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Androgenic Anabolic Steroids: An Overview for Clinicians

Brian C. Lund, PharmD, and Paul J. Perry, PhD

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Introduction

The abuse of androgenic anabolic steroids (AASs) is a remarkably prevalent problem, particularly among competitive athletes. The goal of this article is to summarize the clinically relevant issues regarding AAS abuse, including prevalence, mechanism of action, efficacy, and adverse effects. This information will therefore enable clinicians to better communicate with and counsel their patients regarding the potential risks of AAS use. The Table contains a list of anabolic steroid products.

Epidemiology

The prevalence of AAS abuse has been reported in several populations. The highest estimates have come from male bodybuilders and have ranged from 38% to 55%.[1,2] Lower rates have been reported among intercollegiate athletes, ranging from 15% to 20%.[3] However, rates of AAS abuse vary greatly across individual sports and are used in higher frequency and higher doses by strength athletes (eg, weight lifters).[4] By contrast, only 1% of their nonathletic university student counterparts reported AAS use.[3] Perhaps the most surprising and alarming finding is the rather high rate of AAS abuse among high school students. The typical rate reported in male students is between 5% and 6%,[5-8] but rates as high as 11% have been reported.[9] The most recent estimate reported a range of 4% to 12% for AAS use among US high school boys.[10] In female high school students, AAS abuse rates tend to be lower, but quite worrisome at 1% to 2%.[5, 7, 8, 10]

Physiology

AASs have several proposed mechanisms related to the enhancement of athletic performance. In addition to the promotion of protein synthesis, they include antagonism of glucocorticoid catabolic effects, increased red blood cell production, and central nervous system effects.[11-13] During stress (eg, vigorous athletic training) the catabolic effects of glucocorticoids generate a negative nitrogen balance, which the body counteracts by using protein stores. AASs oppose this effect, possibly through competition for glucocorticoid binding sites.[14] Performance may also be increased in AAS users secondary to increased erythropoietin synthesis and subsequent increases in hematocrit and oxygen-carrying capacity. Historically, one of the few indications for AASs was to increase hematocrit in hemodialysis patients. In conjunction with AAS-induced sodium retention, the blood volume may increase as much as 15%.[11,13] Anecdotal reports have also suggested some central effects of the AASs, including euphoria, decreased fatigue, and, most importantly, shortened recovery time following work-outs, thus enabling athletes to increase and accelerate their training schedules. The mechanism for these effects and the potential benefits for athletic performance are unknown.

Efficacy

Although numerous clinical studies have been conducted, there is limited evidence supporting the efficacy of AASs in enhancing athletic performance. Unfortunately, the AAS literature is littered

with design problems. The most significant methodologic problem is the disparity in dosing strategies between clinical trials and real-world use. When used by athletes, the AASs are typically "stacked." That is, the drugs are administered in cycles of gradually increasing doses and additional AAS agents are added along the way. Stacking cycles typically last between 7 and 14 weeks and often involve 2-3 oral agents along with 1 or 2 long-acting injectable AASs.[15] By contrast, clinical investigators are justifiably restricted from duplicating these regimens in experimental situations for ethical reasons. As a result, studies are typically limited to the use of 1 agent, either oral or injection. Athletes tend to use oral agents in doses similar to those in clinical trials, but often use injectable agents in doses 3-8 times greater than those in clinical studies.[15] Further exacerbating this problem is the issue of effect size. For example, a 1% improvement would be difficult to demonstrate statistically in a clinical trial setting, but in world-class athletics it could be the difference between a gold medal and last place.

These findings lead us, as consumers of the biomedical literature, to the conclusion that past studies of AASs may be of limited value in determining the efficacy and toxicity of these agents under current athletic use. In spite of a lack of comprehensive scientific evidence, however, there is little doubt that AASs can produce a significant ergogenic effect. As with many other substances of abuse, AAS users often possess a more sophisticated pharmacologic understanding than the general population, and counseling patients regarding the effects of these agents is often problematic.

Adverse Effects

The adverse effects of AASs fall into 4 primary categories: hepatic, reproductive, cardiovascular, and psychiatric effects. The following sections provide a brief summary of each category, including a description of potential effects and time course. Since the risk of AAS adverse effects is generally dose dependent, their prevalence in athletes is impossible to ascertain as the supraphysiologic doses utilized by this cohort predispose them to a greater rate of side effects than clinically treated patients.

Hepatic Effects

Elevations in aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and alkaline phosphatase have been reported with AAS use.[12] However, sustained weight lifting alone can result in mild elevations in hepatic enzymes.[16] Hepatic enzyme elevations usually return to normal once the AASs are discontinued. This normalization is one of the primary reasons that athletes administer the AASs on an intermittent rather than continuous basis. If the AASs are continued despite elevations in liver enzyme concentrations, dose-dependent cholestatic jaundice may occur.[17-19] While medically serious, this condition is rarely fatal when associated with AAS use. AAS-induced jaundice is relatively common and typically occurs with the C-17 alkylated agents such as methyltestosterone, methandrostenolone, oxymethalone, oxandrolone, and stanozolol. Nonalkylated agents such as testosterone and nortestosterone are less likely to produce liver damage.[19] As the oral AAS formulations are C-17 alkylated agents, these drugs are typically used at clinically recommended doses to minimize adverse hepatic effects. Injectable formulations of C-17 alkylated agents appear to have the same risk for hepatotoxicity as the oral formulations.

Reproductive Effects

In men, AAS administration produces a predictable, dose-dependent depression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) through negative feedback of the pituitary-gonadal axis. Because both LH and FSH are required for normal spermatogenesis, AAS use can lead to hypogonadotropic hypogonadism. The resulting effects include a decline in sperm count, abnormal sperm morphology, and testicular atrophy.[20, 21] Severe oligospermia is common during

continued AAS use and occurs in an estimated 75% of users.[22] Normalization of sperm counts generally occurs within 4 months of AAS discontinuation. However, the normalization of sperm motility and morphology requires more than 4 months and may take more than a year.[22, 23]

In an attempt to counteract testicular atrophy, male users will occasionally use human chorionic gonadotropin (hCG). hCG can mimic the effect of LH to boost testicular testosterone production and yield an increase in sperm production. However, FSH activity is required for completion of spermatogenesis and is not promoted by hCG. Therefore, in theory, sperm counts may be increased by hCG administration but may not be viable. However, 2 cases of successful treatment of hypogonadotropic hypogonadism with hCG have been reported.[24,25] AASs can also lead to feminization in males from their conversion to estrogenic metabolites. As a result, increased voice pitch and gynecomastia may occur in some men.[1] AAS users have used the antiestrogenic agent tamoxifen to antagonize these effects.[26] The efficacy and safety of this strategy remains unproven. AAS use in women can lead to hirsutism, acne, deepening of the voice, clitoral hypertrophy, decreased breast mass, and male pattern baldness and can sometimes be irreversible, even with discontinuation of the offending agent.[13]

Cardiovascular Effects

Use of AASs can result in adverse alterations in serum lipid concentrations, including decreases in high-density lipoprotein (HDL) and increases in low-density lipoprotein (LDL). Lipid changes are unpredictable and vary among individuals and probably among specific agents. Reported declines in HDL have ranged from 39% to 70% and occur within 1 or 2 weeks after AAS initiation.[27] HDL concentrations typically normalize within 3 to 10 weeks after AAS discontinuation.[27,28] LDL increases generally occur within the first 4 weeks of AAS use and increase an average of 36%.[27] While the percent changes in lipids may seem alarming, in an otherwise healthy athlete, the absolute concentrations may not be pushed into an established pathologic threshold (eg, HDL below 35 mg/dL or LDL above 160 mg/dL). Additionally, as the lipid changes tend to cycle along with AAS use, the long-term impact on morbidity and mortality remains unknown. Elevation of blood pressure in AAS users has been reported and is probably related to fluid retention.[29] This effect has not been well studied in athletes but is well documented in animal studies.[30] As with lipid alterations, the long-term detriment of cyclical elevations in blood pressure is unknown. More serious cardiac effects, including myocardial ischemia and sudden cardiac death, have been strongly associated with anabolic steroid use in numerous reports.[31] However, the precise cardiac risks of the AASs are often difficult to ascertain independently of other agents (eg, amphetamines) present in the polypharmacy regimens employed by many AAS users.

Psychiatric Effects

Several reports of mental status changes associated with AASs have been published. These include acute paranoia,[32] delirium,[33] mania or hypomania,[34,35] and homicidal rage.[36,37] Studies comparing AAS users to nonusing weight lifter controls have found significantly more episodes of depression, anxiety, hostility, paranoia, and aggression in users of AAS.[38, 39] One study comparing AAS users on vs off AASs reported a higher rate of aggressive feelings, verbal aggression, and aggression toward objects, but not physical aggression toward people, while on the agents. AAS users have also been observed to have a significantly greater rate of personality psychopathology compared with community controls.[40,41] As none of these studies are randomized, causality is difficult to establish in the association of AASs and psychiatric changes, including aggression and hypomania.

At least 5 studies have administered supraphysiologic doses of testosterone in a placebo-controlled design to psychiatrically "normal" subjects.[42-46] Overall, these studies indicate that the majority of normal individuals will not experience psychiatric changes with testosterone doses up to 500-600 mg/week. However, this response is not uniform and individual patients will

experience marked affective changes, particularly as the dose increases beyond 500 mg/week. Furthermore, the majority of real-world AAS abusers will use doses greater than the equivalent of 500 mg of testosterone. Patients with underlying psychopathology (eg, antisocial personality disorder) or a general predisposition toward anger are probably more likely to experience an increase in angry or aggressive behavior. This relationship is important because these individuals are probably more likely to use anabolic steroids illicitly, compared with "healthy, psychologically normal men."

The potential for addiction to the AASs has been investigated. In interviews with 49 AAS users, at least 1 *DSM-III-R* symptom of dependence was reported by 94% of the sample, while 3 or more symptoms were reported by 57% of the sample.[47] The authors concluded that AASs were addictive and suggested that dissatisfaction with body size and increases in size and strength obtained with AASs may lead to patterns of dependent use.

Clinical Detection

When should clinicians suspect AAS use among their patients? While clinical testing is the most reliable method of detecting illicit AAS use, there are numerous physical signs that may increase the index of suspicion. In addition to muscular hypertrophy, these include oily skin and acne, jaundice in the skin or eyes, gynecomastia, hepatomegaly, testicular atrophy and edema, as well as mood changes or aggression.[48]

Summary

The desire to succeed in athletic competition can be a powerful force, driving athletes to the illegal and potentially harmful use of AASs. As healthcare professionals, we need to be aware of potential AAS abuse in our patients, particularly when it is unlikely to be voluntarily reported. Counseling our patients regarding the risks of AAS abuse can be challenging as athletes become more sophisticated in their knowledge of these agents. In addition, the true long-term adverse effects of AAS regimens currently in use have not been established. As a result, our patients who choose to abuse AASs are exposing themselves to unknown and potentially serious medical risks.

Tables

Table. Anabolic Steroid Products[26]

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Duchaine D. *Underground Steroid Handbook II*. Venice, California: HLR Technical Books; 1989.

Generic Name	Trade Name	Dosage Form
Agents available in the United States for human use		
Oral dosage forms		
Danazol	Danocrine	50, 100, 200 mg capsules
Fluoxymesterone	Halotestin, various	2-, 5-, & 10-mg tablets
Methyltestosterone	Android, various	10 mg buccal, 10- and 25-mg

		tablets, 10-mg capsules
Oxandrolone	Oxandrin	2.5-mg tablets
Oxymetholone	Anadrol	50-mg tablets
Stanozolol	Winstrol	2-mg tablets
Injectable dosage forms		
Nandrolone decanoate	Deca-Durabolin, various	50, 100, 200 mg/mL
Nandrolone Phenpropionate	Durabolin, various	25, 50 mg/mL
Testosterone (aqueous suspension)	Testandro, Histerone, Tesamone, various	25, 50, 100 mg/mL
Testosterone enanthate	Andropository, various	100, 200 mg/mL
Testosterone cypionate	Depo-testosterone, various	100, 200 mg/mL
Testosterone propionate	various	100 mg/mL
Other dosage forms		
Testosterone	Testopel	75-mg pellets
Testosterone	Testoderm, Androderm	2.5, 4, 5, 6 mg/24 hours transdermally
Underground or veterinary agents		
Oral dosage forms		
Ethylestrenol	Maxibolin	2-mg tablets
Methandrostenolone	Dianabol	5-mg tablets or capsules
Methenolone	Primobolan	5-, 25-, 50-mg tablets
Quinbolone	Anabolicum Vister	10-mg capsules
Testosterone undecanoate	Restandol, Undestor	40-mg capsules
Injectable dosage forms		
Boldenon undecyclenate	Equipoise	25, 50 mg/mL
Dromostanolone propionate	Masteron	50 mg/mL
Methandrostenolone	Dianabol	25 mg/mL
Methenolone acetate	Primobolan Acetate	20 mg/mL
Methenolone enanthate	Primobolan enanthate	20 mg/mL
Mibolerone	Checque	100 mcg/mL
Stenbolone acetate	Anatrofin	25 mg/mL
Testosterone nicotinate	Bolfortan	50 mg/mL
Trenbolone acetate	Finajet 30, Parabolan	30, 76 mg/mL

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Brian C. Lund, PharmD, is Clinical Psychopharmacology Fellow, and **Paul J. Perry, PhD**, is Professor of Psychiatry and Pharmacy, Division of Clinical and Administrative Pharmacy, University of Iowa College of Pharmacy, Iowa City, Iowa.