

ORIGINAL ARTICLE

ABUSE OF ANABOLIC ANDROGENIC STEROIDS

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Lower black market price, easier access to AAS_s, bodybuilding clubs and internet advertising are factors of this increasingly misuse. There is not real data about the prevalence of AAS_s abuse in various populations or countries, because most of athletes or students, due to their prohibition or ethical aspects do not admit to AAS_s abuse. Often they are aware of the risks of their choice and yet, are eager to put themselves at risk without deeper consideration. The abusers use them to improve their physical fitness and appearance.

Present article has been collected to elucidate the risks and adverse effects of AAS_s and explanation of mechanisms of these events.

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Testosterone is the primary male sex hormone and is responsible for the androgenic (growth of sex organs and secondary male properties) and anabolic (nitrogen retention and protein synthesis) effects. Related substances include anabolic androgenic steroids (AAS_s) as well as prohormones, Androstendione (Andro) and Dehydroepiandrosterone (DHEA), which are steroids in the biosynthesis pathway (1, 11). First, French physiologist Charles Edouard Brown-Sequard (1889) recognized the anabolic effect of a testicular extract of dogs and guinea pigs when given subcutaneously

(14). Then, the isolation of testosterone from testicular extract in 1935 and following studies, demonstrated that this substance stimulated a strong positive nitrogen balance in castrated dogs and rats, although its rapid degradation restricted its oral or parenteral administration. In addition, testosterone has a therapeutic index of 1 meaning, there is similarity in the proportion between the anabolic and androgenic effects, and chemically modification became necessary to more active substances with increased anabolic effect and avoid first-pass metabolism, and better systemic availability.

Investigations have led to synthesis of anabolic steroids (10, 11).

"Anabolism" is defined as any state, in which, nitrogen is differentially retained in lean body mass, either through stimulation of protein syntheses and or decreased breakdown of protein anywhere in the body. Since no drugs currently are "purely" anabolic, yet possess some androgenic property which cannot be totally separated from anabolic effect, and all possess at least some androgenic activity, therefore, it is more appropriate to use the term anabolic androgenic steroids (AASs) (9, 14).

Boje (1939) was the first to suggest that exogenous testosterone administration may enhance the athletic performance. The first dramatic reports of anabolic steroid use occurred following the 1954 world weightlifting championships and spread quickly through the 1960's in various Olympic sports (10).

Chemical Structure

All androgens possess the cyclopentanophenanthrene nucleus. (Fig.1)

Structures of testosterone and some of its selected derivatives used as anabolic are shown in Fig 2.

Testosterone undergoes a series of biotransformations when taken orally. Injected testosterone also passes rapidly in the blood and to the liver and is inactivated by the cytochrome P450

isoenzyme. Addition of an alkyl group at position 17 α results in orally active compounds. Alkyl substitution prevents deactivation of the steroid by first-pass metabolism. This alkyl group is commonly a methyl group, but in drugs such as norethandrolone, ethylestrenol and norbolethone an ethyl group is present. This modification is associated with hepatic toxicity (9, 14). A methyl group attached to C-1 can also confer oral activity, as in methenolone or mesterolone, but these compounds have relatively weak pharmacological activity (12). Esterification of the 17-hydroxy group delays the biodegradation. Long-chain esters are longer acting agents. These derivatives are highly androgenic and due to unsaturated C-4, 5 double bond can be aromatized to estrogen (9). Substitution of hydrogen for the methyl group in position C-19 results in 19-nortestosterone (nandrolone). Esterification of nandrolone with cyclohexylpropionate, decanoate, laurate and phenylpropionate yields products with more stabil and anabolic properties (9, 13). Oxandrolone has a lacton ring and an oxygen molecule at the C-2 position, whereas oxymetholone contains a hydroxymethyl group at same position. At present, metandienone (Dianabol)^R that has been banned since 1987 in America and Western Europe, is a frequently used drug among bodybuilders. Stanozolol was the first derivative with a heterocyclic pyrazole ring and is banned in Germany, but approved for the oral application in USA (9). Comparison of anabolic-androgenic ratio for selected AASs is shown in Table-1 (12, 14).

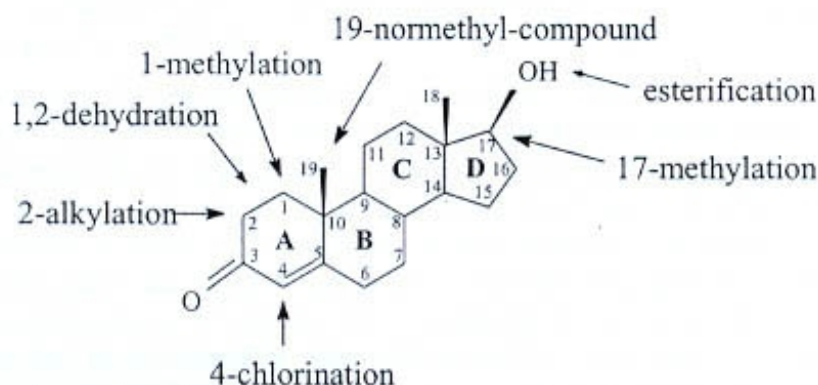


Fig. 1. Basic structure of steroid hormones and the possibilities of chemical derivatization

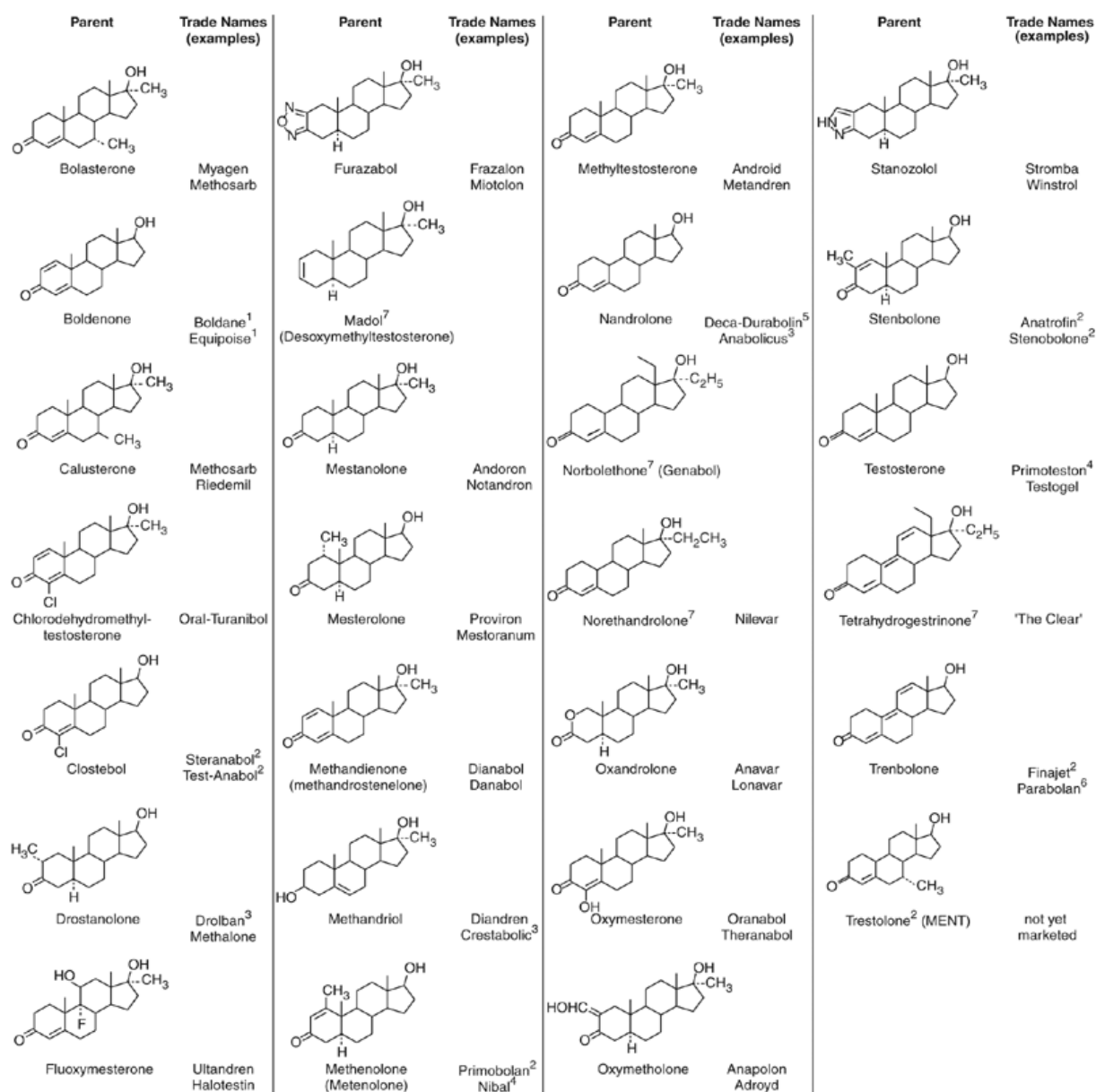


Fig. 2. Structures of testosterone and synthetic derivatives

Table 1. Anabolic:Androgenic Ratio for Selected Anabolic Drugs

Steroid	Route	Reference steroid	Activity		Index value
			Myotrophic	Androgenic	
Chloromethyl T	p.o.	17 α -MeT	0.5	0.10–0.15	3–5
Methandienone	p.o.	17 α -MeT	0.60	0.20	3
Methenolone acetate	p.o.	17 α -MeT	0.86	0.12	7
Nandrolone decanoate	par.	T propionate	3.29–4.92	0.41–0.31	12.1–10.6
Norbolethone ^a	par.	T propionate	3.44	0.15–0.17	20
Norethandrolone	par.	T propionate	0.77–1.0	0.06–0.38	2–16
Oxandrolone ^b	par.	17 α -MeT	3.22	0.24	13
Oxymesterone	p.o.	17 α -MeT	1.34	0.42–0.61	2.2–3.2
Oxymetholone	p.o.	17 α -MeT	3.20	0.45	7.1
Stanozolol	p.o.	17 α -MeT	2.0–3.7	0.33–0.52	6–10.6
T	p.o.	17 α -MeT	0.36	0.28–0.50	0.7–1.3

Mechanism of action and pharmacologic effects

AAS_s have relatively small molecules and can passively diffuse into cells of various tissues. No tissues are devoid of androgen receptors. These receptors belong to the family of nuclear receptor superfamily and different AAS_s bind to these receptors with different affinities, although all receptors distributed throughout the body possess the same binding affinity for a particular steroid (12). After binding to the receptor in target tissue and formation of hormone-receptor complex, AAS_s translocate to binding sites on chromatin, promoting gene transcription and subsequent synthesis of mRNA. Due to the environmental conditions such as the presence of different enzymes (e.g. 5 α -reductase and aromatase) and presence of receptors, AAS_s effects vary in different tissues. Enzyme 5 α -reductase seems to play an important role in converting AAS_s into female sex hormones (7). Young adolescents are more susceptible to androgen action of AAS_s, because they possess a higher number of cytosol androgen receptor (11). Recent studies also have shown that the expression of androgen receptors can be upregulated by exposure to supraphysiologic doses of AAS_s (12, 14).

Supraphysiologic doses of AAS_s can induce gain in muscle size and strength, even without concomitant exercise. At these doses AAS_s interact with various receptors, including progesterone, estrogen and mineralo- and glucocorticoid receptors. They mediate their anabolic action through competitive antagonistic action to the glucocorticoid receptors by preventing glucocorticoid's catabolic effect (7, 11, 12, 14). After administration of AAS_s, the circulating concentrations of thyroxine, cortisol, sex hormone, growth hormone and D-vitamin-binding globulin are decreased. It has also been suggested that AAS_s exert several complementary anabolic effects through pathways such as a psychoactive effect on the brain, glucocorticoid antagonism, stimulation of growth hormone (GH)

and insulin-like growth factor 1 (IGF-1) production (12, 19).

More than 100 synthetic derivatives of testosterone have been developed. They are well absorbed from the gastrointestinal tract, then undergo biotransformation during the hepatic first-pass metabolism and partly exerted via bile to the feces. Since they are potential targets for aromatization and reduction, have various biological properties (11). Their clinical indications include treating of hypogonadism, impotence, delayed puberty (in Turner's syndrome, etc...), catabolic disorders as muscle wasting and cachexia caused by various cancers and HIV infection, diaphragm atrophy due to catabolic-proteolysis effect of glucocorticoids in chronic obstructive pulmonary disease (COPD), osteoporosis, types of anaemia (such as aplastic anaemia, fanconi anaemia, myelofibrosis, etc), endometriosis and fibrocystic breast disease, alcohol hepatitis, wound and burn healing (by increasing collagen synthesis and the activity of dermal fibroblasts), renal failure (specially in patients on hemodialysis) (4, 9, 11, 12, 13). In general, ergogenic effects of these agents are resulted from an increase in muscle size and strength and reduced muscle damage, increase in protein synthesis, increase in lipolysis and body fat percent, increase in bone mineral density, increase in erythropoiesis, hemoglobin and hematocrit and increase in glycogen storage (9, 10).

AAS_s abuse

AAS_s are controlled substances in several countries, including Australia, Argentina, Brazil, Canada, the United Kingdom and the United states. Even so, they are readily available via the internet, black market and sport clubs. In the United states, the majority of substances come from Mexico, Russia, Romania and Greece, whereas in the European market come from countries within the European Union and Russia and sometimes from Thailand, Turkey, Egypt, India and Pakistan (10, 12).

As mentioned before, their beneficial effects on all sports demanding peak physical performance were noticed in the early 1950. It is impossible to estimate the extent of AAS_s use in 1950s and 1960s. The International Olympic Committee included AAS_s on a list of prohibited substances in 1975 and testosterone in 1982, however the percentage of positive doping test results in the summer Olympic Games during 1976-1988 varied between 0 and 2.9%. Due to the secretive nature of doping, estimating the extent of doping abuse in modern organized sports is difficult, but it is clear that throughout the world, the majority of positive doping test results are due to AAS_s abuse (10, 11).

The motive for AAS_s abuse is derived from performance enhancing and self-image improvement. Competitive athletes as well as recreational fitness athletes are aware of the adverse effects of them and consume antiestrogens and HCG to avoid these effects. Other self-administrated drugs among AAS_s abusers are GH, IGF-1, dopamine receptor agonists (bromocriptin), adrenergic β_2 -agonists, stimulants (ephedrine, amphetamine ...), thyroxine, finasteride, diuretics, insulin, oral antidiabetic drugs, aminoglutethimide, antiacne drugs and NSAIDs (11, 19). Multipharmacy (Polypharmacy) that has been reported in more than 95% of 500 abusers in a recent study, could potentiate the severity of adverse effects and may cause difficulty in the separation of side effects (10, 19).

Most of epidemiologic studies of AAS_s abuse have been made in adolescents and young adults, who are considered the most likely abusers. The non-medical use of AAS_s had increased by 50% of male adolescents between 1991 and 1999 in America. Results of several reports suggest a 3-12% prevalence of AAS_s use in Western world (11), and other surveys report that 2/7-2/9% of young American adults have taken AAS_s at least once in their life. Abuse percentage for bodybuilding clubs is estimated 15-30% (19).

According to the results from the 2003 monitoring study, 3/5% of high school seniors (males and females) have history of AAS_s use with a dramatic increase in females over the past few years (1). Abuse prevalence among females is more than 1% (9). Reported data in American high-school girls has been more than 7% in 2004 and it became a topic discussed during the 2005 congressional hearing in sports (5). NIDA (National Institute of Drug Abuse) report in 2007 was 2.3% of boys versus 0.6% for girls (17). There are contrary reports about the influence of public-health advertising, counseling and educational programs on reduction of the AAS_s abuse. Several reports indicate that drug abuse can be decreased by health promotion activities, such as group discussion and health and nutrition knowledge with early preventive efforts (18, 23), whereas in study on 26 subjects in Finland, despite that they followed for one year and received adequate information concerning their health status (all had cardiovascular problem), none of them discontinued substance abuse after the study (11).

Most users take AAS_s in a "cycling" pattern, meaning that athletes will use the drugs for several weeks or months interrupted by shorter resting periods. In addition, users also use agents in a "stacking" regimen in which they consume several different drugs simultaneously to increase the potency of each drug. They will use both oral and parenteral compounds. Often the athletes use drugs in a pyramid (step-up) pattern in which dosages are steadily increased over several weeks. Toward the end of the cycle the athlete will "step-down" to reduce the likelihood of negative side effects. At this point, some athletes will discontinue drug use or perhaps initiate another cycle of different drugs.

In stacking way may be used up to 40 times the recommended therapeutic dosage (10, 15, 17).

Adverse effects

In clinical dosages, AAS_s are well tolerated and their adverse effects are reversible. The severity and

frequency of adverse effects are variable and are related to factors such as type, dosage, use duration, individual response and sensitivity and gender. A survey of 500 abusers shows that nearly 100% of AAS_s users reported subjective side effects (19). AAS_s-induced adverse effects are mainly based on case reports and studies with controlled, a proper study design and matching control group have not been published. Since they have effects on several organ systems, a myriad of side effects can be found. In general the orally forms of AAS_s and 17 α -alkylated compounds have more side effects (11, 15).

Polypharmacy is an important factor. The major side effects associated with AAS_s use are discussed.

Cardiovascular system

In general, cardiovascular changes have been related to four mechanisms:

- 1- Atherogenic lipoprotein changes
- 2- Thrombogenic effects on clotting factors and platelets
- 3- Vasospasm effects on the vascular nitric oxide system
- 4- Direct myocardial toxicity (3).

Physical activity has beneficial effects on heart size, shape and function. Left ventricle (LV) mass is 45% greater in competitive athletes than sedentary controls, however, diastolic function in athletes' heart is generally normal, in contrast to pathological LV hypertrophy that is associated with impaired LV filling. Endurance sports develop larger LV cavity dimensions without a significant increase in wall thickness (eccentric hypertrophy) (11). Although the previous data have shown that LV remodeling is reversible after discontinuation of AAS_s use, present studies by echocardiography suggest the slight concentric LV hypertrophy and cardiovascular changes several years after discontinuation of AAS_s (22).

LV hypertrophy is an independent risk factor for cardiovascular morbidity and mortality and has been

linked to atrial fibrillation, ventricular arrhythmia and sudden cardiac death. AAS_s-induced LV hypertrophy changes diastolic function and is associated with concentric remodeling of LV hypertrophy. There are reports about occurrence of cardiac infarction development of ischemia and cardiomyopathy in AAS_s abusing bodybuilders (9, 10, 11). Although some of researchers have observed hazardous and remodeling effects on heart structure and function in animal studies, they have not attributed such effects in human studies (7).

The lengthening of QT interval among endurance athletes with AAS_s abuse history has been attributed to the increased automaticity. Lengthening of QT interval can generate dysrhythmia and increase the risk of ventricular and atrial fibrillation (3, 11).

Results of study in rats with cardiac ischemia suggest that nandrolone increases the risk of fatal arrhythmia and this event is dose-dependent (20).

Several pathophysiological and histopathological mechanism have been purposed to explain these cardiac events that include:

Ischemic events as a result of the disturbance in mitochondria, increased vascular response to norepinephrine and induction of cell adhesion (3), depressed contractile activity, increased lysosomal fragility (11), hypertension due to the inhibition of monoamine oxidase (MAO) in combination with the increased renal recovery of ions such as sodium and subsequent fluid retention (13), increased cardiac collagen content associated with activation of the local renin-angiotensin system (21) and even possible relation with simultaneous use of other agents such as GH (10).

AAS_s abuse cause harmful changes in lipoprotein profile with increased LDL level (by 40-50%) and decreased HDL level (by 40-70%). Triglycerides levels are decreased by the exogenous administration. Consistent increase in LDL levels might result in the atherosclerosis thrombus formation, coronary artery vasospasm and enhanced coagulation enzyme. The

reduction in HDL is due to a stimulation of hepatic triglyceride lipase (in males) and lipoprotein lipase (in females that regulate serum lipids) by 17α -alkylated compounds mainly (3, 9, 15). There is a report that AASs have a beneficial effect on serum Lp (a) levels, although the HDL/LDL-ratio is reduced. The alterations in the lipoprotein profile reverse after discontinuation of AASs (11).

Hepatic effects

Structure and function of liver as primary site of AASs clearance may be altered. These alterations include intrahepatic cholestasis, jaundice, hyperplasia, benign (adenoma's) and malignant (hepatocellular carcinoma) tumors and peliosis hepatis. Peliosis hepatis is a hemorrhagic cystic degeneration of the liver, which may lead to fibrosis and portal hypertension. Rupture of a cyst may lead to fatal bleeding (9, 15). It seems that hepatic cancers generally occur with higher frequency in males compared to females (10).

Many opinions have been raised based on case reports and conclusions may be contradictory. Although there are hazards particularly with oral products (17α -alkylated) in prolonged use (9, 10).

Some researches have reported the increase in plasma activity of liver enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), lactate dehydrogenase (LDH), whereas findings of gamma glutamyl transpeptidase (GGT) have been controversial. Therefore, the pre-abuse condition of the liver may be an important factor (10, 13, 15). AASs use also results in suppression of clotting factors II, V, VII and X as well as an increase in prothrombin time. In general, drug cessation results in complete recovery (13).

Reproductive and endocrine effects

The effects of AASs on the male reproductive system include reductions in the levels of endogenous testosterone, gonadotrophic hormones, sex hormone-binding globulin, reductions in testicle size, sperm

count and sperm motility, increase in abnormal sperm cells, decreased fertility and changes in libido. After discontinuation of AASs use the changes in fertility usually reverse within some months, however, the situation of hypogonadism may last for long periods (1, 10, 15).

Gynecomastia results from increased levels of circulating estrogens which are formed in males by peripheral aromatization and conversion of AASs. Increased levels of estrogens stimulate breast growth in males. In general, gynecomastia is irreversible and may require to be treated medically or surgically (13, 15).

Also, the incidence of benign prostatic hyperplasia (BPH) or its worsening is probable. In addition, the use of AASs in patients with underlying carcinoma of the prostate is absolutely contraindicated due to the potentiality for hormone-sensitive tumor growth (13).

AASs through increasing in circulating androgens will inhibit the production and release of LH and FSH, resulting in a decline in serum levels of LH, FSH, estrogens and progesterone. Thus AASs abuse in females can induce hirsutism, deepening of the voice, clitoris hypertrophy, breast atrophy, menstrual disorders or amenorrhea, and male pattern baldness (9, 15).

Other effects such as acne as well as hypertrophy of sebaceous glands, oily hair and skin and alopecia are frequently reported in both males and females (15).

AASs have also been shown to alter fasting blood sugar levels and decrease glucose tolerance and induce hyperinsulinemia due to probably hepatic effect or changes in insulin receptors that are reversible alterations (1, 13).

Thyroxine-binding globulin (TBG) and thyroid stimulating hormone (TSH) may be lowered whereas total T4 levels are lowered and free T4 levels remain normal (13, 15).

Psychological and behavioral effects

Historically low doses of AASs have been used to

treat depression and melancholia either as monotherapy or as adjuncts to standard treatment, but misuse of these agents has added a new term to the drug lexicon, "roids rage". Comparison of AAS_s abuser athletes with non-abusers have shown that their abuse is associated with higher incidence and prevalence of affective disorders and psychiatric symptoms such as manic-like presentations (defined by irritability, aggressiveness, euphoria, grandiose beliefs, hyperactivity and violence or dangerous behavior), acute psychosis, exacerbation of tics and depression, acute confusional-delirious states (6), hallucinations, paranoia, anxiety and sleeping disorders (15).

The severity of psychiatric adverse effects is dose-related. It has been demonstrated that 23% of users of medium dose (between 300-1000 mg/week of any AAS) and high dose (more than 1000 mg/week of any AAS) met the DSM-III-R criteria for a major mood syndrome (mania, hypomania, and major depression) and 3.4-12% developed psychotic symptoms.

The symptoms usually resolve within a few weeks after discontinuation of steroid use, although they may persist for as long as 1 month, even if adequately treated with antipsychotic medication (6).

These effects must be viewed as a social-medical problem, because in spite of methodological inadequacies of related studies, AAS_s-induced aggression and irritability (that are beneficial trait for competitive trainings) are clearly demonstrated with AAS_s use and there is claim of attempt murder during AAS-taking phase and also multipharmacy or stacking may increase the severity of violence symptoms (2, 24).

According the psychological studies, following factors are considered as a part of typical AAS_s abuser personality traits: poor self-esteem, poor school performance, higher socioeconomic state, poor body image, a familial history of drug abuse, history of aggression and violence, etc (6).

Behavioral mechanisms of AAS-induced effects are not clearly proved, although hypotheses have been supposed such as allosteric modulation of GABA_A receptor, changes of serotonin receptors and role of hypothalamic arginin-vasopressin system (6, 12).

AAS addiction is considered as a psychic as well physical addiction. Withdrawal symptoms are depression, fatigue, headache, muscle and joint pain, decreased sexual drive insomnia and suicidal thoughts and feelings, which could be named as "withdrawal syndrome".

As many as 23% of users reported major mood syndrome as a result of discontinuation of AAS. Androgen withdrawal is often associated with the desire to resume steroid consumption or "craving" (8, 13).

Human withdrawal mechanism may associated with decreased central dopaminergic activity. Administration of clonidine, tranquilizers, analgesics and antidepressant fluoxetine has been effective in treating of androgen withdrawal syndrome (8).

Musculoskeletal system and connective tissue

AAS_s may lead to premature epiphyseal plate closure through large production of estrogens in aromatization processes. There are reports about the risk of tendon injury, mostly in powerlifters, even the ligamentous ruptures may be due to the excessive loads. AAS_s may cause to the alteration of contractility of myofibrils and collagen fibers and biomechanical properties of tendons (9, 10).

Study in rats suggests that AAS_s abuse is associated with elevation in collagen synthesis and can impair tissue remodeling in tendons of rats undergoing physical exercise by inhibition of matrix metalloproteinase activity (16). Rhabdomyolysis, or acute skeletal muscle destruction may occur after use of AAS_s in combination with weight-training programs (9).

Other adverse effects

Reports of renal side effects are contradictory. High levels of serum urea, serum uric acid and hyperphosphatemia and possible nephrosclerosis with obstructive glomerulosclerosis have been reported (9).

AAS_s have also been associated with suppression of immune function, changes of haemostatic system (7), occurrence of Wilms' tumor (15), infections at the injection site of bacterial or fungal aetiology, increased risk of hepatitis and AIDS as a result of shared needles and syringes (11), increase in hematocrit and hemoglobin and possible polycythemia (13), and sleep apnea. Multiple drug abuse to 'counterbalance the side effect or to support the anabolic effects of AAS_s is also a serious consequence of AAS_s use that may lead to worse conditions. (15)

Conclusion

Although AAS_s use has been forbidden in organized sports nearly thirty years, their abuse remains one of the important problems as a widespread phenomenon in both athletic and nonathletic populations. Due to the secretive nature of their abuse and for ethical reasons, estimating of real prevalence of AAS_s use and the number of users are difficult. The major motive for their abuse is to enhance physical fitness and appearance. Despite evidence of increased risks of AAS_s, abusers are simply manve regarding the dangers of these substances. Although most of adverse effects seem to be reversible, particular concern is the increased risk of cardiovascular and hepatic events and effects on reproductive, endocrinological and psychological systems. AAS_s as well other performance enhancing supplements are widely advertised in fitness clubs and related websites and are available by low price on black markets. Thus, fundamental guidelines must be invented with the means of counseling and educational programs to provide warnings about potential dangers of AAS_s misuse without exaggerated or disregarded attitude.

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