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IM - REVIEW

Anabolic steroids: dependence and complications of chronic use

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Abstract Anabolic steroids are widely used for doping, in professional and domestic sports. The mechanism of action is not completely understood. It may differ somewhat depending on the specific molecule due to structural differences that influence the specificity of binding with steroid receptors. When used by athletes in training, they can improve performance to levels that cannot be attained by almost any combination of sophisticated nonchemical support by modern sport science. The severity of the undesired effects of anabolic steroids depends on a variety of factors, from the type and combination of them, the dose and duration of administration, as well as the gender of the person taking the drug. Younger individuals and women show greater effects caused by anabolic steroids in terms of performance, but are also at greater risk of side effects. This paper presents a review of the literature concerning the major adverse effects of anabolic steroids, focusing the attention on possible situations of addiction from this category of drugs.

Keywords Anabolic steroids · Complications of chronic use · Dependence

Introduction

That the recourse to doping practices is not confined to a cohort of professional athletes, nor limited to the day before competition, is widely recognised. In fact, doping has become a complex phenomenon and various forms of it are acknowledged: the doping of professional athletes, domestic doping, cosmetic doping, etc. The incremental increase in the use of ergogenic substances in sport, in particular from the period after the Second World War, has been influenced by numerous factors: first of all is the progressive importance of sport as business, its importance as an entertainment spectacle, has produced an impressive commercialization and economic importance of almost all sports. The emphasis upon victory at all costs, exaggerated by pressures from sponsors, trainers, coaches, the family and its entourage, and the fans, all induce and push athletes to use drugs for improving performances. A psychological conditioning, an opinion, that it is impossible to win in sports without the use of ergogenic substances, also exists. The idea that rivals are making use of ergogenic substances can place the athlete in a condition of psychological disadvantage that pushes him/her to take the same chemical enhancers. Among other favouring factors are the desires for a freer approach to utilize new substances (that are less easily detected) and the ability of the drug industry to produce more powerful drugs with less toxicity.

The present social and cultural environment, oriented towards efficiency and functionality, contributes to the feeling of frustration if you are not a winner in the Sunday marathon, thus increasing the so-called domestic doping. The model states that success is only measured by being at the top, which leads to the quest for results at all costs, having repercussions for young people and sports amateurs [1].

Other factors have to be taken into account while investigating the reasons for the development of cosmetic doping. Dismorphophobic boys believe they are not robust enough despite time spent working out in gymnasiums.

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While consumed substances increase muscular masses, it is clear that division and disharmony exist amongst the body and mental images. This is in principle a consequence of a cultural- and media-driven imitation of feminine and masculine stereotypes. The image of the body has become the drug of the moment. Amongst doping substances anabolic steroids (AS), occupy a place of primary importance. The use of AS in order to improve sport performance has been known since the 1950s [1, 2]. AS are a group of agents that include the male sex hormone testosterone (TST) as well as numerous synthetic structural derivatives that have increased therapeutic efficacy and anabolic effects, and fewer androgenic effects (masculinization). In recent years, the Internet has facilitated commercialization with fewer controls over availability.

Despite their prevalent use, the current literature provides limited knowledge about the consequences of the use of AS. In fact, many studies, even if correct from a methodological standpoint, have investigated doses that are quite different from those employed in everyday use. Moreover, in controlled clinical trials, the effects of a single steroid are assessed, while it is common real life practice to use several substances simultaneously. The available data thus underestimates potential collateral effects, as a dose-response relationship is clearly present. Additionally, as these substances are available on the black market, their quality and precise doses are difficult to define.

Epidemiology

The test results of athletes published by the International Olympic Committee each year, varies between 1.5 and 2.5%: the positive percentage of AS usage is around 1%. A retrospective review of athletes participating in the modern Olympics Games (1896–2002) reports 29 AS-positive cases [3, 4]. There are several factors that contribute to unreliable figures: the capacity to foresee the clearance of various substances, the fact that the majority of tests are only carried out at the end of the competition, the problem that many substances remain undetectable, the desire to protect a clean image of sport (for political and commercial reasons), etc.

During the 1980s, evidence emerged that the use of AS had spread to non-athletic adolescents in the USA [5]. The percentage of male adolescents in Western countries who have used AS at least once is variable, ranging from 0.5 to about 7%. The reason for this variability, though unclear, is probably associated with the different approaches to conducting surveys. Unfortunately, there are no studies reporting the prevalence of chronic use of AS. Because most of the side-effects of AS probably develop after prolonged use, the life-time prevalence is of doubtful relevance in estimating the number of individuals at risk for such side-effects. It is reasonable to assume that among most groups the long-use prevalence of AS is lower than the life-time prevalence [3].

Mechanism of action

The mechanism of action of the AS is not completely understood. It may differ somewhat depending on the molecule due to structural differences that influence the specificity of binding with steroid receptors. The precursor of AS is TST, which has a variety of effects that differ depending on the target organ that is mediated in part by the two active steroids to which it is metabolized, namely estradiol and dihydrotestosterone (DHT).

When the AS are introduced into the blood system, they pass through the target cells membrane, linking with intracytoplasmic receptors. This complex hormone-receptor is later transported into the nucleus of the cell, where it links up with DNA. After that a transcription in RNA messengers follows, producing specific proteins. Therefore, the AS increase protein synthesis in muscle cells with consequent hypertrophy and augmentation of contractile force, although the total AS actions are more extensive. The AS also: (a) increase muscular mass with a contemporary decrease in adipose tissue [6]—this effect is related to the type of AS and its dose, and shows differences depending on the body area; (b) play an agonist role with mineralocorticoid receptors with retention of water and sodium; (c) have an antagonist action for glucocorticoid receptors (that are activated by stress, and have a catabolic effect)—thus the AS can have an action that is anticatabolic and involved in stress resistance; (d) lastly, the AS have been reported to alter the dopaminergic-mesolimbic circuit, the striatal and hypothalamic opiod-like system, and the adrenergic system that sensitizes neuronal circuits to the pleasing effects of these drugs [7]. The different actions of the AS on the tissues are briefly summarized on Table 1.

Therapeutic uses

The AS are used for therapeutic purposes via an oral route or through parenteral injection, and formulations are available for transdermic, intramuscular or subcutaneous routes, although intravenous preparations are not available. At present, the AS are used for primary and secondary hypogonadism, delayed puberty, suppression of lactation, postgestational and postmenopausal loss of libido [8], non-hypophyseal delayed growth, Turner's syndrome, debilitating conditions (cachexia, post-fracture trauma), burns,

Table 1 Effects of anabolic steroids on tissues

Body composition
Increase of overall body mass
Increase in free peripheral fat mass
Increase in free fat mass of the trunk
Decrease of overall adipose tissue
Reduction of subcutaneous fat
Reduction of deep intramuscular fat
Functionality
Increase in force
Increase in force of muscular contraction
Increase in power of muscular contraction
Myogenesis
Increase in volume of type I/II muscular fibers
Increase in number of myonuclei
Increase in protein synthesis
Reduction in protein catabolism
Increase in number of satellite cells
Increase in myogenesis of pluripotent stem cells
Reduction of adipogenesis of pluripotent stem cells
Cellular messengers
Increase in androgen receptors in pluripotent stem cells
Motor neurons
Increase in androgen receptors
Increase in number and size of motor neurons

HIV [9], refractory anaemia (stimulating erythropoiesis directly and by inducing renal synthesis of erythropoietin), and osteoporosis (by stimulating proliferation of osteoblasts and inhibiting osteoclastic activity) [10].

Anabolic steroids in doping

When used by athletes in training, the AS can improve performance to levels that cannot be attained by almost any combination of sophisticated nonchemical interventions by modern sport science [1]. Generally, the AS are used at high doses in order to facilitate an increase in mass, force, velocity of muscular contraction and recovery after intense workouts [11]. Athletic performance is also improved indirectly through erythropoietic stimulation, which increases the synthesis of 2,3-diphospholglycerate and facilitates the transfer of oxygen to tissues. It thus improves overall tissue oxygenation and reduces the production of lactic acid, increasing both force and resistance to fatigue [12].

The positive effects of the AS are especially pronounced if their administration is combined with correct nutritional supplementation and training [13]. The AS can also influence mood, and may lead to greater aggressiveness and increased competitiveness, which pushes athletes to train even harder [14]. Especially, when taken during training, athletes can suspend their use before competition, thus reducing the risk of testing positive. After suspending the AS, alterations in body return slowly to pre assumption levels, and in general persist for several weeks.

Complications from continuous use

The severity of the undesired effects of the AS depends on a variety of factors, from the type and combination of the AS, dose and duration of administration, as well as the gender of the taker. Except for rare functional complications, there have been no documented adverse events correlated with acute overdosage of AS. Younger individuals and women show greater effects from the AS in terms of performance, but are also at greater risk of collateral events [15]. While the therapeutic indications for the AS follow precise dosages and administration intervals, in doping the doses taken are much higher. As one example, in hypogonadism the dose of TST is between 75 and 100 mg per week, with a maximum of 200–250 mg in oligospermia; in doping, it is common to taken up to 1 g per week [16].

The long-term risks associated with the use of high-dose AS for non-therapeutic purposes, unfortunately, are not well-studied [17]. Many of the AS side effects are reversible after suspension of their use; however, chronic users can show permanent damage. Possible complications from continuous use of the AS are detailed in Table 2.

Cardiovascular complications

Regarding cardiovascular complications, several points should be made: (1) adverse cardiovascular effects are often reversible following suspension of use; (2) the risk increases if the individual takes other doping substances such as erythropoietin, growth hormone (GH), etc. [18]; (3) the risks increase with increased dosages and durations of administration [19]; (4) there is a large difference between the dosages used in controlled studies and those in doping. As such, the value of controlled trials is limited in terms of interpreting the effects of doping [20].

The AS can accelerate the initiation of atherosclerotic processes up to the rupture of fibro-calcified plaques and successive ischaemic events through a number of different mechanisms [21]as follows: (1) an increase in LDL and a reduction of HDL [22]; (2) favour the oxidation of LDL at the endothelial level [23]; (3) induce the expression of adhesion molecules and increase the migration of myocytes and adhesion of vessel wall monocytes with the formation of "foam cells"; (4) promote platelet aggregation and the formation of thrombus through induction of thromboxane

Table 2 Complications from continuous use of anabolic steroids

Genito-urinary and reproductive complications
In women
Hirsutism
Lowered voice tone
Menstrual irregularities
Amenorrhea
Infertility
Reduction in breast size
Clitoral hypertrophy
Uterine atrophy
In men
Testicular atrophy
Oligo-azospermia
Hair loss
Painful gynecomastia
Prostatic hypertrophy
Prostate carcinoma
Renal carcinoma
Metabolic complications
Increased LDL cholesterol
Decreased HDL cholesterol
Glucose intolerance
Digestive system complications
Cholestatic jaundice
Hepatic purpura
Benign hepatic adenoma
Hepatocarcinoma
Hepatic angiosarcoma
Cardiovascular complications
Stroke
Myocardial infarction
Arterial hypertension (infrequent)
Myocardial hypertrophy
Increased platelet aggregation
Thrombophlebitis
Polycythemia
Skin complications
Allergic cutaneous eruptions
Cystic acne
Sebaceous cysts
Hair greasiness
Peripheral edema due to fluid retention
Skeletal-muscular complications
Tendons sprains and rupture
Premature growth cessation
Neurological complications
Cephalea
Drowsiness
Loss of concentration
Psychiatric complications
Aggressiveness, irritability
Depression
Maniac behaviour
Paranoid psychoses
Dependence
Tendency of multiple drug abuse
Antisocial behaviour

A2, to a decrease of prostacyclin (PGI-2), and increase the concentration and activity of procoagulant factors IX and VII; (5) can cause vasospasm thus reducing the levels of PGI-2, inhibiting the synthesis of nitric oxide and increasing the synthesis of endothelin [24].

The studies that have analysed the hypertrophic action of the AS by measurement of echocardiographic parameters are quite equivocal. The majority have shown differences (greater mass of the left ventricle and posterior wall, thickening of the interventricular septum, compromised diastolic filling and ejection fraction), while others have reported no significant differences [25–28]. It should be pointed out that secondary cardiac hypertrophy as a result of constant training is usually associated with good contractile function, and does not compromise diastolic filling. Animal studies also demonstrate negative functional and structural effects on the myocardium even in the case of abuse of AS for short periods. It has, therefore, been hypothesized that echocardiography is not sensitive enough to identify early alterations in cardiac function [28].

Arrhythmic episodes can also occur, especially during exertion in subjects treated with supraphysiological doses of AS. The individuals at risk include the following: (1) subjects with structural heart diseases or primary arrhythmia where AS exerts a causal effect (hypertrophic cardiopathy, dilatation, right ventricular arrhythmia, Wolf Parkinson White syndrome); (2) subjects with hereditary/familial cardiopathies at risk for sudden death (Brugada syndrome, congenital long QT syndrome); subjects predisposed to ventricular tachycardia during physical activity (congenital long QT syndrome, polymorphic ventricular tachycardia) [29].

To date, there are no definitive conclusions regarding the effects of AS on arterial pressure: modifications in blood pressure, when demonstrated, seem to be reversible and modest [21]. Some studies demonstrate a role of endothelial-derived factors that cause hyperpolarization of potassium channels on smooth muscle cells during administration of AS [30]. The AS can also inhibit the effects of nitric oxide, inducing vasospasm [31].

In conclusion, the available data concerning the cardiovascular complications of AS provide evidence for a

relationship between the use and changes in blood lipid profiles, but only inconclusive evidence for cardiac hypertrophy. At the same time, there are no epidemiological data to confirm that the use of AS potentiates the risk for cardiac diseases. The prevalence of prolonged AS use is probably rather low in the general population, and many of the suggested cardiovascular side effects may take some time to develop. Therefore, retrospective case–control studies of cohorts would now appear to be the most feasible strategy for obtaining epidemiological information. Prospective follow-up of such a cohort could also be useful. Cross sectional autopsy examinations comparing exposed to non-exposed subjects could be another useful approach to this question. However such investigations require reliable post-mortem detection of prolonged use of AS, which is very difficult [3].

Urogenital and reproductive complications

The administration of AS determine an inhibitory feedback mechanism for production of follicle stimulating hormone (FSH) and luteinizing hormone (LH) at the hypophyseal level. In males, hypogonadotropic hypogonadism has been observed with consequent testicular atrophy [32]. Spermatogenesis can be markedly suppressed with oligo-azospermia, a phenomenon that is nonetheless reversible after suspension of the AS [33]. The AS also can induce prostatic hypertrophy, and increase the development of prostate and renal neoplasms. Gynecomastia is a consequence of the conversion of some of the AS into estrogens: a case has been reported in which surgical removal of a mammary gland was necessary [34]. In women, the following have been observed: increased virility and lowering of voice tone, baldness, irregular menstruation with infertility, reduction in breast size, hypertrophic clitoris, and increased sexual desire. With prolonged treatment, some undesirable effects may become irreversible [35, 36].

Other complications

The consumption of the AS can lead to rupture of tendons due to excessive load at insertion points that, according to some studies, is related to alterations in the structure of collagen fibers [37]. Laboratory tests can reveal increases in creatine kinase. Cases of rhabdomyolysis have also been reported [38]. In adolescents, accelerated skeletal maturation may also occur with premature closure of epiphyses and termination of growth [39].

Chronic administration of the AS should be considered as a risk factor for liver damage, and transitory increases of liver enzymes may be seen (ALT, AST, alkaline phosphatase, LDH) as well as cholestatic jaundice. Jaundice is in fact common among chronic users of AS, and is also used as an 'indicator' to regulate their assumption by chronic users. Hepatic cysts may also develop. During follow-up ultrasound studies, regression of lesions has been observed after suspension of the AS consumption [40]. Additionally, other forms of hepatic lesions may be found, even if quite rare, which include cholestatic hepatitis, benign adenomas, and hepatocarcinoma [41].

Many studies have investigated the effects of AS on serum lipids, and while the majorities have not revealed alterations in either total cholesterol of triglycerides, increases in LDL cholesterol and decreases in HDL cholesterol have been documented [25]. The AS can also cause insulin-resistant secondary glucose intolerance and alterations in thyroid function [42]. The presence of cystic acne localized to the back can also result in severe scarring [25]. Last, the risk of infections in AS users may be increased due to inappropriate use of syringes and non-protected sexual activity [43].

Functional complications

Episodes of aggressiveness, as well as alterations in mood and substance dependence have been reported in AS users [44]. In fact, several cerebral areas that influence behaviour and mood (hypothalamus, limbic system) contain receptors for the AS, and drastic changes in the level of steroids can lead to profound psychological effects, even in subjects without a history for mental disturbances [45]. Some chronic users perceive the alterations induced by the AS as positive, with increased self-esteem and optimism [14]. Chronic users of AS are often dissatisfied with their appearance. Pope et al. [46] report that one amongst ten body-builders, who use the AS has disturbances in regard to self perception that can be described as dysmorphophobia. This results in the fact that, even if the desired muscle mass is achieved, one still believes that the muscular component is inadequate, and additional agents may then be utilized in a compulsive manner in order to gain additional muscle mass [47]. A significant proportion of chronic AS users have personalities that can be described as narcissist, histrionic, and antisocial [48].

Several studies and case reports document increases in aggressiveness [25]. Some authors have hypothesized that this effect may be related to the personality of the individual and the intensity of training. Nevertheless, psychiatric complications following high doses of the AS have been reported in studies with healthy volunteers without previous history of either intense physical activity or mental disturbances [46, 49]. Schulte [50] and Yesalis [51] report on the social consequences of the use of AS; several alterations in behaviour are seen such as domestic violence, injury to other persons with a tendency for impulsive

manner, undervaluation of risks, and a reduced capacity of overall good judgment [52].

There have also been reports of depression in addition to symptoms of mania, hypomania, and episodes of paranoid psychoses with hallucinatory delirium [25]. Depression can arise during assumption of AS, or even more commonly, during suspension of their use. Cognitive alterations such as loss of concentration and memory, and sleep disturbance have also been documented. The appearance and severity of such functional disturbances appear to be dose-dependent [25]. One of the few studies that attempted to quantify the functional complications of AS use, estimates that the prevalence of manic and hypomanic episodes in chronic users is around 5% [49].

Dependence

In the literature there are no documented cases of dependence of AS at therapeutic doses, suggesting that dependence is likely found at higher doses [53]. Compared to other agents, the AS have a modest reinforcement mechanism that is not comparable to either cocaine or heroin, but more similar to substances with a lower reinforcement mechanism such as caffeine, nicotine, and the benzodiazepines. Multiple factors can determine dependence on the AS: individuals with low endogenous levels of TST (such as those in women, adolescents, and the elderly) have a lower probability of developing dependence to AS [54].

Several possible risk factors for abuse/dependence of the AS have been investigated. The most relevant appears to be participation in competitive sports (the most important risk factor) with intense workouts and rigid dietary schemes; at least 1 year of regular AS assumption; assumption of high doses at a young age; use of combinations of different types of AS and use of injectable AS; male gender (relative risk 2–3 times higher compared to women), use of other illegal substances, weak parental figures, low scholastic performance, and low perception of body image (likely the second most important risk factor) [55].

Several epidemiological studies reveal that 15–30% of subjects who take AS do not participate in any regular sport [56]. The mechanisms through which the AS led to dependence remain unclear, although both positive and negative reinforcement mechanisms have been identified. The former is both ‘myoactive’, (due to improvements in muscular form and physical capacity) and ‘psychoactive’: animal studies suggest that supraphysiological doses of AS on reward systems [57] lead to increased levels of beta-endorphins [58]. The fact that the primary reinforcement is not due to a direct psychoactive effect of the substance differentiates the AS from traditional mechanisms of substance abuse (cocaine, heroin, etc.). The negative reinforcement is due to withdrawal symptoms characterized by craving, asthenia, depression, akathisia, anorexia, insomnia, chronic fatigue, and muscle and joint pain [53].

Treatment approaches for the chronic user of AS

Users of AS rarely seek medical attention due to problems that arise from their use, and do not communicate to their physician that they use AS [59]. Nonetheless, several objective signs can help the physician identify potential chronic users of AS. Acne, injection marks in large muscles, baldness in men, hirsutism in women, edema due to fluid retention, generalized muscle hypertrophy, hepatomegaly, painful gynecomastia in men, mild scleral icterus, atrophy of breast tissue in women, etc. Even laboratory examinations can be indicative of chronic AS use: increased hemoglobin, alterations in muscle and hepatic enzymes (ALT, AST, GGT, LDH, CK, total bilirubin), alterations in metabolic and hormonal profiles (increased LDL cholesterol, reduction in HDL cholesterol, alterations in blood glucose, altered levels of TST and estradiol, alterations in thyroid function). Last, instrumental examination can be of use: abdominal ultrasound can reveal hepatomegaly, and the ECG can show signs of ventricular hypertrophy; an echocardiogram may also demonstrate functional alterations, etc. [53].

Some authors have proposed that information about the risks associated with the use of the AS be made available such as how to maintain physical targets using alternative methods, use of periodic blood and instrumental workups, and support therapies [60]. It has even been advocated that the AS should be administered under the supervision of a physician. Such a possibility would help prevent the patient from coming into contact with the AS on the black market, and further allow the patient to be subjected to a series of controls before taking the AS; subjects with certain pathologies could then avoid taking them. Taking the AS under the supervision of physician would also reduce the risk of adverse effects using dangerous therapeutic protocols [61].

At present, there are no defined treatment protocols. In situations in which the patient appears particularly aggressive, agitated, and manic, an antipsychotic should be administered. Depressive symptoms are frequently observed, and should be treated using selective serotonin reuptake inhibitors (SSRIs) [53]. In the long-term, cognitive behavioural therapy may be indicated. In patients with substance abuse problems, counseling may be beneficial.

Conclusions

A large percentage of subjects use the AS for long periods of time, and therefore the potential for complications is substantially increased. As a result, the overall risk of complications in the medium-long term is increased. Young adults should be informed about the secondary effects of the AS on health, and the educational objectives should be guided towards prevention of consumption through increased awareness about the health risks of AS. This should be supplemented by increasing one's self-image, reinforcing self-esteem, independent thought (as opposed to group identity), achieving the ideal muscular volume and resisting social pressure [62]. Recent studies have indicated that general practitioners have insufficient knowledge regarding doping. Therefore, more information is needed regarding the use of doping agents as their use and abuse has become a public health risk [63].

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