

However, unlike most other drugs it is well-known that different substances with androgenic actions were used by people without any medical diagnosis, in order to increase muscle mass, strength and endurance[1-4]. Available data show that those were first German soldiers[1], later Russian and American athletes[2,3], and since the eighties of the last century these substances have "entered" into the widest population of young and middle-aged individuals whose physical appearance and muscle mass have become the basic life preoccupation[4]. In official literature these substances got the status of lifestyle drugs (LD)[5]. Possible risks and consequences of their use, including cases of death, are well-documented[6-8]. The extent and importance of this problem is indicated by the data that in some countries, such as Netherlands, an outpatient clinic for past and current users of those substances was established in 2011 in order to acquire more knowledge about the health risks associated with anabolic androgenic steroids abuse[9].

The objective of this review was to evaluate critically and in detail the current cognition about A physiology, their pharmaceutical development and place in modern medicine. Special aspect was to explore the reasons and potential consequences of their use for non-medical purposes as so-called LD and to point out the importance of better education and preventive strategies in this area, especially in youth population.

Methods

Various literary sources were used to write this review. Initial data were obtained from textbooks, monographs and other books in pharmacology and clinical pharmacology, physiology, pharmacy, endocrinology and various sports sciences. The inclusion criteria for these publications were the following: a publication of a newer date which is internationally recognized (or used in university teaching), written in English and issued by a renowned publisher. Older date publications that are not of an international character and not published in English were not taken into account. For a more detailed insight into individual parts of this review, we searched the "PubMed" database, using a number of keywords and determinations. Here the criteria for inclusion were the following: publication had to be original scientific paper or review (including studies on animals and other types of experimental studies) published in English in the period 2000-2018. Priority was given to the results of randomized, controlled, double-blind clinical studies with a large number of participants. In exceptional cases, older papers were quoted, where this was of substantial importance for the research subject. Case studies, papers without the author's name and papers which weren't written in English were not taken into consideration. The last source of information was official websites of internationally recognized regulatory institutions (European Medicines Agency-EMA, Medicines and Healthcare products Regulatory Agency-MHRA and World Anti-Doping Agency-WADA) from which the latest reports, recommendations and documents were taken. The authors accessed these sites for the last time in November 2018.

Androgens as physiologically important substances - can we live without them?

Testosterone (T) is a major natural A. It is mostly synthesized in testicular Leydig's cells and smaller amounts in the ovaries and adrenal cortex from cholesterol as the initial substance. In a healthy adult male, 4-9 mg of T is excreted daily and only 1-2% is free in plasma[10].

Androgenic effects of T are spermatogenesis and development of primary and secondary sexual characteristics of a man, including characteristic hair distribution on the body, baldness, a specific voice depth, increased skin thickness and firmness of the subcutaneous tissue, increased secretion of the sebaceous glands with the appearance of acne, etc. Anabolic effects of T include protein synthesis and muscle development, bone growth and calcium storage, increased basal metabolism, increased number of erythrocytes, and others[11]. Behavioral effects of T include the regulation of sexuality, aggression, cognition, emotion, and personality[12,13].

T precursors, dehydroepiandrosterone (DHEA) and androstenedion are less potent A which are synthesized in the gonads and adrenal cortex in both sexes. In the liver they are being converted into more potent T[14]. DHEA and its metabolites regulate glandular and neurotransmiter secretions, influence glucose homeostasis and cyclic release of GnRH, control the activity of skeletal and smooth muscle and increase the tolerance to ishemia[15]. Additional neuroprotective effects, positive modification of human mood, emotions and behavior were also found[16]. Although in recent decades the popularity of these substances has grown because of their use in doping[17], existing data doesn't confirm their effectiveness regarding the lean body mass, muscle strength or performance improvement compared with placebo[18,19] (Figures 1 and 2).

In most peripheral tissues T is being converted in more active dihydrotestosterone (DHT) by 5alpha-reductase. Inhibitors of this enzyme (finasteride and dutasteride) have being traditionally used in the

Figure 1. Structural formula of dehydroepiandrosterone.

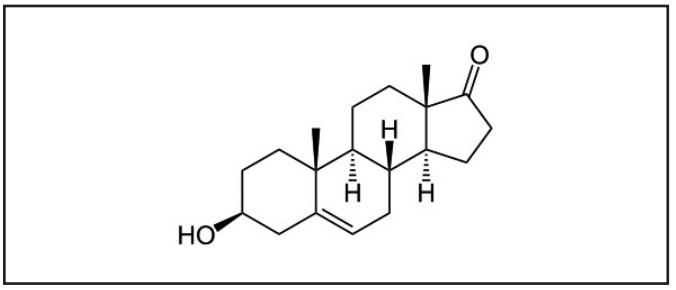
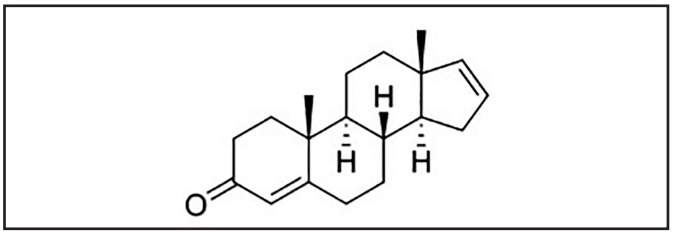


Figure 2. Structural formula of androstenedione.



treatment of benign prostatic hyperplasia. Their use reduces the incidence of low-grade prostatic carcinoma in high-risk patients[20,21]. Recent studies in experimental animals have found some non-hormonal effects of these medicines, such as reduction of dyskinesia in Parkinson's disease, anti-nociceptive and anti-inflammatory actions and the improvement of motor, EEG and celular changes in hepatic encephalopathy[22-24]. This could expand the existing knowledge about A physiology and open new possibilities in the treatment of some CNS diseases. Paba S, *et al*.[25] identified the 5alpha-reductase as possible novel therapeutic target in the treatment of schizophrenia.

Androgens as medicines - is the science fully dedicated exclusively to the well-being of the patient?

There have always been pathological states that have caused a lack or complete absence of A in the body of a man, with accompanying clinical manifestations. In that sense, it was imposed the need for designing and synthesizing substances which could, if applied exogenously, replace their deficiency and improve clinical symptoms. According to recent data, approximately 2.4 million males in USA aged 40-69 years old suffer from hypogonadism[26]. About 2.3% of men in their 40s and 3.8% of men in their 60s were taking some form of T replacement therapy in 2011[27].

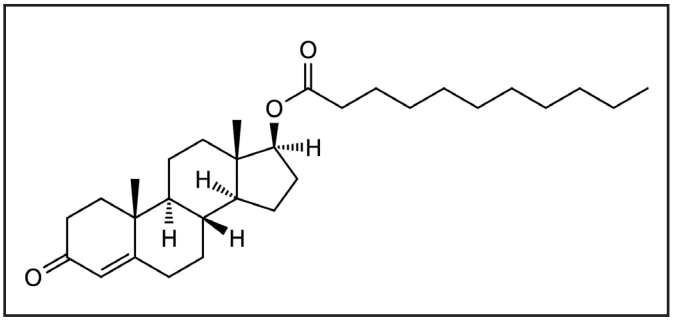
Testosterone and testosterone esters

Knowing the fact that T administered orally is the subject of so-called "metabolism of the first pass" through the liver to a significant extent[14], Butenandt and Ruzicka synthesized T in the injection for the first time in 1935, that is considered as the beginning of the golden age of steroid chemistry. Four years later these scientists got the Nobel Prize in Chemistry[1]. However, T administered even in this way had a short duration of action due to intense biotransformation (half-life of 10 minutes)[28], so patients were forced to receive it frequently.

In order to ensure the prolonged action of T, the science went on. In the 1940s and 1950s, the first T esters were synthesized (propionate, cypionate, enanthate). These esters are still in use and they are administered as intramuscular depot injection at intervals of 1-6 weeks, according to patients individual requirement[29,30].

In the mid-seventies there was a new progress. It was synthesized T undecanoate, also T ester in the form of depot intramuscular injection[10]. It has provided stable plasma levels of T over three months, which has been a significant advantage for patients[31] (Figure 3).

Figure 3. Structural formula of testosterone undecanoate.



Certainly, the revolutionary discovery of the 1980s was transdermal application of T as an alternative to painful injection[28]. The first effective transdermal patches were applied in the scrotum area because of very good pharmacokinetics and potency[10,29]. Smaller skin surface area and application challenges (hair clipping), as well as the apparence of transdermal patches which could be applied at back, abdomen, upper arms or thighs limited the use of formulations for scrotum application[29].

Further discoveries went in the direction of hydroalcoholic gels/liquid solutions for transdermal absorption[10]. In order to minimize transfer, recommended sites for their application are areas which will be covered by clothing[29]. There are also formulations for application to buccal mucosa, from which T is gradually absorbed, bypassing hepatic metabolism[10]. Modern T implants for subcutaneous administration provide the replacement of T for a period of even 6 months[29]. The latest discovery was nasal gel, as another non-invasive treatment[29].

Synthetic androgens

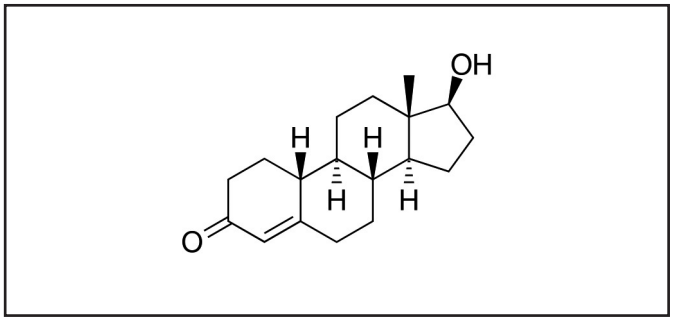
There were three main reasons for design and synthesis of synthetic androgens (SA): the possibility of oral administration, the prolongation of biological activity in vivo and the increase of anabolic compared to androgenic effects[32]. Those modifications were expected to improve the possibility of clinical application of SA, that can be considered justified from the professional, scientific and ethical point of view.

Oral activity was achieved by substitution of the 17α-H on the steroid nucleus with a methyl or ethyl group, which prevented the deactivation by first-pass metabolism in the liver[12]. Methyltestosterone was the first synthesized medicine in this group (1935), and others were synthesized later[17]. However, the attempt to introduce these medicines into the long-acting replacement therapy (LART) was unsuccessful because of their hepatotoxicity[17].

Another form of structural modification of A was 5α- reduction. Mesterolone was synthesized in this way, but it's oral administration in LART was limited due to relatively weak pharmacological activity[12] and unconfirmed efficacy in standard doses[33].

Nandrolone (N) is 19-demethylated analogue of T which also cannot be taken orally because of extensive first-pass metabolism in the liver[34]. However, the third goal (very high ratio of anabolic to androgenic action[12] was achieved with N, that could be an explanation for its current status of the most popular A in sports doping and bodybuilding[35] (Figure 4).

Figure 4. Structural formula of nandrolone.



In order to enable its medical application, there were developed long-acting pro-drug esters of N (but not for oral use, for intramuscular injection again!), such as N decanoate (ND). Both experimental and clinical studies confirmed positive effects of ND on bone tissue. Li X *et al.* found ND blocked bone loss by inhibition of bone resorption in ovariectomized rats with osteopenia[36]. Newer investigation on young adult rats found a positive effect of ND on bone callus formation after a complete femoral fracture[37]. In women with postmenopausal osteoporosis ND increases bone density and reduces the incidence of fractures[38,39], but according to reference recommendations, such as UK Clinical Guideline for the Prevention and Treatment of Osteoporosis[40], bisphosphonates are considered as drugs of the first choice.

Androgens as medicines - what does the evidence-based medicine say?

Substitution therapy

T is used as substitution therapy of the first choice in conditions which cause primary testicular insufficiency, such as bilateral anorchia, Klinefelter's karyotype (XXY), surgical removal of the testes, chemotherapy and radiotherapy, but also in secondary testicular insufficiency which occurs as the result of disturbance on the hypothalamic-pituitary axis. Another reason for T clinical use is delayed puberty in boys ages 16 and older[10].

Substitution of T in aging men in andropause, according to some authors[41-43] has a positive effect on bone mineral density and lean mass, sexual function, mood, general sense of well-being and reduction of the amount of adipose tissue. Considering this issue in recent review, Singh P concluded that "disparate results of clinical trials suggest an incomplete picture of complex interaction between aging and A deficiency". Before commencing T treatment, he suggested clear discussion with the patient about potential benefits and risks of the therapy, as well as to consider the assessment of prostate and other risk factors[44].

Controversies regarding the diagnosis of female hypoandrogenism and possible T substitution are still unresolved[45]. T therapy is not approved for women in North America[46]. In EU, T-containing medicines are licensed only for the treatment of male hypogonadism[47]. Additionaly, the long-term side effects of T in women have not yet been fully investigated[48,45].

Due to relatively weak anabolic effect, as well as adverse A effects, T is rarely used in catabolic conditions. The exception is hypogonadism as the consequence of the AIDS[17]. Rabkin JG *et al.* found in their double-blind, placebo-controlled trial that T is effective and well tolerated in the short-term treatment of clinical hypogonadism in men with symptomatic HIV illness, restoring libido and energy, alleviating depressed mood and increasing muscle mass[49]. Long-term studies regarding this issue are still missing.

Pharmacological therapy

Except in physiological doses that are used in replacement therapy, A may be administered in considerably higher doses as pharmacological therapy. This type of therapy was mainly used in some non-reproductive diseases in order to improve the patients' quality of life (QoL) by enhancing muscle, bone, or other A-sensitive functions, but without ability to influence the course of underlining disease[35]. This type of A therapy was mentioned in the literature mostly from the last decades of the XX century for several medical indications, including anemia as a result of bone marrow aplasia or renal failure[50-51], osteoporosis[38-39], advanced ER-positive breast cancer[52-53], endometriosis[54-55], burn injuries[56-57], and others[35,58]. Woerdeman J, *et al.*[59] analyzed relevant clinical studies with anabolic androgenic steroids (AAS) in the treatment of non-hormonal chronic disorders published in the period 1950-2010 and they concluded that although the beneficial effects of AAS were promising, clinically relevant endpoints such as QoL, improved physical functioning and survival were mainly missing or not significant, except for burn injuries. Both Woerdeman[59] and Handelsman[35] pointed to the need for additional, high-quality clinical studies with the exact clinical end points in order to confirm the long term safety and efficacy of AAS in other non-hormonal clinical conditions. An additional reason for current status of A as adjuvant, supportive or adjunctive second-line therapy is the introduction of newer, more selective and more effective medicines in these indications (erythropoietins for anemia in renal failure, biphosphonates for osteoporosis, etc.).

After the previously stated, it can be concluded that modern, evidence-based medicine clearly positions T and its esters as the first-line therapy in LART in men, but when it comes to the pharmacological application of SA with dominant anabolic activity, the only reasonable indication is severe burn injuries, while others have to be proven.

Anabolic steroids - medical indications as a goal or a justification?

According to Thieme D, *et al.*[1], anabolic steroids (AS) were first synthesized by German scientists during the Second World War, shortly after the discovery of T itself. They are believed to have been tested on people, especially prisoners, but those results have never been published. Some personal war experiences of the surviving German soldiers speak of how they were given AS in order to increase the strength and aggressiveness. Adolf Hitler also used steroids in order to strengthen his aggressive personality, that was confirmed by notes of his doctor[1]. Thus, the first use of AS in healthy people and for non-medical purposes was

in German soldiers during the Second World War in order to increase their strength, endurance and aggressiveness.

The use of AS in athletes was noted for the first time at the weight-lifting championships in Vienna in 1954 by Russian competitors[2]. Two years later CIBA Laboratories in Basel synthesized metandienone (Dianabol®) for the US Olympic Team[3]. In following decades A abuse quickly spread into competition bodybuilding, track and field events and other sports where performance is dependent on muscle strength or speed of recovery during training[60].

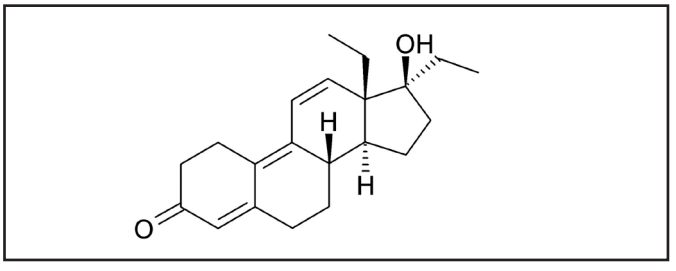
However, at the beginning of 1980s, the conditions were changed globally and AS gradually shifted from top-class sports to the general population[4]. According to Kanayama G, *et al.*[4], a typical "user" of AS nowadays is young to middle-aged man whose motivation for their use is primarily personal appearance and muscle mass. It is clear that the use of those substances in this context is not caused by any existing medical diagnosis.

Although 23 different definitions of LD can be found in the literature[61], the most operational one is that "LD are drugs that could modify or change non-medical or non-health-related goal or conditions at the margins of health and wellbeing" [62,63]. The examples of LD should be sildenafil citrate in the treatment of erectile dysfunction, minoxidil for the baldness, botulinum toxin for "ironing" wrinkles, etc.[61] Satisfying the criteria of LD definition, AS "found their place" among substances of the modern times which alter not only the personal appearance, but also the physical and mental capabilities. Although all of these substances have the status of LD, a significant difference should be noticed: erectile dysfunction and male-pattern hair loss are official medical diagnoses that are treated by licensed medicines, but facial wrinkles and personal dissatisfaction with the amount and tonus of muscle mass in own body are not yet, that doesn't mean that they will not be soon. Or, maybe they actually exist, but we still don't know their name(s).

Designer steroids - did things get out of control?

Designer steroids (DS) are AAS which are synthesized from a known parent steroid and chemically modified with the intent to circumvent controlled substances laws[64-65]. They are often identical to physiological substances and/or their metabolites whose concentrations in human plasma otherwise vary significantly, which makes it difficult to detect them[5]. The first DS, tetrahydrogestrinone (THG) was discovered in 2003 in the Olympic Analytical Laboratory at the University of California, Los Angeles[66] (Figure 5).

Figura 5. Structural formula of tetrahydrogestrinone.



The disappointing thing is that, unlike the previously described AS, the discovery and development of DS have never been linked (in theory or practice) with any medical indication, which could justify their design and synthesis to a certain extent, at least from the ethical point of view. Cheating athletes have a double motivation to use DS: to achieve performance enhancement and to escape from testing positive in anti-doping tests. Both can be considered as deception in sport and human sense. The fact that the first and probably many other DS were synthesized in laboratories belonging to universities could be considered as the deception of science. In their discovery and development are working persons (scientists) for which the ethics and the truth should be the basic principles of their professional dealing. An increasing number of DS on the market which are mainly sold as dietary supplements[67] should be the next fraud in sequence. "Bypassing" a strong regulatory rules that refer to licensed medicines, DS become more easily accessible and potentially more dangerous for end-users.

According to Pope HG, *et al.* (2004), AAS users rated physicians as no more reliable source of information about those substances than their friends, Internet sites, or the persons who sold them the steroids[68]. On the other side, most general practitioners had some contact with AAS users in their practice, but only 40% of them reported that they would be willing to provide harm minimization advice[69].

Previously stated indicates the seriousness and complexity of this phenomenon globally, as well as the need for additional effective actions at different fields.

How anabolic steroids act on healthy human organism - do we know possible consequences?

For years, AS have been the most commonly detected doping substances in athletes[70]. In 2015, according to the WADA report, AS participated exactly 50% in all positive findings on doping[71]. In combination with training and high protein intake, AS undoubtedly increase muscle mass and body weight, but there is little evidence that they increase muscle strength more than it would have been possible by the training itself, or that their use would improve sports results in general[5].

Given the disturbing fact that in the last decades AS have been increasingly used to improve the physical appearance of young people who are not primarily athletes[4] for aesthetic, psychological, sociological and other non-medical and non-sporting reasons, then we can state regrettably that, in this sense, these substances are likely to satisfy the needs of their users, at least for a limited period. On the other hand, since they are applied for a long time in supra-physiological doses, which are usually up to 50-100 times higher compared to endogenously produced T in an adult healthy male[72], their application is associated with long-term and serious adverse effects, of which cardiovascular, neuroendocrine and psychiatric are dominant[6,7]. The entity of side effects depends on the sex, the dose, the duration of treatment, whether AS are taken during exercise training or under sedentary conditions, and individual susceptibility to A exposure[73].

Adverse *cardiovascular disorders* include hypertension, an increase of LDL and reduced HDL, potentiation of thrombosis and cardiac arr-

hythmias, cardiomyopathy, left ventricular hypertrophy and myocardial ischemia[74,75]. Melchert and Welder[76] categorized cardiovascular effects of AS in four types of actions: vasospastic, atherogenic, thrombotic and direct myocardial injuries. Frati P, *et al*. (2015) identified nineteen sudden cardiac deaths (SCD) in AS users in the period 1990-2012[8], which probably could be attributed to an imbalance of autonomous nervous system activity[77]. Some authors suggest that in the cases of SCD in athletes the use of AS should be excluded[74].

The *endocrinological effects* of AS depend on the age and sex of the person using them[14]. In adult males, anabolic effects may be accompanied by salt and water retention. The skin becomes thick and often darker, the sebaceous glands become more active, resulting in the appearance of acne[14]. AS use causes gynecomastia, priapism, hypogonadism, inhibits spermatogenesis and reduces the man's fertility[78]. These influences adversely affect the mood, that forces a man to take these substances repeatedly. BPH and prostate cancer in AS users were also described[78]. In women AS cause hairiness, male pattern baldness, menstrual cycle disorders, breast atrophy, changes in voice depth, acne, etc.[14,78]

At the *psychological plane*, AS cause a sense of well-being, increase competitive spirit and aggressiveness, in some cases even to the level of psychosis[14]. Violence, aggression and impulsivity are explained by some authors as the consequence of decrease in the functional correlation of key centers in the brain responsible for emotional and cognitive behavioral regulation[79]. Depression which usually requires long-term psychiatric treatment develops very often at the end of applied "cycle" of AS[5]. A numerous cases of suicide in AS users with some specificities in comparison to suicides caused by psychoactive substances were described[80,81]. AS users more easily take other substances in order to increase muscle mass, reduce fat tissue and improve body appearance[82]. These substances, so-called "body image drugs" include other hormones (growth hormone, insulin), beta-agonists (clenbuterol), stimulants (amphetamine, ephedrine), laxatives, diuretics, etc.[82] Even greater problem is that AS users are more likely to reach to so-called "street" drugs, predominantly opiates, compared to people who do not use AS[83]. Particularly worrying are the results of Arvary and Pope[84] according to which 9% of male sex heroic users began using it during the use of AS, that as many as 81% of respondents bought opiate for the first time from the same dealer who sold them AS, and 67% of the respondents took opiates in order to fight with AS abstinence syndrome. Ten years ago, Graham et al. accused the medical profession who didn't accept the fact that AAS use dependency is a psychiatric condition[85].

Adverse effects of AS on the liver include adenomas, hepatocellular carcinoma, cholestasis and peliosis hepatis[86,87]. Bond P, *et al*.[88] assume oxidative stress as the causative factor of AS-induced hepatotoxicity.

At the end of this chapter, the question arises is there the need to use other medicines in order to cure the "lifestyle improvement" caused by AS?

Conclusions

The hormonal effects of A are generally known in the professional, but also in general population, through various ways and levels of formal and informal education and experience. Scientists' attention is now occupied by non-hormonal effects of A, metabolites and enzymes involved in their biotransformation. These substances and enzymes have been shown to influence the various aspects of human functioning, primarily the CNS, that opens up the new possibilities in the treatment of certain diseases.

In clinical terms, T and its esters are clearly positioned as the first line replacement therapy in male hypoandrogenism, while T-containing medicines, in the absence of effective evidence, are still not licensed for women. When it comes to the type and selection of T pharmaceutical formulations, it can be concluded that there is a fairly wide selection of effective and safe preparations, both traditional and modern, which ensures a good patients compliance and minimal negative impact on their QoL.

When SA are concerned, it can be concluded that in the pharmacokinetic sense their discovery and development fulfilled the expectations, but in clinical terms it is still not the case. Although there are undoubtedly promising results, scientific and professional community are still expecting the outcomes of high-quality clinical studies in order to confirm the long-term efficacy and safety of SA in most non-hormonal clinical conditions they are proposing.

However, thanks to their anabolic properties, SA have long been present in the population of healthy people without medical diagnosis. First of all they were soldiers, and then athletes. In the past decades, tight muscle and physical appearance were imposed as superior living values, which SA "have dropped" into the population of "ordinary" people around the world and give them the status of LD in reference literature. It went so far that nowadays DS are synthesized and used as dietary supplements without any medical reason, in order to deceive in achieving sports results and to circumvent the institutional control, that is disappointing from many aspects.

Existing research shows that both healthcare professionals and AS users don't know enough about them. Users don't have too much trust in doctors, and doctors admit that they don't know enough about these substances. Although they have the status of LD, numerous side effects, including deaths, warn and point to the need for development of additional comprehensive measures and clear strategies at different levels in order to prevent or minimize potential risks and consequences of AS abuse.

Conflict of interest

The authors do not declare a conflict of interest.

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