Current Concepts in Anabolic-Androgenic Steroids

Nick A. Evans,* MD
From the UCLA-Orthopaedic Hospital, Los Angeles, California

Anabolic-androgenic steroids (AAS) are synthetic derivatives of testosterone. According to surveys and media reports, the legal and illegal use of these drugs is gaining popularity. Testosterone restores sex drive and boosts muscle mass, making it central to 2 of society's rising preoccupations: perfecting the male body and sustaining the male libido. The anabolic effects of AAS have been questioned for decades, but recent scientific investigation of supraphysiologic doses supports the efficacy of these regimens. Testosterone has potent anabolic effects on the musculoskeletal system, including an increase in lean body mass, a dose-related hypertrophy of muscle fibers, and an increase in muscle strength. For athletes requiring speed and strength and men desiring a cosmetic muscle makeover, illegal steroids are a powerful lure, despite the risk of subjective side effects. Recent clinical studies have discovered novel therapeutic uses for physiologic doses of AAS, without any significant adverse effects in the short term. In the wake of important scientific advances during the past decade, the positive and negative effects of AAS warrant reevaluation. Guidelines for the clinical evaluation of AAS users will be presented for sports medicine practitioners.

Keywords: anabolic steroids; testosterone; androgen; anabolism; athletic performance; doping

In 1991, data from the National Household Survey on Drug Abuse indicated that there were more than 1 million anabolic-androgenic steroid (AAS) users in the United States and that the lifetime use was 0.9% for males and 0.1% for females. Despite the fact that AASs were added to the list of Schedule III Controlled Substances in 1990, recent data suggest that AAS use has increased. Current estimates indicate that there are as many as 3 million AAS users in the United States and that 2.7% to 2.9% of young American adults have taken an AAS at least once in their lives.63 Surveys in the field indicate that AAS use among community weight trainers attending gyms and health clubs is 15% to 30%.13,49,69 Furthermore, two thirds of AAS users are noncompetitive recreational body builders or nonathletes, who use these drugs for cosmetic purposes rather than to enhance sports performance. An estimated 10% of AAS users are teens, and the prevalence of AAS use among American adolescents is 3% to 12% in males and 0.5% to 2% in females.22,45,90 Approximately 375,000 adolescent males and 175,000 females have used an AAS at least once during their lives.103 Surveys indicate that AAS use among National Collegiate Athletic Association athletes is approximately 5% to 14%.59,72

Despite the fact that athletes have used AAS for half a century, the anabolic effects of AAS have long been the subject of scientific debate among the medical profession. In retrospect, previous studies were poorly designed and failed to recognize a key concept: that athletes were self-administering supraphysiologic doses of testosterone. During the past decade, careful scientific study of suprapharmacologic doses supports the anabolic efficacy of these AAS regimens. Furthermore, recent years have seen an increasing interest in the medical use of AAS for the treatment of hypogonadal men, age-related sarcopenia, and HIV-related muscle wasting.98 An estimated 4 million American men take doctor-prescribed testosterone replacement therapy, and as a result of the growing trend in both the medical and nonmedical use of AAS, androgen sales in the United States are rising 20% to 30% each year.

The purpose of this Current Concepts article is to provide an up-to-date overview of AAS, summarizing the recent advances relevant to the orthopaedic sports medicine specialist. Emphasis is placed on the anabolic effects of AAS on the musculoskeletal system, the medical and nonmedical use of these drugs, their side effects, and the clinical evaluation of a suspected AAS user.

PHYSIOLOGY

Testosterone is the primary male hormone synthesized in the testes. It serves distinct functions at different stages of life. During embryonic life, androgen action is central to the development of the male phenotype. At puberty, the hormone is responsible for the secondary sexual characteristics that transform boys into men. Testosterone regulates many physiologic processes in the adult male including...
Anabolic-Androgenic Steroids

Muscle protein metabolism, sexual and cognitive functions, erythropoiesis, plasma lipids, and bone metabolism. 

During adult life, the average male produces approximately 7 mg of testosterone daily, about 2500 mg of testosterone each year, and a total of 130 g by 75 years of age. 

The normal range of plasma testosterone in males is 300 to 1000 ng/dl, but the average value declines by age 80 to approximately 50% of that at age 20 years. 

In females, the circulating testosterone levels are typically about 10% of those observed in men.

AASs are synthetic derivatives of the male hormone testosterone, manufactured to maximize anabolic and minimize androgenic effects. 

AAS formulations may be administered orally, parenterally by intramuscular injection, and transdermally by patch or topical gel. The active ingredient, testosterone, has several possible metabolic derivatives. 

First, it binds to the androgen receptor (AR) in target tissues to exert its androgenic and anabolic effects. 

Second, it is 5α-reduced in some target tissues (including skin and liver) to dihydrotestosterone, which also acts on the AR. Finally, it can be aromatized to estradiol to exert estrogenic activities.

Chemical modifications of testosterone have been useful pharmacologically to alter the relative anabolic-androgenic potency, slow the rate of inactivation, change the pattern of metabolism, or decrease the aromatization to estradiol.

Most orally active AAS preparations are 17α-aliphatic derivatives of testosterone that are relatively resistant to hepatic degradation. 

Esterification of the 17β-hydroxyl group makes the molecule more soluble in lipid vehicles used for injection and, hence, slows the release of the injected steroid into the circulation. The common formulations of synthetic testosterone are shown in Table 1. All of the listed drugs possess both anabolic and androgenic activity; none are absolutely selective. Testosterone has an anabolic:androgenic ratio of 1, whereas the ratio for nandrolone is 10 and that for stanozolol is 30. However, all AASs are virilizing if administered for long enough, at high enough doses.

| TABLE 1 | Anabolic-Androgenic Steroids in Common Use |
|-------------------------------------------------|
| Oral Agents | Injectable Agents |
| 17α-alkyl derivatives | 17β-ester derivatives |
| Methandrostenolone | Testosterone esters: blend, cypionate, enanthate, heptylate, propionate |
| Methyltestosterone | Nandrolone esters: decanoate, phenpropionate |
| Oxandrolone | Boldenone |
| Oxymetholone | Methenolone |
| Stanozolol | Trenbolone |
| Ethylestrenol | Stanozolol |
| Fluoxymesterone | Dromostanolone |
| Danazol |

Anabolic Efficacy

Anabolism is defined as any state in which nitrogen is differentially retained in lean body mass through the stimulation of protein synthesis and/or a reduction in protein breakdown. 

There is a growing body of evidence that AASs have positive anabolic actions on the musculoskeletal system, influencing lean body mass, muscle size, strength, protein metabolism, bone metabolism, and collagen synthesis.

Skeletal muscle is a primary target tissue for the anabolic effects of AAS. Supraphysiologic doses of testosterone enanthate administered to healthy young men over periods lasting 10 to 20 weeks increase lean body mass, muscle size, and strength, with or without exercise. 

The observed effects of testosterone and strength training are additive.

The testosterone-induced increase in muscle size is due to a dose-dependent hypertrophy that results from an increase in cross-sectional areas of both type I and type II muscle fibers and an increase in myonuclear number. 

Evidence suggests that these morphometric effects are the result of a testosterone-induced increase in muscle protein synthesis. 

The testosterone-induced increase in strength may be the result of muscle fiber hypertrophy. However, strength increases may also reflect changes in muscle architecture because testosterone-treated muscles exhibit an increase in muscle pennation—a finding typically associated with high-force, low-velocity contractions. 

AASs have also been shown to improve exercise tolerance and the adaptability of muscle to overload by protecting against muscle fiber damage and increasing the rate of protein synthesis during recovery. 

Collagen and bone are also target tissues for the anabolic actions of AAS. In soft connective tissues, AASs enhance collagen synthesis in a dose-dependent manner. 

In bone, testosterone supplementation increases bone mineral density via a direct suppressive effect on osteoclasts.

Mechanism of Action

The anabolic effect of AAS is mediated primarily by ARs in skeletal muscle. 

The AR regulates the transcription of target genes that may control the accumulation of DNA required for muscle growth. It was previously thought that ARs are saturated at physiologic levels of testosterone and that providing supplemental exogenous testosterone offered no additional benefit. However, recent studies demonstrate that ARs can be up-regulated by exposure to AAS and that AR number is increased by strength training. 

This suggests a possible mechanism by which supraphysiologic doses of AAS combined with exercise might complement each other.
It has also been suggested that AASs exert several complementary anabolic actions, including a psychoactive effect on the brain, glucocorticoid antagonism, and stimulation of the growth hormone (GH) insulin-like growth factor-1 (IGF-1) axis. The behavioral effects of AAS may influence training intensity, thus indirectly increasing muscle size and strength. ARs are widely distributed throughout the brain, and testosterone exhibits diverse effects on several central nervous system neurotransmitters. High-dose AAS administration in normal volunteers increases euphoria, energy, and sexual arousal, and the cerebrospinal fluid of testosterone-treated men contains higher levels of 5-hydroxyindoleacetic acid that correlates significantly with AAS-related effects.

An anticycatabolic mechanism has also been proposed for the anabolic effects of AAS, but because testosterone can increase net protein synthesis without slowing protein degradation, the specific contribution of glucocorticoid antagonism has not been demonstrated equivocally. Testosterone may also influence anabolism via a direct induction of GH and IGF-1.

THERAPEUTIC USES

A number of clinical studies using a variety of experimental designs have shown that the potent anabolic effects of AAS have positive benefits to various patient populations. Physiologic replacement doses of testosterone have been used therapeutically to:

- restore hormone levels in hypogonadal men, thereby increasing fat-free mass, muscle size and strength, and bone density;
- improve mood and alleviate depression;
- increase body weight, muscle mass, and strength in eugonadal patients with secondary wasting syndromes, such as infection with HIV, when maintaining lean body mass may be beneficial for long-term survival; and
- augment muscle mass in older men and prevent age-related sarcopenia that contributes to frailty and falls.

Future Applications

A more widely accepted use of androgen therapy has been hampered by the lack of orally active preparations with good efficacy and safe profile. Progress has been limited in developing synthetic molecules that could separate the desired anabolic effects from other androgenic effects that were undesirable or had dose-limiting effects. A new class of molecules is currently under investigation. The so-called selective androgen receptor modulators exhibit tissue specificity in targeting the AR. In the future, it is likely that testosterone derivatives will be further tested for a broad range of medical conditions.

In orthopaedic sports medicine, we might anticipate the novel use of AAS as adjuvant medical therapy in fracture healing, soft tissue healing, or postoperative rehabilitation.

Recent studies demonstrate that AASs promote the healing of muscle contusion injury and that AASs can reduce immobilization-induced muscle atrophy. Low-dose AASs have also been shown to improve functional outcome in elderly women after hip fracture, exhibiting a beneficial effect on muscle mass and bone mineral density.

ATHLETIC USE

Information on the self-administered AAS used nonmedically to enhance athletic performance or improve physical appearance is relatively sparse. Several observational studies have surveyed the unsupervised drug habits of AAS users in “natural” settings. This kind of study is subject to selection bias because AAS users are recruited on a voluntary basis, and information bias may arise when the participants recall their experience. Nevertheless, field studies of AAS users are a valid source of information regarding self-administered AAS regimens.

The larger observational studies of AAS users indicate that drug regimens follow a typical pattern. Combinations of different oral and injectable AASs are “stacked” to create a mega-dose regimen that is self-administered during drug “cycles” lasting 4 to 12 weeks. In a survey of 100 male AAS users, the drug dosages ranged from 250 mg to 3200 mg per week of testosterone or its equivalent. Fifty percent of the AAS users in this sample reported using a weekly dose of at least 500 mg. To achieve these supraphysiologic doses, 88% of AAS users in this sample combined 2 or more different types of AAS—a process known as stacking. Some bodybuilders who chose to be precise with their dosages reported calculating their dosages using the following formula: 1 mg of steroid per kilogram of body weight per day. In another field study of 88 AAS users, 28% reported using at least 1000 mg of testosterone or its equivalent per week.

In most surveys, the duration of steroid administration or steroid cycle lasts between 4 and 12 weeks. The time interval between steroid cycles is more variable. Regular users allow a 4- to 6-week drug holiday to “clear the system,” whereas less frequent users may remain drug-free for months. In 1 survey, approximately half of the sample reported that their total annual AAS use was less than 6 months, whereas the other half used AAS for more than 6 months each year. Three of the 100 AAS users surveyed admitted to continuous steroid use for 52 weeks of the year.

The most commonly used AASs are listed in Table 1. Two recent surveys indicate that the majority (76%-96%) of AAS users self-administer injectable (intramuscular) formulations of AAS. Sample self-administered AAS regimes of new and veteran users are shown in Table 2.

Drug use by AAS users is not confined to anabolic steroids. Up to 90% of AAS users have a palate for polypharmacy, taking a mix of muscle-shaping drugs, in addition to stacking different brands of steroids. These “steroid-accessory” drugs are used for a variety of reasons and can be grouped according to their desired effect (Table 3). Some of these accessory drugs are potentially...
more dangerous than AAS; the unsupervised use of insulin, diuretics, and thyroxine can precipitate a number of medical emergencies.

NEGATIVE EFFECTS

Historically, the side effects of AAS use have been overstated. Serious health problems are rare, and the more common adverse effects are benign and reversible. The incidence of complications associated with the nonmedical use of AAS as performance-enhancing drugs is unclear because the denominator of drug use in athletes is not well defined. However, data from larger observational studies suggest that the majority (88%-96%) of AAS users experience at least 1 minor subjective side effect, including acne (40%-54%), testicular atrophy (40%-51%), gynecomastia (10%-34%), cutaneous striae (34%), and injection site pain (36%). Recent prospective clinical studies report a good safety profile for pharmacologic and suprapharmacologic doses of AAS when used in the short term. With the exception of a few reversible laboratory abnormalities—decreased HDL, elevated hemoglobin, and raised liver enzymes—high doses of AAS administered for periods of up to 20 weeks failed to demonstrate any significant systemic toxicity.

The potential adverse effects of AAS can be divided into several categories, including cardiovascular, hepatic, endocrine/reproductive, behavioral, dermatologic, and injection related (Table 4).

### Cardiovascular

Several AAS-induced adverse cardiovascular effects have been reported, including hypertension, left ventricular hypertrophy (LVH), impaired diastolic filling, arrhythmia, erythrocytosis, altered lipoprotein profile, and thrombosis. Although the incidence of AAS-induced adverse cardiovascular events is unknown, surgeons should be aware of their potential for increasing the perioperative risk in athletes using AAS who are undergoing elective surgery.

### Hepatic

AAS can induce elevations in liver enzymes (alanine- and aspartate-aminotransferases), but this effect is typically seen with orally administered 17-alkylated AAS that exhibit high first-pass effects in the liver.

### Dermatologic

Dermatologic changes such as acne, striae, alopecia, and hirsutism are induced by the action of dihydrotestosterone on ARs in skin and sebaceous glands. High doses of AAS cause acne by increasing skin surface lipids and the cutaneous population of propionibacteria acnes. Cutaneous striae are the result of rapid gains in body mass, in which the skin is unable to accommodate the rate of stretch, and a secondary effect that AAS may have on collagen reducing skin elasticity.
Exogenous AAS administration produces a dose-dependent depression of luteinizing hormone and follicle-stimulating hormone via the negative feedback loop of the hypothalamic-pituitary-gonadal axis. The adverse endocrine effects are gender specific. In males, this endocrine suppression can lead to hypogonadotrophic hypogonadism, testicular atrophy, reduced sperm count, decreased sperm motility, abnormal sperm morphology, infertility, and changes in libido. These effects generally worsen with larger doses of AAS taken for longer periods of time. This AAS-induced hypogonadal state is transient and reversible after discontinuation of AAS. However, restoration of hypothalamic-pituitary homeostasis, endogenous testosterone, and spermatogenesis takes between 3 and 12 months, and AAS-induced hypogonadism may require treatment with human chorionic gonadotrophin.

AAS can also produce feminization (gynecomastia) in males, from the aromatization of exogenous testosterone to estrogen metabolites.

Female-specific side effects of AAS include hirsutism, increased facial hair, voice deepening, clitoral hypertrophy, oligomenorrhea, amenorrhea, reduced breast tissue, and male-pattern baldness. Even after the discontinuation of AAS, some of these changes, such as a deeper voice, facial hair growth, and loss of scalp hair, may be permanent and devastating.

Behavioral

AASs have been negatively associated with depression, mania, psychosis, and aggression but have also been used therapeutically to improve mood and alleviate depression. Placebo-controlled trials indicate that at least 5% of AAS users will have manic or hypomanic reactions, and the likelihood of psychiatric effects are increased with prior psychiatric history, alcohol, and other drug abuse. A withdrawal syndrome has been described on discontinuation of AAS that can persist for several months. Withdrawal-type symptoms including reduced muscle size and strength, fatigue, depressed mood, and reduced libido can affect up to 88% of AAS users. Such symptoms generate a strong desire to resume AAS administration (craving), leading to drug habituation.

Injection Related

In addition to the pharmacologic side effects of AAS, complications also result from the injection technique used in self-administration. Infective complications usually result from nonsterile injection technique, reusing needles, sharing needles, sharing multidose vials, and contaminated drugs. Infections reported with AAS injection include bacterial abscesses, septic arthritis, septic shock, and cross infection with blood-borne pathogens HIV, hepatitis B, and hepatitis C. Other injection complications arise from chronic needle stick injury or poor injection technique. Frequent repeated injection into the same site can result in inflammation, intramuscular fibrosis, dystrophic calcification, and oil-induced granuloma. Misplaced injections have resulted in needle stick injury to the sciatic, radial, and axillary nerves.
Tendon Injury

Tendon rupture has been linked with AAS use on the basis of a small number of published case reports, and it has been suggested that these drugs predispose to tendon rupture by altering collagen structure. AASs appear to induce reversible changes in the biomechanical properties of tendon producing a stiffer, less elastic tendon, but the ultimate strength of the tendon is unaffected. Although AASs increase tendon stiffness, no consistent AAS-induced ultrastructural or biochemical alterations have been found to account for the changes in biomechanical properties, and distinction should be made between loss of elasticity and actual tendon rupture. It is possible that the rapid strength adaptations produced by AAS in skeletal muscle are not simultaneously matched by slower adapting, less vascular tendon structures, making tendons the weakest link in the chain.

Long-Term Health Risks

The health risks associated with long-term therapeutic doses of testosterone and chronic supraphysiologic doses of AAS are unknown. With chronic AAS use, doses tend to increase and cycles become longer and more frequent, until some athletes take the drugs almost continuously. The most severe consequences of long-term AAS use may be on the cardiovascular system. Pathological AAS-induced left ventricular hypertrophy, impaired diastolic filling, and arrhythmia may lead to an increased risk of myocardial infarction and sudden death. The risk of mortality among chronic AAS users is reported to be 4.6 times higher than non-AAS users. Although AASs have been proposed as etiologic factors for some cancers, case reports linking these drugs with hepatic tumors, renal carcinoma, and testicular tumors are rare. There are no reports linking AAS with prostate cancer, and androgen treatment in older men does not induce significant increases in prostate-specific antigen.

CLINICAL GUIDELINES

Evaluation of potential, suspected, or known AAS users should include a specific history, physical examination, and laboratory testing. Young men who participate in weight training, bodybuilding, or sports that require strength and power are at highest risk for AAS use. A high index of suspicion is warranted during the clinical evaluation of these individuals. Fearing the possible legal consequences or a competitive ban, individuals may not admit to using these drugs.

History

The drug history should be taken in a systematic manner. Begin by inquiring about the use of nutritional supplements and over-the-counter ergogenic aids. The use of ephedra, creatine, and pro-hormones like androstenedione commonly precedes or accompanies AAS use. Then, ask if the patient knows other people who use AAS because athletes at high risk of using AAS are more likely to know other users than low-risk nonusers are. Next, the clinician should ask whether the patient has ever tried AAS. If there is a positive history of current or previous AAS use, a detailed drug history should ensue. It is important to establish the athlete’s self-administered drug regimen, documenting the quantity of AAS, weekly dosages, relative durations of the AAS cycles and off-cycles, and approximate date when the athlete first began using AAS. It is important to distinguish the hypogonadal or aging male receiving low-dose pharmacologic testosterone replacement from the athlete abusing higher suprapharmacologic doses of AAS. The latter individual is at greater risk of AAS-related complications. Finally, because the majority of AAS users have a palate for poly-pharmacy, ask about the use of other performance-enhancing drugs, such as GH (Table 3). The clinician should also undertake a systematic inquiry regarding the common subjective side effects of AAS use, such as acne, gynecomastia, and so forth.

Physical Examination

When a physician suspects chemical enhancement in an athlete with pronounced skeletal muscle hypertrophy, there are several physical signs that point a finger toward AAS use. A simple, strategic physical evaluation is all that is required to detect an anabolic steroid user (Table 5). In the well-muscled athlete, the physician should look for acne, gynaecomastia, and cutaneous striae in the deltopectoral area. Four out of every 5 steroid users exhibit at least 1 of these physical side effects of AAS. If, in addition, the physician discovers needle-stick marks (in the buttocks, thighs, or deltoid) and testicular atrophy, the diagnosis of AAS use is a slam-dunk. The female AAS user may exhibit muscular hypertrophy, hirsutism, male-pattern baldness, voice deepening, breast tissue atrophy, or clitoral hypertrophy.

Management

AAS users may present to an orthopaedic sports physician with symptoms relating directly to their drug abuse or with unrelated sporting injuries or trauma. Common AAS-related problems manifest as dermatologic (acne,
gynecomastia, injection related), endocrine (testicular atrophy; decreased libido, infertility), or psychiatric symptoms (mania, withdrawal, depression).

During preoperative evaluation, a suspected or positive history of AAS use has special relevance. An apparently healthy AAS user may be at increased risk of complications during the perioperative and postoperative period, and a high index of suspicion is key. It is advisable for athletes with a positive history of AAS use to undergo medical clearance before surgery. These individuals may exhibit cardiac abnormalities such as hypertension, left ventricular hypertrophy, impaired diastolic filling, and rhythm irregularities. A raised hematocrit and potential for hypercoagulopathy places AAS users at risk of adverse circulatory events. Altered lipoprotein profiles and liver enzyme changes may also be relevant. It is also important to be aware of the high rate of poly-pharmacy among AAS users.27 Nine out of 10 AAS users are likely to be taking other drugs in addition to AAS, including stimulants (ephedra, amphetamine, cocaine), anabolic agents (GH, insulin, IGF), recreational drugs (methyleneoxymethylamphetamine, opiates), and other miscellaneous drugs (diuretics, thyroxine). Patients should be advised to stop all performance-enhancing drugs, herbal supplements, and nonprescribed medications prior to elective surgery.

To identify potential perioperative risks, the preoperative workup should include a detailed drug history; a complete physical examination; blood work, including CBC and liver function; and an EKG (Table 6). Abnormal findings may require further investigation and rectification prior to elective surgery under general anesthesia. Discussing the concerns with the patient will provide an incentive for the individual to discontinue their drug use.

Counseling the patient regarding the risks of AAS use is a valuable health education tool during the physician-patient consultation. The physician should make the athlete aware of the high risk of short-term subjective side effects that affect 4 out of 5 AAS users. Common subjective symptoms such as acne, gynecomastia, decreased libido, and alopecia may serve as a more potent deterrent to drug use than the less common, subclinical long-term risks. AAS use by adolescents and females should be strongly discouraged because of the high risk of irreversible complications even with short-term use. Several other suggestions may be of benefit to adult male AAS users. For instance, reducing the dose and duration of AAS use can help minimize the risk of complications. Weekly doses of 600 mg of testosterone or its equivalent for cycles lasting less than 12 weeks appear to cause few side effects during scientific studies. Furthermore, esters of testosterone that possess powerful androgenic properties are more likely to induce a potent insult to the hypothalamic-pituitary axis than other less androgenic formulations. Both the physician and patient should also recognize the risk of withdrawal symptoms on cessation of AAS use and how this leads to a physical dependence, habituation, and long-term AAS usage. A useful axiom is, the bigger the dose, the bigger the muscle, the bigger the problem.

**TABLE 6**

| Laboratory Abnormalities in Anabolic-Androgenic Steroid (AAS) Users
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**REFERENCES**


