Abuse of Supraphysiologic Doses of Anabolic Steroids

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Abstract: The following article is a literature review of supraphysiologic doses of anabolic-androgenic steroids (AAS). This article contains a brief review of the history of AAS, the chemistry of the varying forms of AAS, and proposed mechanisms of action. The article then focuses on how AAS are used in an illicit manner by the general population. Terms such as "stacking" and "pyramiding" are discussed. The article concludes by looking at the major detrimental side effects, such as liver damage and cardiovascular changes, which physicians may encounter when treating AAS abusers.

Key Words: anabolic steroids, psychiatric effects, pyramiding, side effects, stacking

In 1889, Charles E. Brown-Sequard, the famous physiologist, made the first public claims about the effects of anabolic-androgenic steroids (AAS). He announced that he had extracted a substance from dog and guinea pig testicles, which had increased his strength, improved his intellect, provided relief from constipation, and increased the arc of his urine. It was not until the 1930s that Butenandt isolated the first androgen of androsterone. By 1945, Paul de Kruif, in his book about testosterone, *The Male Hormone*, reiterated many of Brown-Sequard's claims. This book did much to educate both the scientific community and the lay public about AAS and their potential strength-enhancing effects. 3

By the 1950s, case reports of athletes (some of whom were still in high school) using anabolic steroids to improve their performance began to appear in the medical literature.³ By 1980, it was reported that one in five NCAA Division One athletes had used AAS at some point in their career.⁴ Anabolic-androgenic steroids had become such a problem that in

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1990 the Anabolic Steroid Control Act was passed, which made it a felony to possess or distribute AAS for nonmedical purposes. Around this time, it was estimated that there were more than 1 million people in the United States (of which 250,000 were still in high school), who spent upward of \$100 million per year in the pursuit of black market anabolic steroids.^{5,6}

The abuse of AAS is still rampant today, as evidenced by its mention in the 2004 State of the Union address by President Bush, the recent disqualification of 20 international weightlifters before the Olympic games in Athens, and the suspension of several Olympic athletes in Athens for "doping."

Basic Steroid Effects and Proposed Mechanism of Action

"Anabolic" refers to a compound that promotes anabolism or the building of complex chemical compounds from smaller simpler compounds.^{3,7} Anabolic effects range from

Key Points

- Anabolic steroid abuse has become a major problem in the United States, with more than 1 million individuals abusing these drugs.
- Specific pharmacology that permits the production of "designer" molecules has produced a vast underground market for these illicit substances.
- The metabolism of these classes specifically affects their side effect profiles and physiologic effects.
- Stacking occurs when abusers choose medications of different classes to neutralize or enhance certain desired effects.
- The majority of abusers begin use by age 16 years and obtain their drugs on the black market, with physicians supplying a significant number of these abusers.
- The abuse of these compounds is often associated with the abuse of other substances.
- All, when taken in supraphysiologic doses, can produce significant mental changes including irritability, aggressivity, euphoria, grandiose beliefs, hyperactivity, and reckless and dangerous behavior.

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increased muscle mass, decreased body fat, accelerated growth of bone before epiphysial closure, increased bone density, stimulation of erythropoiesis, and increase in heart, liver, and kidney size. The anabolic effects of steroids generally take place in the nonreproductive tissues such as muscle.

"Androgenic" refers to a substance having a masculinizing effect. The body changes attributed to the androgenic aspect of AAS include increased spermatogenesis, enlargement of genital size and function, and "male" body hair distributions (axillary, facial, and pubic hair). Other androgenic effects include laryngeal enlargement, vocal cord thickening, and the development of an increased sex drive and potency. 2,8-12

Steroids are tetracyclic cyclopenta[a] phenanthrene skeletal compounds that pass through cell membranes and bind to cytoplasmic receptors, forming a new complex that binds to DNA. Once bound to DNA, the steroid receptor complex starts a process that eventually leads to the production of proteins and other cellular structures.2 The end result is a positive nitrogen balance for cells. Despite the wide array of responses caused by different AAS compounds, all AAS bind directly to one identified androgen receptor (AR).^{2,13} The AR is encoded on the X chromosome and is a 120-kDa cytosolic protein. To date, only one cDNA for AR has been identified, but each AAS has a different binding affinity for this receptor, which varies from tissue to tissue in the body. 10 It is believed that this varying receptor affinity for specific intracellular environments partially explains the varying effects produced by different AAS.1

Since there are a limited number of AR, which are essentially saturated in males who have normal physiologic levels of testosterone, it has been hypothesized that a secondary mechanism exists by which AAS create a positive nitrogen balance when taken in excess. 1,2 One theory is that AAS are able to block or displace cortisol from glucocorticoid receptors, thereby inhibiting the catabolic effects of cortisol. 1,2,8,14 Cortisol is excreted at times when the body is under stress, such as during illness and physical exertion. It is this blockage of catabolism that may increase muscle mass. 15,16

Other proposed methods of regulation include downregulation of the myostatin gene, which is believed to be a negative regulator of muscle growth. In myostatin knockout animals, muscle growth is twice that of control animals. ¹⁷ In various cachectic and muscle-wasting states, such as AIDS-associated sarcopenia, aging, and bed rest, serum myostatin is increased. ^{18–20} When androgens naturally decrease, as in aging, myostatin levels increase. For this reason, it is thought that AAS may either directly or indirectly suppress the expression of myostatin. ¹

Anabolic-androgenic steroids also have a direct effect on the central nervous system. Brown-Sequard noted an "increased intellect" with steroid use. Anabolic-androgenic steroid users describe a "steroid rush" (ie, a sense of euphoria associated with a decreased awareness of fatigue). It has been hypothesized that this "steroid rush," along with increased aggression and drive, may help people improve muscle strength by increasing one's ability to exercise. 14,15,21,22

Types of Anabolic-Androgenic Steroids

The classic AAS is testosterone, which is metabolized into the active metabolites of dihydrotestosterone, androstanolone, estradiol, androsterone, and androstenedione. Testosterone has a short free-circulating half-life due to its rapid metabolism by the cytochrome P450 family of hepatic isoenzymes. To remedy this rapid metabolism, many artificial AAS, synthesized from testosterone's molecular backbone, have been designed to have longer circulating half-lives.

There have been more than 1,000 testosterone derivatives formulated. The most commonly used are shown in Table 1. The AAS fall into three categories of modification. Class A modification is esterification of testosterone at the $17-\beta$ -hydroxy position with varying carboxylic acid groups. This modification increases the lipophilic/hydrophobic properties of the AAS by decreasing the polarity of the molecule, which results in increased androgenic properties and slower absorption when given as an intramuscular injection. It is the long carbon chains in the esterification that result in the increased lipid solubility of the molecule. 1,8,24

Natural testosterone would need to be injected multiple times per week, but the class A anabolic-androgenic steroid derivatives only require intramuscular dosing once every 2 to 12 weeks, depending on the carboxylic acid groups added. After injection, the class A AAS are hydrolyzed by the body and are metabolically identical with endogenous testosterone. The levels of AAS peak shortly after class A injection and then gradually decline to baseline levels by the time of the next injection. Hetherolone acetate and testosterone undecanoate class A AAS are exceptions, as they can be given orally and either bypass the portal circulation or have slower liver metabolism.

Class B derivatives have undergone alkylation at the 17- α -hydroxy position, which results in a testosterone derivative that can be given orally with retarded hepatic degradation. The potency of these compounds as a group is weaker than injected testosterone or class A AAS. They have also been shown to cause hepatic toxicity and increase hepatic enzyme production, particularly complement 1 inhibitor. As α

Class C AAS derivatives undergo an alkylation modification of the A, B, or C rings of the steroid backbone. The alkylation of the steroid ring leads to similar properties as the class B AAS (ie, oral availability) but have decreased to nonexistent hepatic metabolism. ^{1,26} The class C compounds are excreted in the urine or feces either unmodified, as metabolites, or as conjugates. ¹ Class C derivatives can also undergo a class A esterification, becoming class AC analogs. These analogs can also be administered orally. ²⁶

Table 1. Common testosterone derivatives^a

Administered orally	Administered intramuscularly	Administered transdermally	
Fluoxymesterone	Boldenone undecylenate (Equipoise ^b)	Testosterone	
(Halotestin, Android-F, Ultandren)	Methenolone enanthate (Primobolan depot)	(Androderm, AndroGel, Testim, Testoderm)	
Mesterolone	Nandrolone decanoate (Deca-Durabolin)		
(Mestoranum, Proviron)	Nandrolone phenpropionate		
Methandienone, methandrostenolone	(Durabolin)		
(Dianabol)	Nandrolone undecanoate (Dynabolan)		
Methyltestosterone	Stanozolol (Winstrol-V ^b)		
(Android, Testred, Virilon)	Testosterone cypionate (Depo-Testosterone, Virilon IM)		
Mibolerone	Testosterone enanthate (Delatestryl)		
(Cheque Drops ^b)	Testosterone esters blends (Sustanon, Sten)		
Oxandrolone	Testosterone propionate (Testoviron, Androlan)		
(Anavar, Oxandrin)	Testosterone undecanoate (Andriol, Restandol)		
Oxymetholone	Trenbolone acetate (Finajet, Finaplix ^b)		
(Anadrol-50, Hemogenin)	Trenbolone hexahydrobencylcarbonate		
Stanozolol	(Parabolan)		
(Winstrol)			

[&]quot;Some foreign brand names are listed but are included because of the widespread illicit use of foreign steroid preparations in the United States.

There are generally three reasons why new testosterone derivatives are synthesized. The first is to enhance potency. The second is to increase the drug's anabolic characteristics while decreasing its androgenic side effects. To date, no "pure" or "clean" anabolic steroid has been identified or created. For some, the third reason is to make AAS that are difficult to detect by blood or urine testing. AAS that are difficult to detect by blood or urine testing. ABC Each modification not only changes the drug's androgenic/anabolic profile, but also changes its side effect profile.

Illicit Use of Anabolic Steroids

The Anabolic Steroids Control Act of 1990 made it a felony to possess or distribute AAS for nonmedical purposes.³ However, illicit anabolic steroid use among adolescents and adults remains a significant public health problem. 22,28,29 The prevalence of use by males in US high schools is estimated to be between 4 and 11%. 30-36 The rate of use for female high school students has been reported to be as high as 2.5%. 31,33,35,37 Mid 1990s data suggested that AAS use among male high school students was plateauing, but noted increasing incidence and prevalence among female students. 6,36 More recent data have suggested that male use may again be on the rise.31 Two thirds of AAS abusers reported that they began their abuse by age 16 years.³² Most AAS are obtained on the black market (85.2%), with physicians being responsible for illegally supplying 7.4 to 21% of users.^{5,32} Anabolic-androgenic steroids may also be obtained from other sources, such as veterinary drugs.²⁴

The major differences between medically used AAS and the recreational abuse of these drugs are the dosage and schedule of administration used by illegal users. Usually, medical usage is at a physiologic replacement level (eg, hypogonadism 6 to 10 mg/d), on a continuous basis, and with regular intervals of use.² Recreational users generally develop com-

plicated multidrug regimens (using oral and intramuscular preparations) that progressively increase in dose until 40 to 100 times physiologic levels are reached.^{8,17,19,36,38,39} This practice is referred to as "stacking." It is not uncommon for users to take multiple forms of AAS (five different drugs on average) from multiple classes of steroids to take advantage of the different pharmacokinetic properties of these drugs.^{3,15,24,40} The perceived physiologic basis for stacking is to maximize AAS receptor binding and to activate multiple steroid receptor sites. To date, no scientific research has shown that either of these effects occurs with stacking.³

Stackers will take supraphysiologic doses of anabolic steroids for 4 to 18 weeks, followed by a drug-free holiday period of anywhere from 1 to 12 months. ^{13,39} The purpose for the holiday is to minimize side effects, promote recuperation of various hormonal systems, and avoid detection during competition. ²⁸ Some abusers will try to taper off AAS at the end of a stacking cycle to reduce side effects and withdrawal, a practice called "pyramiding." Due to the intricate nature of these stacking regimens, many users have a "coach" who helps coordinate the schedule and drugs given. The coach and/or abuser may change the anabolic steroids used during the course of a stacking cycle to avoid tolerance if performance is perceived to plateau. ^{3,39} It has been estimated that the average teenager who uses AAS has gone through at least five cycles of stacking. ⁴¹

Anabolic-androgenic steroid users are often polysubstance abusers, using either traditional recreational drugs or misusing prescription drugs.⁴² The desire to "bulk up" can deter some AAS abusers from using other recreational drugs such as marijuana or heroin because they may interfere with training. Even those who avoid traditional recreational drugs are still enveloped in the drug culture to obtain their steroids (eg, suppliers or pushers), to find ways to administer them

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^bVeterinary compound.

(eg, finding large-gauge needles), and to develop the means to continue to use (eg, hiding and paying for their AAS).⁶ This immersion in the drug culture often leads to the abuse of other substances.^{3,6} Studies looking at AAS as a gateway drug have found that 29% of people who abuse both steroids and opioids started with steroids and were later introduced to opioids by the person who supplied them with the AAS.⁴³ DuRant et al⁶ found that 25% of AAS abusers shared needles to inject drugs and that a positive correlation existed between AAS abuse and the use and abuse of cocaine, injectable drugs, and marijuana.

For those who use steroids to enhance "bodily health," the use of other drugs to further enhance the AAS or decrease AAS side effects is common. Other drugs that are frequently abused as adjuncts include human growth hormone, which acts synergistically with AAS; human chorionic gonadotropin to block the testicular side effects of the anabolic steroids; diuretics to prevent water retention and improve visual muscle appearance (rippled effect); and antiestrogens such as tamoxifen to block gynecomastia. ^{6,10,44} To help hide the fact that steroids are being used, some AAS abusers will take antibiotics and antiacne medications to help prevent testosterone-induced acne, which often involves the face, neck, and torso.

Health Effects of Supraphysiologic Doses of AAS

Because their use is illegal, reports of side effects associated with AAS abuse are difficult to define with any precision, as the patient is often unaware of what or how much AAS they are actually using. 12 Anabolic-androgenic steroid abusers may take steroid preparations that were not meant for human consumption (eg, veterinary medication). This makes it difficult to determine if side effects are due to the hormone or to the carrier medium. For ethical reasons, giving super high doses of AAS to induce side effects cannot be studied in laboratory settings. Data defining cumulative effects caused by stacking remains speculative and is derived from case reports and medical literature from lower level doses. 11,39 Side effects can be as benign as acne or fluid retention and extend to more distressing effects such as gynecomastia, decreased high-density lipoprotein (HDL), and sleep apnea. Extreme side effects can lead to lethal complications such as liver failure and the development of certain cancers^{9,45} (Table 2).

The alkylated AAS (class B and class C) are highly hepatotoxic, causing hepatocellular and intrahepatic cholestasis, which can lead to hepatic failure. 24,46 Other hepatic effects seen with AAS abuse include peliosis hepatis (which can also occur with replacement doses), hepatocellular adenoma, and hepatocellular carcinoma. 47 Other liver changes include cholestasis, subcellular changes of hepatocytes, hepatocellular hyperplasia, and general hepatic damage evident by increased alkaline phosphatase, lactate dehydrogenase, as-

Table 2. Possible complications of supraphysiological doses of anabolic steroids^a

Acne	Hypothyroidism	
Addiction/dependency	Increased LDL cholesterol	
Aggression	Infertility	
Alopecia	Libido changes	
Azoospermia	Masculinization (females)	
Cardiac arrhythmias	Mood swings	
Cholestatic jaundice	Myocardial hypertrophy	
Decreased HDL cholesterol	Oligospermia	
Decreased testicular size	Peliosis hepatis	
Depression	Pituitary axis changes (decreased FSH, LH, GRH)	
Erythrocytosis		
Genital enlargement (eg, clitoromegaly)	Psychosis	
Gynecomastia	Stroke	
Hepatocellular adenoma	Tendon weakness/rupture in adolescents	
Hepatocellular carcinoma	Thrombocytopenia	
Hypertension		

[&]quot;HDL, high-density lipoprotein; LDL, low-density lipoprotein; FSH, follicle-stimulating hormone; LH, luteinizing hormone; GRH, gonadotropin-releasing hormone.

partate aminotransferase, alanine aminotransferase, and conjugated bilirubin.^{2,27,46} Some growths, initially believed to be hepatocellular carcinomas, were found to be benign hyperplastic lesions, which regressed with the discontinuation of AAS abuse.^{47,48}

Anabolic-androgenic steroids taken at supraphysiologic doses also produce cardiovascular side effects. ^{11,49,50} The alkylating agents, such as stanozolol, lower the HDL by approximately 33%, particularly HDL₂, which is reduced 23 to 80%. ^{24,51} The effect of testosterone is much less dramatic, with only an approximately 9% reduction in HDL. ⁵¹ The alkylating AAS have also been shown to increase hepatic triglyceride lipase activity between 21 to 123% and low-density lipoprotein by as much as 29%, whereas testosterone has been shown to decrease low-density lipoprotein by 16%. ^{24,51}

Several case reports document myocardial infarction and stroke in 20- to 30-year-old weightlifters who used AAS. ^{52,53} This increased risk for myocardial infarction and stroke is attributed to the increased platelet count and platelet aggregation that occurs in people who abuse AAS. ^{54–56} Testosterone, even at concentrations in which it does not effect thrombus risk, can potentiate cocaine's effects on both the endothelium and platelet function. Therefore, the often reported concomitant use of testosterone and cocaine increases the risk of thrombus, stroke, and myocardial infarction. ⁵⁵ Steroids also cause hypertrophy of the myocardium, which

also increases the likelihood of arrhythmias, sudden death, systolic and diastolic hypertension, and myocardial infarction. ^{39,44}

Whereas muscle and bone strength are increased by AAS, an interesting and almost paradoxical effect of high-dose AAS use is decreased tendon strength caused by the dysplasia of collagen fibrils. ^{11,57–59} The net result is that people who abuse steroids to gain strength are at an increased risk for development of either short-term or long-term disabling tendon ruptures. Several studies document the increased risk of rare triceps, biceps, and bilateral quadriceps ruptures in AAS abusers. ^{60–62}

When AAS levels are elevated, they undergo aromatization, being converted by fat and other cells to estrogens in peripheral tissue.^{2,39} This rise in estrogen levels can produce either a reversible or irreversible gynecomastia in males.^{2,3,30} In females, elevated AAS levels result in menstrual irregularities and breast atrophy. There can also be permanent virilizing effects such as male-pattern baldness, deepened voice, hirsutism, and clitoromegaly.^{2,30,63}

Pope and Katz⁶⁴ noted that anabolic steroids produce clear psychiatric effects, particularly in individuals using excessive doses (more than 1,000 mg/wk) of these compounds and stacking the drugs. The most prominent psychiatric features were manic-like presentations defined by irritability, aggressivity, euphoria, grandiose beliefs, hyperactivity, and reckless or dangerous behavior.²² Other presentations have included the development of acute psychoses, exacerbation of tics, and the development of acute confusional states.¹¹ Individuals using high doses over prolonged periods may undergo steroid withdrawal with the development of depressive symptoms, anhedonia, fatigue, impaired concentration, and even suicidality. It has been noted that these withdrawal effects may contribute to a syndrome of dependence.⁶⁵

Summary

Anabolic-androgenic steroids are dangerous recreational drugs that are frequently forgotten by physicians, who are generally more concerned about the abuse of other illicit substances such as heroin and cocaine. It is hoped that this review will give physicians information to help them understand AAS, their mechanism of action, frequency and population of use, and serious and sometimes life-threatening complications. ^{12,38,66}

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Abuse of supraphysiologic doses of anabolic. steroids. South Med J 2005;98(5):550–5. [26] Hartgens F, Kuipers H. Effects of androgenic–anabolic steroids in. athletes. Sports Med 2004;34(8):513–54. Effects of supraphysiologic doses of. testosterone on mood and aggression in normal men. Arch Gen Psy The subjects who received steroids did get a supraphysiologic dose of testosterone, meaning the dose was higher than what the body would normally produce or higher than what one would receive from testosterone replacement therapy. For comparison: A male receiving TRT from his doctor may get around 100 mg. per week to bring his T levels up to "high normal." Firstly let me start by saying that No doses of anabolic steroids is better than even low doses. But to answer your question, yes low doses are relatively safe than high dose. where cases of high dosage are present that's when you see bad sides. if you only use it and don't abuse then you should be fine provided you have done your research and do your homework. Respect it for what it is and don't misuse it. Original Editor - Lester Ryan Top Contributors - Kylie Volk, Matthew Wolfe, Christine Beavers, Marilyn Kozlowski and Ryan Lester. Anabolic-androgenic steroids (AAS) abuse is often associated with a wide spectrum of adverse effects. These drugs are frequently abused by adolescents and athletes for aesthetic purposes, as well as for improvement of their endurance and performance.