



# Anabolic-Androgenic Steroid Use in Sports, Health, and Society

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## ABSTRACT

BHASIN, S., D. L. HATFIELD, J. R. HOFFMAN, W. J. KRAEMER, M. LABOTZ, S. M. PHILLIPS, and N. A. RATAMESS. Anabolic-Androgenic Steroid Use in Sports, Health, and Society. *Med. Sci. Sports Exerc.*, Vol. 53, No. 8, pp. 1778–1794, 2021. This consensus statement is an update of the 1987 American College of Sports Medicine (ACSM) position stand on the use of anabolic-androgenic steroids (AAS). Substantial data have been collected since the previous position stand, and AAS use patterns have changed significantly. The ACSM acknowledges that lawful and ethical therapeutic use of AAS is now an accepted mainstream treatment for several clinical disorders; however, there is increased recognition that AAS are commonly used illicitly to enhance performance and appearance in several segments of the population, including competitive athletes. The illicit use of AAS by competitive athletes is contrary to the rules and ethics of many sport governing bodies. Thus, the ACSM deplores the illicit use of AAS for athletic and recreational purposes. This consensus statement provides a brief history of AAS use, an update on the science of how we now understand AAS to be working metabolically/biochemically, potential side effects, the prevalence of use among athletes, and the use of AAS in clinical scenarios. **Key Words:** TESTOSTERONE, HYPERTROPHY, SKELETAL MUSCLE, ANDROGEN, STRENGTH, PERFORMANCE

## SYNOPSIS

This consensus statement is an update of the previous position stand from the American College of Sports Medicine (ACSM), published in 1987 (1). Since then, a substantial amount of scientific data on anabolic-androgenic steroids (AAS) has emerged and the circumstances of AAS use has evolved in the athletic, recreational, and clinical communities. The objective of this consensus statement is to provide readers with a brief summary of the current evidence and extend the recommendations provided in the 1987 document (1). Key topics discussed are the brief history of AAS, epidemiology,

methods, and patterns of AAS use, androgen physiology and ergogenic effects, side effects of AAS, and clinical uses of AAS (see Box 1). The writing group used the rating system of the National Heart Lung and Blood Institute (Table 1) and a consensus approach to synthesize the available evidence from clinical trials and case reports, narrative and systematic reviews, and meta-analyses (3). The recommendations represent the consensus of the writing panel, the ACSM, and incorporate guidance from other professional organizations with expertise in the area.

## INTRODUCTION

Anabolic-androgenic steroids are drugs chemically and pharmacologically related to testosterone (T) that promote muscle growth and are not estrogens, progestins, or corticosteroids. An *androgen* is any natural or synthetic steroid hormone capable of promoting the development of male primary and secondary sexual characteristics via binding to androgen receptors at the tissue level. The term *anabolic* describes a hormone or other substance capable of enhancing the growth of somatic tissue, such as skeletal muscle and bone. In a sport-related setting, this is typically used to describe the enhancement

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## BOX 1. ACSM Consensus Statements and Recommendations Summary.

## Consensus Statements and Recommendations

1. The administration of AAS in a dose-dependent manner significantly increases muscle strength, lean body mass, endurance, and power. The effects are primarily seen when AAS use is accompanied by a progressive training program. *Evidence Category A.*
2. Historically, AAS use was primarily seen in competitive athletes and aspiring bodybuilders and powerlifters. Recreational AAS use appears to have surpassed athletic AAS use indicated by survey prevalence estimates demonstrating that recreational trainees are the leading consumers of AAS. The ACSM deplores the illicit use of AAS for recreational purposes. *Evidence Category C.*
3. AAS are classified as schedule III drugs, banned by several sport governing bodies, and are illegal to use for athletic purposes. The ACSM deplores the illicit use of AAS for recreational use and performance enhancement in athletes. *Evidence Category D.*
4. Coaches, trainers, and medical staffs should monitor and be cognizant of visible signs of AAS use and abuse. These include (but are not limited to): a substantial increase in muscle mass, strength, and power in a relatively short period of time (or the reverse which could denote AAS withdrawal); acne that is resistant to medical treatment; development of unexplainable rash, gynecomastia, increased body hair, and prominent increases in surface vascularity; changes in temperament, mood, and aggressive behavior (severe depression or suicidality could indicate AAS withdrawal); facial masculinization and fluid retention; and muscle mass that appears disproportionate to body structure or pubertal status in young athletes. In addition, the presence of AAS-related materials (books, articles, websites, dealer information, needles, vials) on the individual could reflect intent and may warrant further dialogue from the coaching, trainer, and medical staffs. Medical staff should be aware of regulations and documentation requirements regarding use of AAS for athletes with medical indications for their use. *Evidence Category C.*
5. Use and abuse of AAS is associated with several notable adverse effects in men and women including (but not limited to) suppression of the hypothalamic-pituitary-gonadal axis, psychological changes, immunosuppression, and unhealthy cardiovascular, hematological, reproductive, hepatic, renal, integumentary, musculoskeletal, and metabolic effects. Several adverse effects may be reversible upon discontinuation but some could pose health risks beyond the duration of AAS use. *Evidence Category B.*
6. Use of AAS in prepubertal and peripubertal children may lead to early virilization, premature growth plate closure, and reduced stature. *Evidence Category C.*
7. Coaches, trainers, and medical staffs should be cognizant of the reasons for AAS use and abuse and deter use when possible. Prevention programs based on education may assist; and providing the individual with scientific nutrition and training advice is a recommended strategy to mitigate the temptation of AAS use. *Evidence Category D.*
8. Androgen replacement therapy is approved for the medical treatment of several clinical diseases and abnormalities. The ACSM acknowledges the lawful and ethical use of AAS for clinical purposes and supports the physicians' ability to provide androgen therapy to patients when deemed medically necessary. The reader is referred to guidelines established by the Endocrine Society (4). *Evidence Category C.*

of skeletal muscle. Table 2 presents nomenclature associated with AAS. In the United States, AAS are classified as Schedule III controlled substances (5). Although AAS have legitimate medicinal use, nontherapeutic use among athletes and recreationally active young men and women is performed to

improve strength, power, increase muscle mass, and improve appearance. Athletic and recreational (i.e., noncompetitive) use of AAS has been widespread over the last 50 yr, creating considerable interest by the scientific and medical communities, as well as sport governing bodies, in examining the potential medical, legal, and ethical issues surrounding the use of these substances. All major national and international sports organizations have banned the illicit use of AAS by athletes.

## HISTORICAL PERSPECTIVES

Anabolic-androgenic steroids use has been examined extensively in various chapters, books, meta-analyses, and reviews (5–12). The effects of testicular extracts and castration on animals and humans have been a source of fascination for thousands of years (13,14). Suggestions that the consumption of testis tissue could improve impotence were noted ~140 BC (13). The mid 1700s to late 1800s marked a time where interest in testicular endocrinology increased (14). Table 3 depicts a brief historical timeline of some key events in AAS use in athletes. Testosterone was synthesized and biochemically described in the late 1920s and 1930s, and a host of different synthetic variations have been developed since (5,15,16). Testosterone or AAS use by athletes began in the 1940s and 1950s, and increased considerably thereafter, culminating in high usage during the 1968 Olympic Games (5,6). It has been speculated that the first appearance of AAS use among female athletes dates back to the late 1950s/early 1960s in Soviet track and field athletes (17).

The sophistication of AAS use by athletes in the late 1960s was characterized by a host of different “stacking routines” (i.e., the consumption of two or more drugs in an attempt to improve the response) using various oral and injectable AAS preparations (5). Initially, many physicians did not believe AAS improved performance, and the International Olympic Committee (IOC) did not include AAS on the banned substance list. The ACSM adopted this position in their first AAS position stand in 1977 but later corrected in the 1987 publication (1). Although the 1970s marked a time where AAS use was known mostly among competitive athletes, the 1980s marked a time where AAS use spread well beyond athletics to gyms, health clubs, and public awareness of AAS use increased. The *Anti-Drug Abuse Act* (1988), *Anabolic Steroid Control Act* (1990,

TABLE 1. Evidence categories.

Evidence Category	Sources of Evidence	Definition
A	RCT (rich body of data)	Evidence is from endpoints of well-designed RCT (or trials that depart only minimally from randomization) that provide a consistent pattern of findings in the population for which the recommendation is made. Category A therefore requires substantial numbers of studies involving substantial numbers of participants.
B	RCT (limited body of data)	Evidence is from endpoints of intervention studies that include only a limited number of RCT, <i>post hoc</i> or subgroup analysis of RCT, or meta-analysis of RCT. In general, Category B pertains when few randomized trials exist, they are small in size, and the trial results are somewhat inconsistent, or the trials were undertaken in a population that differs from the target population of the recommendation.
C	Non-RCT and observational studies	Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.
D	Panel consensus judgment	Expert judgment is based on the panel's synthesis of evidence from experimental research described in the literature and/or derived from the consensus of panel members based on clinical experience or knowledge that does not meet the above-listed criteria. This category is used only in cases where the provision of some guidance was deemed valuable but an adequately compelling clinical literature addressing the subject of the recommendation was deemed insufficient to justify placement in one of the other categories (A through C)

Modified from (2).

RCT, randomized controlled trial.

TABLE 2. Definition of terms associated with AAS.

Testosterone	Hormone with strong anabolic and androgenic effects. produced by the testes in males. lesser quantities are produced by ovaries in women and by the adrenal glands in both sexes. the hypothalamus and pituitary regulate testosterone production in humans.
Testosterone derivative	Chemically altered testosterone resulting in changes in solubility, pharmacokinetics, and/or clinical effects.
Testosterone esters	Testosterone derivative with an ester group bound to testosterone to enhance oil solubility. This slows testosterone absorption and increases duration of effect, and allows for depot injections of testosterone
SARM	Drugs designed to optimize anabolic tissue growth, while minimizing androgenic side effects. No current clinical applications, but research suggests potential therapeutic benefit in cancer, prostatic hyperplasia, and hypogonadism
Designer anabolic-androgenic steroids	Synthetic steroids fabricated with intent to evade drug testing, or current laws prohibiting nonprescribed use
Testosterone enhancers/boosters	Variety of substances purported to increase testosterone levels or effects, usually by increasing endogenous testosterone production or decreasing metabolism
HCG	An analog to LH. Stimulates Leydig cells in the testes. Increases testosterone levels and sperm production
Clomiphene citrate (Clomid)	Estrogen receptor modulator. Increases LH production. Has been shown relieve hypogonadal symptoms and maintain testosterone levels in men with symptomatic hypogonadism for up to 3 yr
Kisspeptins	Peptide that appears to be important for onset of puberty and regulation of sperm production. Current evidence not definitive in regards to effects on androgen production in humans.

SARM, selective androgen receptor modulators; HCG, human chorionic gonadotropin.

2004), and *Dietary Supplement Health and Education Act* (1994) were enacted, in part, to stem the growing use of AAS. Only a few studies (~17) on AAS use and strength/hypertrophy increases were conducted before the 1980s, and these cumulatively showed minimal effects in untrained men, but significant responses in trained men, despite doses less than that used by many athletes (6,7,10). The sophisticated protocols and array of drugs used recreationally and by athletes remained a “black box” from a research perspective.

Of current concern is the ease by which AAS users may obtain AAS via the Internet and the proliferation of men’s health clinics. In addition to the use of AAS by competitive athletes, a growing segment of AAS users are nonathletes. Management of men with damaged hypothalamic-pituitary-gonadal regulatory pathways became a new area of medicine resulting in indiscriminate AAS use (18). Interest in AAS persists as research identifies new information regarding the performance and health aspects of the drugs and through stories of purported use in the sports world. The World Anti-Doping Agency (WADA) has developed new antidoping measures, including blood sampling, guidelines for international information gathering and sharing and revamping their “Athlete Biological Passport” guidelines. While AAS use in sports continues, increases in AAS use in the general population appear to have outpaced athletic use in the last decade (19).

## EPIDEMIOLOGY OF AAS USE

Peer-reviewed studies examining the frequency of illicit AAS use have declined in the past decade despite concern over the growing AAS epidemic in the United States. These studies

often rely on self-reports and are fraught with sampling bias, small sample sizes, possible confusion regarding supplement and AAS use, and suboptimal ascertainment (5). Many AAS users are secretive, with one survey finding that 56% of respondents would not disclose their physicians’ use (20). Athletes may be unwilling to discuss their use with researchers even when anonymity and confidentiality are guaranteed for fear it may jeopardize their career; thus, leading to differences in what athletes reported on surveys versus their actual activities (21).

In 2014, the National Institute on Drug Abuse estimated that 1.3 million Americans were AAS users, while the Endocrine Society estimated between 2.9 and 4.0 million Americans have used AAS at some point in their lives (18,22,23). Other reports showed that the number of users might be as high as 4 million men in the United States, with ~100,000 new AAS users annually (6,23,24). The age of onset of use begins later than most drugs, with only 6% of users starting before 18 (23).

Although the general public and medical communities attribute AAS use primarily to competitive athletes (6), research does not support this misperception. Muscle dysmorphia (“megarexia”) is a dominant risk factor for illicit AAS use and indicates that AAS use is often used in pursuit of a more muscular appearance rather than for enhanced athletic performance (25). Recreationally active individuals age 15 to 24 yr are more likely to use AAS than athletes participating in organized sport (26). However, reports on the prevalence of illicit AAS use in athlete and nonathlete populations are widely variable. Anabolic-androgenic steroids have been reported in 9% to 67% of elite athletes, while reports of AAS use among gym attendees ranged from 3.5% to 80% (27). In all areas, men report higher prevalence than women, although the prevalence in women is increasing (28). Studies in girls have shown prevalence rates between 0.4% and 1.0% in adolescents, ~1.2% in collegiate athletes, and ~10.3% in elite athletes (27). Others have reported AAS use in young athletes ranging between 0.6% and 6.6% in teenage boys, 0.0% to 3.3% in teenage girls, and between 0.8% and 9.1% for collegiate male athletes (29–32). Peer-reviewed studies report the highest prevalence of use in weightlifters, powerlifters and bodybuilders, with rates ranging from 33.3% to 79.5% (31,33).

Several studies have examined sport and activity participation among self-reported AAS users. A survey study of >500 male AAS users (mean age of 29) showed ~70% were recreational exercisers versus 12% competitive bodybuilders, 8% competitive weightlifters, and 9% competitive athletes in other sports (34). Participation in high school sports was not associated with an increased risk of AAS use (34). A survey of 12 female AAS users indicated that 33% of the women were recreational users, while 67% participated in competitive bodybuilding and weightlifting. These women used a polypharmacy approach, but their weekly dose was lower than male AAS users (35). Female users were less likely to stack, more likely to pyramid and less likely to inject AAS than male users (35).

Rates of AAS use in athletes are sometimes inferred from rates of positive doping tests. However, this data has some inherent limitations, including ongoing updates to banned substances lists, variable drug testing methodologies, and

TABLE 3. Timeline of some key historical events related to AAS use.

Year	Event
1889	Brown-Sequard suggest increases in muscle strength and endurance can occur following the injection of testicular extracts over a span of 2 wk
1896	Zoth and Pregel first suggested androgen use in athletes and investigated effects of testicular extracts on muscular strength and athletic performance
1927	Fred Koch and Lemuel McGee (University of Chicago) isolated an impure but potent form of T by pulverizing several tons of bull testicles
1928	The IAAF were first to ban doping agents
1935	Testosterone was isolated and the first two papers on testosterone synthesis were published—oral and injectable preparations were available to the medical community shortly thereafter—Kochakian reported T stimulates anabolism and suggested therapies could be useful for several disorders
Early 1940s	Case studies suggested that human subjects were given testosterone in Germany and undocumented reports suggested AAS was administered to German soldiers during World War II
1942	Samuels, Henschel, and Keys published “Influence of methyl testosterone on muscular work and creatine metabolism in normal young men” in the <i>Journal of Clinical Endocrinology and Metabolism</i> —an early study investigating AAS in men
1945	De Kruif published “The Male Hormone” and suggested interest in athletes using testosterone to see the beneficial effects
Late 1940s	West Coast bodybuilders began experimenting with T preparations
1952	Legendary strength athlete and coach Bob Hoffman of York Barbell speculates that Soviet athletes were using hormones during the Olympic Games
1954	Dr. John Ziegler was told by Soviet coaches that Soviet Weightlifters were using testosterone—he returned to United States and experimented on himself along with some weightlifters
1958	Ciba Pharmaceutical Company manufactured Dianabol—soon thereafter Dr. Ziegler began administering the drug to some of the York Barbell Weightlifting team
1963	Reports of NFL players first using AAS
1964	Androgen use increased greatly primarily in strength and power sports
1965	Oral Turinabol was synthesized by a German state-owned pharmaceutical company
	A few scientists gained interest in studying AAS and performance in men as 2 studies were published between 1965 and 1969
1967	The IOC established a medical commission and developed a list of prohibited substances and methods
1968	Large increases in AAS use was seen including stacking and doses exceeding 2–5 times therapeutic doses—estimated that at least 1/3 of US track & field team and most of the German team used drugs in the 1968 Olympics
1969	The editor of <i>Track &amp; Field News</i> (John Hendershott) called AAS the “Breakfast of Champions”
1973–1974	First testing procedures for androgens proposed radioimmunoassay and gas chromatography and mass spectrometry (RIA, GC-MS) and used in 1974 at the Commonwealth Games in Auckland New Zealand where 9 of 55 samples testing positive for androgens
1976	Drug testing instituted at the Olympic Games in Montreal—only 8 of 275 tests were deemed positive despite the majority of athletes admitting to using AAS in training—athletes began shifting to T from AAS as a result of drug testing
1976	The ACSM National Conference included a symposium and roundtable meeting on AAS in sports—two polarized groups evolved: those who thought AAS were “fool’s gold” or “myth” versus those who understood the ergogenic potential of the drugs—the prevailing medical opinion was that AAS were ineffective until the 1980s (possibly to dissuade use in part) which lead to mistrust between athletes and the medical community leading athletes to the black market for drugs and information
1977	The ACSM publishes the “Position statement on the use and abuse of anabolic-androgenic steroids in sports”—concluded that “... there is no conclusive evidence that extremely large doses of anabolic-androgenic steroids either aid or hinder performance ...”
1980	Dr. Manfred Donike developed a method for testing testosterone—the 6:1 T:E ratio
1981	1st edition of the <i>Underground Steroid Handbook</i> (by Dan Duchaine [nicknamed “The Steroid Guru”]) was published
1982–1983	Methods to circumvent T:E ratio (i.e., use of hCG, clomiphene, epitestosterone, and timing of T administration) were used to enable doping without detection
1984	ACSM National Conference included symposium on “Drug Use in Sports” with >12 scientific presentations with several focusing on AAS in athletes
1987	The ACSM publishes an updated position stand “The use of anabolic-androgenic steroids in sports”—revised position to AAS in the presence of an adequate diet and training can contribute to increases in lean body weight and muscular strength
1988	Testing for masking agents and diuretics begins—US government passes the Anti-Drug Abuse Act which made distribution or possession of AAS for nonmedical reasons a federal offense
1990	US government passes Anabolic Steroid Control Act—inserted 27 AAS and related drugs as Class III drugs where simple possession could result in incarceration
1994	US Congress passes Dietary Supplement Health and Education Act to protect consumers from certain substances
2001	The WADA was formed
2002	The advent of designer AAS began
2004	The Anabolic Steroid Control Act is revised to include 26 new compounds including prohormones
2005	T:E ratio lowered to 4:1 by WADA for a positive doping test

Constructed from various sources (1,5,6,9,12,15,16).

E, epitestosterone; IAAF, International Amateur Athletics Federation.

variable lists of targeted substances tested by organizations that do not follow WADA protocols. It has been estimated that drug testing alone may underestimate drug use in elite athletes by 8-fold (21). The Anti-Doping Administration and Management System maintained by WADA now allows any sports body to share drug testing information. While AAS use in particular divisions, such as men’s vs women’s and underage athletes is still difficult to obtain, the testing databases now include much larger numbers of athletes than in the past. Anabolic agents constitute 87% of atypical findings reported by WADA and 46% of all adverse analytical findings (International Amateur Athletics Federation) (36,37). Stanozolol and nandrolone have the highest number of AAF at 20% and 14%, respectively, while an “unidentified anabolic agent” (e.g., “designer” AAS) was the third most common at 11% (36).

The true nature of AAS use and abuse in athletes and recreationally trained individuals is difficult to discern and is often underestimated. In addition to surveys and doping

results, other sources of information on AAS use include investigated journalism and government hearings. Unfortunately, all of these methods have significant methodological issues that reduce their estimation accuracy (17). Journalists have interviewed current and former athletes, coaches, team physicians, and trainers whose estimate of AAS use in sports is much higher than survey reports. There has been an inconsistency between the number of individuals demonstrating signs of AAS use and the statistical prevalence generated via surveys. Drug testing is often limited by circumventing positive tests and has done little to quantify “real-life” use or dissuade AAS use at high levels of competition. Obtaining accurate measures of AAS use in athletes is difficult given the challenges of reducing bias; testing issues, and sincerity needed during interviews and survey completion, for example, fear of accountability, fear of loss of potential income or suspension, or fear of being perceived as a cheater or athlete who needed drugs to be successful.



TABLE 4. Reported motivators for AAS use by athletes.

↑ muscle mass, strength, power, endurance, speed, fitness levels, energy, blood volume, BMD	Encouragement from friends, family, coaches to do so
↑ sex drive	↑ recovery between workouts and competitions, pain tolerance
↑ athletic success, chances of winning, individual performance, strive to maximize potential	Fear their opponents are using and they must use AAS in order to maintain competitive balance
↑ social recognition, peer acceptance, self-confidence, aggression, mental intensity and alertness	Lack of fear in getting caught or being held accountable by sport governing bodies
↑ financial gain, chance at scholarship, notoriety	↓ body fat and injury risk, ↑ weight loss
Improve appearance, self-esteem, mood, personal protection	↓ aging effects, likelihood of muscle dysmorphia

Modified from (34,41).

Attempts have been made to identify the type of individual prone to using AAS (38–40). Hildebrandt et al. (39) reported 4 clusters of users from highest to lowest risk, each with different levels of motivation for AAS use: 1) polypharmacy (i.e., use of multiple drugs) approach with high risk (~11%); 2) fat burning (~17%); 3) muscle building (~21%); and 4) low-risk use designed to reduce fat and build muscle (~52%). Others have reported a four-level typology: 1) *expert type* (exemplifies controlled risk-taking, is knowledgeable about AAS and fascinated with effects on the human body, is scientific and may be focused on muscularity); 2) *athlete type* (interested in performance enhancement and is competitive); 3) *well-being type* (interested in looking and feeling good with low risk-taking); and 4) *YOLO* “You Only Live Once” type (is haphazard using risky behavior, quick improvements, impressing others and peer recognition is important) (38,40). Despite the typology, athletes’ motivation to use AAS is multi-faceted and influenced by many factors (Table 4).

Several extensive, national studies indicate an overall downward trend in lifetime AAS use among adolescents since peaking in the early 2000s (42). Monitoring the Future (MTF) is administered annually to a sample of 8th, 10th, and 12th grade students (43). The MTF reported peak prevalence rates for lifetime AAS use in 2000 to 2002 of 3% to 4% compared with 2018 data in Table 5 (i.e., ~1%–3%). The Youth Risk Behavior Survey (YRBS) is administered annually to a sample of high school students and reports an overall prevalence of 2.9% in 2017 (See Table 6), after peaking in 2001 at 5% (44). Although the YRBS is widely cited, concern has been raised that the term “steroid” is vague and potentially conflated with corticosteroids or steroid-like dietary supplements (45). Surveys that delineate the type of steroid show usage rates that are markedly lower than those seen in the YRBS data (45). Although AAS use rates in adolescents are low, ~1 in 8 AAS users initiates their use before age 18 (23). Several correlates of increased AAS use risk in this group include fitness-related activity (46,47); weight-related concerns (perceptions of very underweight or overweight status) (48,49); sexual preference and gender identity (25,44); and race and ethnicity (43,44). Some view current AAS use as an epidemic given the emergence of AAS availability through internet/mail order and “backroom” laboratories (18,50).

## METHODS/PATTERNS OF AAS USE

Patterns of AAS use in athletes and resistance-trained populations vary greatly and depend upon: AAS type, self-administration routes, dosages, cycling patterns and durations, and ancillary drugs. A “polypharmacy approach” is commonly used where supraphysiologic doses of injectable and oral AAS are stacked and pyramided progressively in cycles, while ancillary drugs are consumed to minimize side effects, promote other areas of health and fitness, and/or enhance T levels during off-cycles, or periods in between cycles (Table 7). Figure 1 depicts survey results from two studies on usage patterns for >2400 predominately male AAS users (34,41). These studies indicated that 99.2% of users reported using injectable AAS or a combination of oral and injectable AAS, and >40% used ancillary drugs, such as antiestrogens (41). Ip et al. (34) reported that 79% of AAS users “stacked” drugs, 18% used the “pyramid” approach (i.e., where drug intake is progressively increased, plateaus, and then is decreased or tapered until the end of the cycle), and only 9% thought physicians and pharmacists were knowledgeable about AAS. Interestingly, AAS users spent an average of  $268 \pm 472$  h researching AAS prior to use (34).

## ANDROGEN PHYSIOLOGY

Testosterone is the principal androgen and has both androgenic (masculinizing) and anabolic (tissue building) effects. Testosterone is synthesized from cholesterol via the  $\Delta$ -4 or  $\Delta$ -5 pathways through the sequential action of several enzymes (Fig. 2). In men, >95% of T is synthesized in the Leydig cells of the testes (with smaller adrenal contributions) under control of the hypothalamic-anterior pituitary-gonadal axis where gonadotropin-releasing hormone stimulates the release of luteinizing hormone (LH). Healthy men produce ~4 to 9 mg of T per day ( $10$ – $35$  nmol·L<sup>-1</sup>) whereas women have approximately 0.5 to 2.3 nmol·L<sup>-1</sup> of circulating T in the blood (5). Gonadotropin-releasing hormone function is under the control of hypothalamic neuropeptides, such as kisspeptins, neurokinin-B, dynorphin-A, and phoenixins (51). In women, androgens are produced primarily by the ovaries and adrenal glands (52). Skeletal muscle produces small amounts of androgens (53). Testosterone circulates in the blood bound to sex hormone-binding globulin (44%–60%), albumin, orosomucoid, and cortisol-binding globulin. Testosterone and other 19-carbon

TABLE 5. Lifetime prevalence data from the 2018 MTF survey based on answers to the following query: “Anabolic steroids are prescription drugs sometimes prescribed by doctors to treat certain conditions. Some athletes, and others, have used them to try to increase muscle development.” The question then asks, “on how many occasions have you taken steroids on your own—that is, without a doctor telling you to take them?”

	8th Grade	10th Grade	12th Grade
Overall	1.1%	1.2%	1.6%
Male	1.0%	1.3%	2.2%
Female	1.1%	0.9%	0.9%
White	1.0%	1.1%	1.4%
African American	1.2%	1.3%	2.9%
Hispanic	1.1%	1.0%	1.3%

TABLE 6. Lifetime prevalence data from the 2017 YRBS survey based on answers to the following query: "During your life, how many times have you taken steroid pills or shots without a doctor's prescription?"

	Overall	Females	Males
Ever used steroids	2.9%	2.4%	3.3%
By race/ethnicity			
Black	2.2%	1.8%	2.7%
White	3.6%	2.6%	4.6%
Hispanic	3.5%	3.1%	3.8%
By sexual contact			
Opposite sex only	3.9%	2.6%	4.9%
Same sex or both sexes	8.0%	7.2%	10.1%
No sexual contact	0.7%	1.0%	0.5%

androgens can be converted to 5 $\alpha$ -dihydrotestosterone (DHT) by the action of steroid 5 $\alpha$ -reductase or converted to estradiol or estrone by the aromatase enzyme. The liver inactivates T, and the resultant metabolites are excreted in the urine.

Androgens perform many ergogenic, anabolic, and anticatabolic functions in skeletal muscle and neuronal tissue, leading to increased muscle strength, power, endurance, and hypertrophy in a dose-dependent manner (54). A meta-analysis concluded that short-term AAS use increases muscle strength substantially more than placebo and that strength gains and muscle hypertrophy are greater in trained individuals than in nontrained individuals (55). Gains in body mass and lean body mass (LBM) of ~5% to 20% from AAS use have been reported (56). Figure 3 depicts some physiological ramifications of androgens that could affect physical performance. However, the findings of controlled clinical trials of T and other AAS may differ from the practical experience of athletes due to the inclusion of mostly untrained subjects in controlled clinical trials; the use of lower doses of T or AAS in clinical trials than those used by many athletes; the use of multiple AAS in stacks with other drugs over long periods; and differences in nutritional patterns, training programs, and study design (5,27).

Exogenous androgens are often administered orally or parenterally but are also available in cream, nasal spray, buccal, subcutaneous pellets, patches, and gel. Orally administered T is absorbed well but is degraded rapidly. The esterification of the 17-beta-hydroxyl group (e.g., T enanthate, cypionate, decanoate, undecanoate, propionate) makes the androgen more hydrophobic, causing a slow release from the muscle into circulation, increasing the duration of action. When administered intramuscularly, the androgen ester is slowly absorbed into the circulation, where it is then rapidly de-esterified by esterase enzymes to T. Intrinsic potency, bioavailability, and rate of clearance from the circulation are determinants of the biological activity. Other oral and injectable AAS are T, DHT, or 19-nortestosterone derivatives (e.g., methyltestosterone, methandrostenolone, fluoxymesterone, nandrolone decanoate, oxandrolone, trenbolone, stanozolol, and other designer-AAS).

An important and relevant question is how long the effects of a dose of AAS would last in an athlete? That is, how long would potential strength gains or gains in muscle mass persist? The answer to the question is undoubtedly complex and dependent on the AAS being used and their potency (see Fig. 1), the history of AAS in the athlete (57), the athlete's training

age, sex (58,59), and potentially the developmental stage of the athlete relative to puberty and adulthood (i.e., 18 yr of age). The literature in this area is, unsurprisingly, sparse, but some studies suggest that the effects of AAS persist for weeks after taking the steroids, but at ~12 wk after taking AAS that the effects, at least insofar as strength and muscle mass are concerned, are largely absent (55,60). For example,

TABLE 7. AAS and ancillary drugs used by athletes.

AAS	
Anabol 4–19 (nortestebol acetate)	Myogen (bolasterone)
Anadrol (oxymetholone)	Parabolan (trenbolone hexahydrobenzylcarbonate)
Anavar (oxandrolone)	Primobolan (methenolone)
Cheque drops (mibolerone)	Primobolan depot (methenolone enanthate)
Dianabol (methandrostenolone)	Proviron (mesterolone)
Deca durabolin (nandrolone decanoate)	Testosterone (androderm, AndroGel, Striant, testoderm)
Durabolin (nandrolone phenylpropionate)	Testosterone blend (Sustanon, Omnadren, Equitest, Sten, Testoviron)
Dynabol (nandrolone cypionate)	Testosterone cypionate (Depo-Testosterone)
Dynabolon (nandrolone undecanoate)	TE (Delatestryl)
Equipose (boldenone undecanoate)	Testosterone propionate (Oreton)
Finajet (trenbolone acetate)	Testosterone suspension (Andronaq)
Genabol (norbolethone)	Tetrahydrogestrinone
Halotestin (fluoxymesterone)	Trenabol (trenbolone enanthate)
Madol (desoxymethyltestosterone)	Turinabol (chlorodehydromethyltestosterone)
Masteron (drostanolone)	Winstrol (stanozolol)
Metandren (methyltestosterone)	
Metribolone (methyltrienolone)	
Miotolan (furazabol)	
Banned Prohormone/OTC Steroids	
1-Testosterone	Epi-DHT
4-Hydroxytestosterone	19-Norandrostenediol
Boldione	19-Norandrostenedione
Androstenediol, 1-,4-Androstenediol	Halodrol
Androstenedione, 1-,5-Androstenedione	Superdrol
1-Androsterone	Methylhydroxynandrolone
Androstanolone	Prostanozol
Epiandrosterone, 1-Epiandrosterone	
SARM	
Andarine (S4)	RAD-140 (testolone)
Ligandrol (LGD-4033)	YK-11
Ostarine (enobosarm)	
Antiandrogens	
Arimidex (anastrozole)	Faslodex (fulvestrant)
Aromasin (exemestane)	Femara (letrozole)
Clomid (clomiphene citrate)	Fertodur (cyclofenil)
Cytadren (aminoglutethimide)	Lentaron (formestane)
Evista (raloxifene)	Nolvadex (tamoxifen citrate)
Fareston (toremifene citrate)	Teslac (testolactone)
Ancillary Drugs	
Accutane (isotretinoin)	Lasix (furosemide)
Cardarine	Cytomel (liothyronine sodium)
Abuterol	Synthroid (levothyroxine sodium)
Clenbuterol	Human growth hormone (somatotropin, protropin, nutropin, humatrope, genotropin, norditropin)
Ephedrine	GHRH secretagogues (CJC-1295, Mod GRF 1–29, Egrifra [tesamorelin acetate], Geref [sermorelin acetate])
Catapres	Growth hormone releasing peptides (Lenomorelin [Ghrelin], GHRP-1 to GHRP-6, hexarelin [examorelin], ipamorelin, ibutamoren mesylate [MK-677])
Aldactone (spironolactone)	GH fragments (GHG fragment 176–191, AOD-9604)
Dyrenium (triamterene)	IGF-1 and variants (Increlex [mecasermin])
Hydrodiuril (hydrochlorothiazide)	Mechano growth factor
Epitestosterone	Insulin
Probenecid (masking agent)	
Synthol (site enhancer)	

THG, tetrahydrogestrinone.

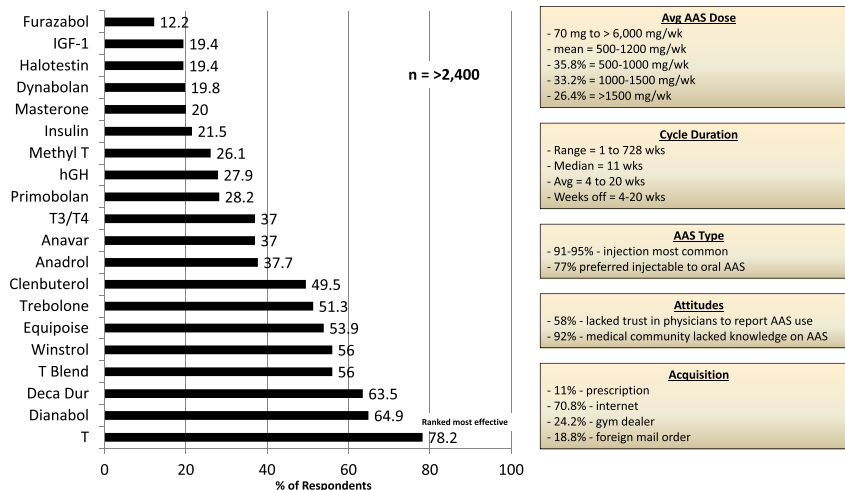


FIGURE 1—Usage patterns of steroids in predominantly male AAS users; data from (34,41).

Giorgi et al. (61) showed that testosterone enanthate (TE) ( $3.5 \text{ mg} \cdot \text{kg}^{-1}$ ) administration for 12 wk during training resulted in greater increases in strength, muscle girth, and muscle thickness than a group given a placebo. However, after 12 wk without TE administration, but while still training, there was a reversion of strength and muscle in the TE group to levels no different from the placebo group. In contrast, others have observed preservation of AAS-induced gains in strength and LBM that persist after AAS usage has ceased, at least in the short-term (62).

Persistent and long-term (at least 5 yr) AAS use in a mixed sample of strength (strongman and powerlifters) and aesthetic sport (bodybuilding) athletes has been reported, in comparison to non-AAS, to result in persistent (i.e., in comparison to a matched group) elevations in LBM, muscle fiber area, capillary density, myonuclei density, and strength that were dose-dependent (57). The observation that long-term AAS use results in increased myonuclei density (57) suggesting that a much longer ‘muscle memory’ is perhaps possible in AAS users, particularly those who use AAS early in life.

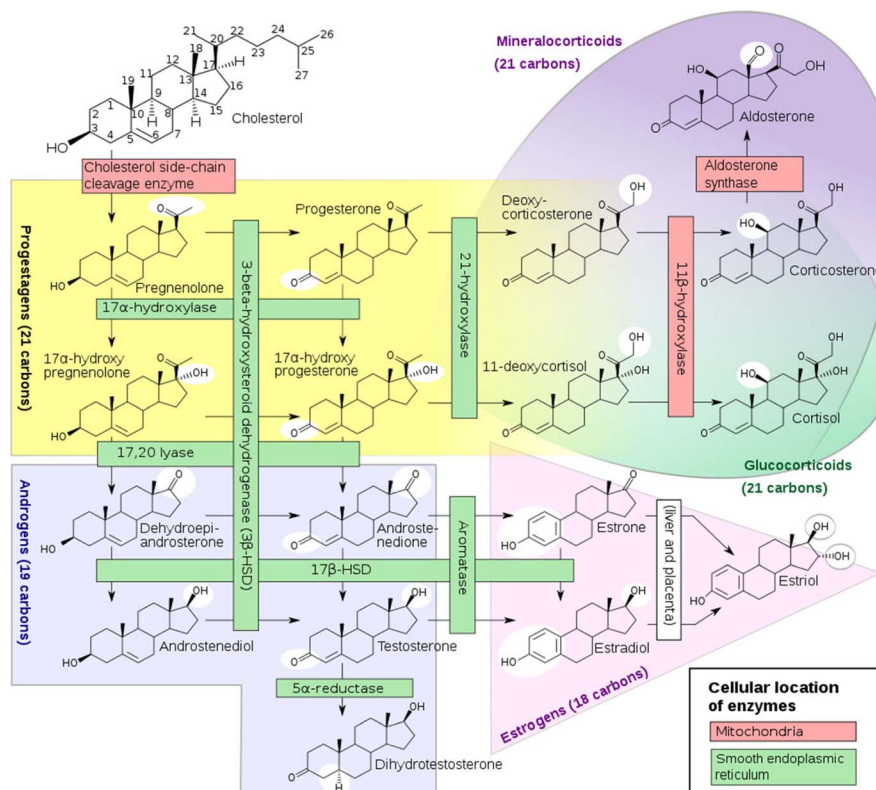
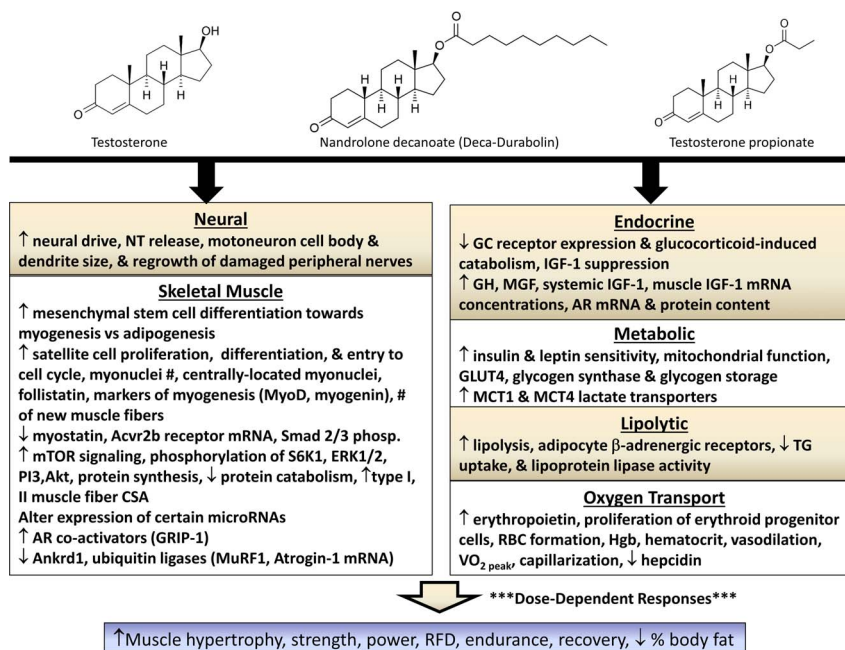


FIGURE 2—Testosterone (and related steroid hormones) biosynthesis from cholesterol (File: Steroidogenesis.svg [Internet]. Wikimedia Commons, the free media repository; 2020 Sep [cited 2020 Sep 30]. Available at: <https://commons.wikimedia.org/w/index.php?title=File: Steroidogenesis.svg&oldid=450817886>).





**FIGURE 3—Physiological and molecular-level consequences of AAS usage that may affect physical performance.** NT, neurotransmitter; CSA, cross-sectional area; AR, androgen receptor; GC, glucocorticoid; GH, growth hormone; Acvr2b, activin receptor type-2B; TG, triglyceride; RBC, red blood cell; Hgb, hemoglobin; S6K1, ribosomal protein S6 kinase beta-1; ERK1/2, extracellular signal-regulated kinase 1 and 2; PI3, phosphoinositide 3-kinase; AKT, protein kinase B; Ankrd1, ankyrin repeat domain 1; MuRF1, muscle RING-finger protein-1; MGF, mechanogrowth factor; MCT1/4, monocarboxylate transporter 1 and 4; RFD, rate of force development.

Evidence for such a mechanism comes from preclinical models (10), where young mice were exposed to AAS and subsequently increased their myonuclear content, resulting in a substantial hypertrophic advantage later in life. The authors of this work (63) even went so far as to suggest, "... the benefits of even episodic drug [AAS] abuse might be long lasting, if not permanent, in athletes. Our data suggest that the World Anti-Doping Code calling for only 2 yr of ineligibility after... [a doping violation for AAS] use... should be reconsidered." Support for whether an AAS-induced increase in myonuclear number in humans is lacking; however, if present, then AAS-induced increases in myonuclei are theoretically advantageous to an athlete even if strength and lean mass advantages have been lost.

Residual effects of endogenous testosterone exposure in testosterone-suppressed transgender females are areas of active study and debate. These effects vary greatly depending upon the developmental stage of treatment initiation and will be much less when treatment is initiated before pubertal onset. There is a dichotomy when looking at measures of prepubertal athletic performance. Studies evaluating age-group athletic records report no significant differences in top age-group performances between boys and girls younger than 10 to 12 yr old (64–66). However, some studies evaluating more specific measures of strength and aerobic capacity reveal an 8% to 10% advantage in prepubertal biologic males relative to females, even after normalizing for body size (67,68). These performance differences may be residual effects from higher testosterone levels during early infancy (e.g., "mini-puberty") and/or nonandrogenic genetic factors. Currently, there are no data on the durability

of these performance differences in transgender females who start gender-affirming treatment before puberty.

Postpubertal testosterone suppression has variable impacts on performance-related parameters. Within 3 months of starting hormone suppression, hematocrit decreases by 4% to within normal values for cisgender females (69). A recent systematic review also evaluated evidence to date regarding treatment-related reductions in muscle size, strength, and LBM (70), summarized in Table 8. Although the changes documented in Table 8, along with an increase in fat mass, may contribute to significant reductions in athletic performance, the current lack of data in active or athletic populations makes the magnitude of these changes difficult to assess.

## ANDROGEN SIGNALING

Androgen signaling at the tissue level occurs primarily genomically through the classical androgen receptor (AR) with

**TABLE 8.** LBM, strength, and muscle size of cisgender females and transgender females.

	Cisgender Males (Reference)	Cisgender Females (Relative to Cisgender Males)	Transgender Females (Pretreatment, Relative to Cisgender Males)	Reductions in Transgender Females with T Suppression (12 mo Posttreatment)
LBM	100	70%	94%–92%	–1% to 5.5%*
Muscle CSA	100		94%–88%	–1.5% to 12%
Strength	100	64% (handgrip)	90%–86% (handgrip)	1.5% to –7% (handgrip)

The right column shows changes in transgender females after 12 months of testosterone suppression (70).

\*One study reported changed from 12 to 31 months posttreatment of –4.7%; summarized in (70).



multiple levels of integration with other anabolic/catabolic pathways (71). Testosterone, DHT, and other AAS bind to cytoplasmic AR (72). Androgen receptor activity is altered at various sites; phosphorylation may augment androgen/AR transcriptional action (in the presence or absence of androgens) (73). Androgen receptor signaling is activated primarily by ligand binding, but under some circumstances through ligand-independent mechanisms (e.g., insulin like-growth factor-1 [IGF-1] induced mitogen-activated protein kinase-ERK1/2, p38 and c-Jun N-terminal kinase phosphorylation) (74) that may sensitize it to anabolic signals in the presence of low androgens (75). The AR is up-regulated following resistance training and short-term androgen administration (54).

Upon androgen binding to the ligand-binding domain (LBD) of the AR, the liganded AR undergoes phosphorylation, dimerization, and conformational changes, recruits coregulators, and translocates into the nucleus, where it regulates the transcription of androgen response elements (ARE) of the androgen-responsive genes (76). Androgen binding activates and stabilizes the AR, which is selectively induced by T, DHT, and AAS (77). Greater stability is seen with DHT than T (78). Binding affinity for the AR varies between androgens. Nandrolone and metenolone have a higher binding affinity than T, while stanozolol, methandienone, and fluoxymesterone have a lower binding affinity than T; and oxymetholone has a minimal binding affinity (79). Androgen binding to the AR completes the pocket that serves as a recruiting surface for co-activators (80). Some co-activators include BAF57 and 60a, SRC1 and 3, and ARA50 and 74. The activity of these co-regulators and the role of T in ribosome biogenesis may be important in mediating the anabolic effects of AAS on skeletal muscle.

Androgen/AR binding activates signaling through the Wnt- $\beta$ -catenin pathway. The presence of T (in a dose-dependent manner) increases AR- $\beta$ -catenin interaction and transcriptional capacity (81). Androgens promote myogenesis via multiple pathways. Satellite cells and myoblasts express AR and androgen binding, increasing satellite cell activation, proliferation, mobilization, differentiation, and incorporation into skeletal muscle (82). Androgens increase myogenesis via increased Notch signaling of satellite cells (83) and increased expression of IGF-1 (84). Androgen binding to AR on pluripotent mesenchymal cells increases their commitment to myogenesis and inhibits adipogenic differentiation via  $\beta$ -catenin signaling (85,86). Testosterone upregulates follistatin expression (which blocks signaling through the TGF $\beta$ -SMAD 2/3) and increases myogenic differentiation (82,84,86–88). Androgens may be anticatabolic by decreasing glucocorticoid receptor (GR) expression, interfering with cortisol binding, or the AR-T complex may compete with the cortisol-GR complex for *cis*-element binding sites on DNA (88–91).

Nongenomic AR signaling is rapid, with short latency periods acting independently of nuclear receptors (92). Nongenomic effects are thought to be mediated by direct binding to a target molecule, through intracellular AR activation (i.e., Src kinase), through a transmembrane AR receptor, or via changes in membrane fluidity (92). Nongenomic signaling involving

G-protein 2nd messenger system and may either increase intracellular calcium concentrations via PI3K, phospholipase C, and IP<sub>3</sub> signaling (93), stimulate the activation of mitogen-activated protein kinase signaling (94), and mammalian target of rapamycin pathway signaling (95). Cross-talk between IGF-1 signaling and nongenomic AR signaling appears critical to mediating some anabolic effects (96). Nongenomic signaling occurs rapidly within seconds to minutes, much faster than classic genomic signaling, which takes hours and requires the constant presence of androgens to maintain intracellular signaling.

## SIDE EFFECTS ASSOCIATED WITH ANDROGEN USE AND ABUSE

Investigations examining the safety of androgen use in various populations have been largely inadequate as there is tremendous variability in androgen dosages and patterns of use, including stacking of multiple AAS and concurrent use of accessory drugs (5). Figure 4 depicts the variety of adverse physiological and psychological effects associated with AAS use. These include relatively rare effects and those that are commonly expected, particularly with long-term AAS abuse (30).

A survey of 500 AAS users (99% male) who had extensive experience (8 wk to 25 yr with 95% having >1–3 yr of AAS use) with high doses showed that 23% to 64% of respondents reported minor side effects (e.g., testicular atrophy, acne, fluid retention, insomnia, sexual dysfunction, gynecomastia) (97). Other common effects of AAS use include deleterious changes in cardiovascular (CV) risk factors: decreased plasma high-density lipoprotein (HDL) cholesterol (98), changes in clotting factors (99), and mood or psychiatric disturbances (79). Suppression of the hypothalamic-pituitary-testicular axis and spermatogenesis may result in infertility, while elevations in liver enzymes may reflect liver dysfunction (100–102). In one study, competitive athletes who used AAS during their competitive careers were more likely to die prematurely than athletes who did not (103). The use of nonsterile needles and needle sharing practices for intramuscular injections increase the risk for infection, muscle abscess, sepsis, and communicable diseases, such as human immunodeficiency virus (HIV) and hepatitis B and C (5).

Although CV effects are commonly reported with AAS use, based on an extensive review, the FDA concluded that “...the studies have significant limitations that weaken their evidentiary value for confirming a causal relationship between testosterone and adverse cardiovascular outcomes” (104). Part of the difficulty in studying the effects of AAS on CV health is that the impacts of androgens on CV function vary with dose, method of administration, and aromatization potential (5). Parenteral administration of physiologic T replacement doses are associated with CV function and vary with dose, method of administration, and aromatization potential (5) with small decreases in plasma HDL, with little or no effect on total cholesterol, low-density lipoprotein (LDL) or triglycerides (105–107). However, supraphysiologic T doses are associated with significant reductions in HDL (108,109). Orally administered

## Possible Adverse Side Effects of AAS Use &amp; Abuse

<b>Psychological</b> ↑ Aggression, self-confidence, appetite, psychological disturbance, depression, mood swings, drug dependence, violent tendencies ( <i>roid rage</i> ), risk of suicide & homicidal death, hypomania & mania, insomnia: ---Withdrawal: depression, muscle dysmorphia, ↓ sex drive
<b>Cardiometabolic and Hematologic</b> Hypertension, nose bleeds, headaches & dizziness, ↑ insulin resistance, glucose intolerance, blood clotting abnormalities & polycythemia, ↑ LDLs, ↓ HDLs, ↓ ApoA1, ↑ TC, homocysteine, ↑ risk for heart attack & cardiac sudden death, arterial & venous thrombosis, stroke, atherosclerosis, ↑ LV myocardial hypertrophy, ↑ incidence of arrhythmias, impaired diastolic function, abnormal ECG (QRS > 114ms)
<b>Musculoskeletal</b> Premature growth plate closure, avascular necrosis, ↑ risk for tendon/ligament injury, collagen fiber dysplasia
<b>Liver (Hepatic)</b> Peliosis hepatitis, cholestasis, hyperbilirubinaemia, ↑ liver damage, ↑ risk for adenomas & carcinomas
<b>Renal</b> ↑ rhabdomyolysis, creatinine, cystatin C, glomerulosclerosis, renal failure, cholemic nephrosis
<b>Integumentary/Immune</b> ↑ sebaceous gland secretions/sweating, acne & skin rash, alopecia/baldness, hirsutism, striae distensae (stretch marks), abscess from injection, infections from needle sharing, immunosuppression
<b>Endocrine/Reproductive</b> ↓ testicular size, sperm count, levels of T (hypogonadism), breast tissue, ↑ estrogen levels, gynecomastia, masculinization, benign prostate enlargement, clitoral enlargement, infertility, erectile dysfunction, menstrual disturbances anovulation, amenorrhea, dysmenorrhea, change in body habitus, fluid retention, deepening of voice, ↑ libido, altered thyroid function

**FIGURE 4—Potential adverse physiological and psychological effects associated with AAS use. TC, total cholesterol; ApoA1, apolipoprotein A1; LV, left ventricle; ECG, electrocardiogram; T, testosterone.**

17- $\alpha$ -alkylated, nonaromatizing AAS produce greater reductions in HDL and increases in LDL than when AAS are administered parenterally (110). Angell et al. (111) reported that self-administering AAS (median daily dose = 228 mg) for >2 yr was associated with smaller longitudinal LV strain, right ventricular (RV) ejection fraction, and altered diastolic function compared with nonusers. Others showed impaired RV free wall strain and strain rate associations with AAS abuse in competitive bodybuilders (112). D'Andrea et al. (113) showed associations between AAS use (~31 wk; weekly dose = 525 mg) and left atrial impairment (a marker of diastolic burden) in elite bodybuilders compared with nonusers. An increase in left ventricular (LV) mass occurs during resistance training (114–116); however, potential additional effects from AAS use in humans are unclear. In rats, only high T doses (up to 20 mg per kg body mass) induced cardiac hypertrophy with an impaired contractile process (117).

Deceased men who had used AAS showed greater cardiac mass than nonusers (118). Multivariate analysis indicated that increases in heart size were explained by increased body mass and by AAS use. Risk for adverse cardiac events associated with LV mass is supported by case reports detailing sudden death among power athletes who self-administered AAS (100,119–122). Case reports are largely anecdotal, and a causal relationship between AAS use and risk of sudden death has not been established. Strength/power athletes self-administering AAS have short QT intervals but increased QT dispersion compared with endurance athletes with similar LV mass who have long QT intervals but do not have increased QT dispersion (123). The interval from the peak to the end of the ECG T wave (Tp-e), Tp-e/QT ratio, and Tp-e/QTc ratio increases in AAS users, suggesting a link between AAS and ventricular arrhythmias, which may increase the risk for sudden death (124).

Increases in liver enzymes, cholestatic jaundice, hepatic neoplasms, and peliosis hepatitis are associated with the use of oral, 17- $\alpha$  alkylated AAS (102,125,126), but not with parenterally administered T or its esters (127). The association

between liver toxicity and AAS use is based on increases in AST and ALT. These enzymes are not liver-specific and are often elevated from muscle damage after resistance exercise (101,128); thus, possibly overstating the risk of hepatic dysfunction (128,129).

Endogenous LH and follicle stimulating hormone secretion are suppressed during AAS use, with subsequent effects on testicular T secretion and sperm count (130,131). Depending on the dose and duration of AAS use, endogenous T, LH, and follicle stimulating hormone may take weeks to months to return to homeostatic levels (132), and the long-term effects are not well understood. High-dose androgen administration in men is associated with breast tenderness and enlargement, for example, gynecomastia (5,133), thought to result from peripheral conversion of androgens to estrogens in men administering aromatizable AAS (134). The prevalence of gynecomastia is unknown, but prevalence rates as high as 54% were reported in AAS users (5). The use of nonsterile needles and needle-sharing practices for intramuscular injections increases the risk for infection, muscle abscess, sepsis, and communicable diseases, such as HIV and hepatitis B and C (5).

There is no evidence that T causes prostate cancer, but testosterone replacement therapy (TRT) is associated with a small increase in prostate specific antigen levels in older men with low T, which increases the risk of urological referral for prostate biopsy (5). Because many older men harbor subclinical prostate cancer, a prostate biopsy may lead to subclinical low-grade prostate cancer detection. Notably, however, TRT increases the risk of prostate biopsy.

The psychological effects of AAS use have garnered much publicity, especially on issues of aggression and suicide. However, the evidence is inconclusive due to the lack of sensitivity of the research instruments used to measure aggressive behavior, large variability in RT programs, preexisting personality or psychiatric disorders, and prevalence of multiple high-risk behaviors and use of other substances, such as alcohol, psychoactive drugs, and dietary supplements (5). Interestingly,

physiologic T replacement in hypogonadal men may improve mood and attenuate negative aspects of mood (4). Morrison et al. (135) reported that the aggression and anxiety-provoking influences of androgens in animals are likely a developmental phenomenon and that adult exposure may be anxiolytic over the long term. However, underlying psychological dysfunction may cause a greater susceptibility to AAS use, and high doses of AAS may provoke a “rage” reaction in some individuals with preexisting psychopathology (136,137). Self-administration of AAS may increase the risk for mood disorders, such as mania, hypomania and depression (136,138). Resting T concentrations are related to posttraumatic stress (PTSD), in which higher T is associated with a lower risk for PTSD (139). Further, long-term use of AAS in former weightlifters was associated with poor cognitive function and negative changes in brain morphology (140,141). Approximately 30% of illicit AAS users will develop AAS dependence, and there is some overlap between AAS dependence and the mechanisms and risk for opioid dependence (142,143). Sudden discontinuation of exogenous AAS use in those who are dependent or have suppressed endogenous production may result in severe depression and suicidality (142,143). A multidisciplinary and medically supervised treatment program is indicated for individuals with AAS dependence.

Women self-administering AAS may undergo masculinization and experience hirsutism, deepening of the voice, enlargement of the clitoris, widening of the upper torso, decreased breast size, menstrual irregularities, and male pattern baldness (144). Some of these adverse effects may not be reversible (5).

Many of the side effects in adults may be seen in adolescents, but information on use in children is scant. Exogenous AAS exposure in preadolescence triggers pubertal onset and may result in early epiphyseal maturation and closure, leading to loss of ultimate height potential (40). Although mild acne is common during adolescence (40), AAS use may result in severe nodular acne, particularly on the back and shoulders, which is often resistant to treatment.

## CLINICAL USES OF ANDROGEN THERAPY

Although athletes and recreational trainees have reported obtaining AAS from physicians for illicit purposes (26,33,50), several clinically approved uses of T exist. Of concern are potential illicit use stemming from a clinical prescription of T given the increased number of antiaging and wellness clinics. The sale of therapeutic T preparations in the United States quadrupled between 2001 and 2011 (145), and an estimated >2.3 million men received physician-prescribed T therapy as of 2013 (146). In military treatment facilities, the number of androgen prescriptions increased > twofold (23% per year) from 2007 to 2011, mainly in 35- to 44-yr-old men (147). Currently, therapeutic T is mostly used to treat primary (i.e., testicular failure) and secondary (i.e., reduced LH) hypogonadism (148). Androgen therapy has numerous clinical uses outlined in Table 9 (145,146). A substantial fraction of young men receiving T prescriptions are former AAS users trying to

restore endogenous T production (149–151). The Endocrine Society Clinical Practice Guideline (148) details decision making regarding androgen therapy and the reader is referred to their specific guidelines on the diagnosis, treatment, and monitoring of hypogonadism in men (134).

Testosterone replacement therapy has been shown to improve sexual activity (152–155), vertebral and femoral bone mineral density (BMD) and microarchitecture (156,157), hemoglobin content (158,159), LBM, maximal voluntary strength and physical function (160–164), and reduces body fat and BMI (162,165,166). There have also been reports of TRT reducing neuroinflammation and depressive symptoms (167–169), reducing blood pressure and improving lipid profiles (166), and neuronal regeneration (154,156,170–177), and may not change or improve cognitive function in older men (174,178,179). There is a low frequency of adverse events associated with TRT (2,148,153,180–190). However, all TRT should be accompanied by a structured monitoring plan (148). The Endocrine Society recommends evaluating symptoms, adverse events, lower urinary tract symptoms, and measurements of T levels, hematocrit, and prostate specific antigen at baseline, 3 to 6 months after starting treatment, and annually thereafter (148).

Testosterone and free T levels decline with advancing age after peaking in the second and third decades of life (191–194), leading to increased risk of sexual dysfunction; decreased muscle mass and strength, BMD, mobility; increased falls and fractures, late-life low grade persistent depressive disorder (dysthymia), and CV mortality (148,195). Low T is associated with an increased risk of diabetes, metabolic syndrome, and increased carotid artery intima-media thickness (196,197). Whether older men with age-related T decline should receive TRT remains a matter of debate. The Endocrine Society Guideline for TRT of hypogonadal men recommends against routinely prescribing T to all men, 65 yr or older, with low T levels (148). Decisions regarding TRT should be individualized

TABLE 9. Indications and contraindications for therapeutic use of testosterone.

<b>Indications</b>
Male hypogonadism
Primary
Examples: Testicular trauma/torsion/irradiation, cryptorchidism, orchiectomy, Klinefelter syndrome, chromosome abnormalities, LH and follicle stimulating hormone receptor gene mutations, androgen synthesis disorders, myotonic dystrophy, hypothyroidism
Secondary
Examples: Irradiation/tumor of hypothalamus or pituitary, drugs/medications (opioids, marijuana, glucocorticoids, AAS), alcoholism, sleep deprivation, surgery, trauma, eating disorder/relative energy deficiency, Kallman syndrome, Prader-Willi syndrome
Mixed primary and secondary
Examples: diabetes, obesity, HIV infection, chronic obstructive pulmonary disease, chronic kidney disease, liver disease, aging, cancer
Hypogonadal sexual desire disorder in postmenopausal females
Constitutional delay of growth and puberty
Gender-affirming treatment for transgender males
<b>Contraindications:</b>
Cancer: prostate, breast, skin
High prostate specific antigen
Erythrocytosis/polycythemia
Sleep apnea
Venous thromboembolism
CV disease
Fertility problems

after discussing potential risks and benefits in men with both symptoms suggestive of consistent T deficiency and burden of symptoms (e.g., low libido, unexplained anemia, osteoporosis) and presence of other co-morbid conditions that increase the risk of T treatment (148). The shared decision making should weigh the patient's and clinician's values. In male children, physiologic doses of T are used for brief periods to initiate pubertal development in those with constitutional delay of growth and puberty. Testosterone is needed permanently for children with congenital or acquired hypogonadism.

Recent interest has focused on the role of T in athletic performance in transgender and sexual developmentally distinct athletes. Individuals transitioning to females may require a therapeutic-use exemption for spironolactone, which is often used to block the androgen receptor and lower overall testosterone levels. Currently, trans female athletes subject to WADA testing must document subthreshold T levels for at least 12 months before being allowed to compete as a female. The IOC sets this threshold at <10 nM, and World Athletics (formerly the International Amateur Athletics Federation) at <5 nM. Interested readers can obtain a much deeper discussion of this topic in several reviews (198–200).

## CONCLUSIONS

Anabolic-androgenic steroids include a wide spectrum of compounds that exert their effects through various mechanisms. Anabolic-androgenic steroid use is advantageous in athletic performance predominantly through enhancements in strength, power, increases in muscle mass, reduced recovery time, and other factors. Major competitive sporting bodies ban the use of AAS; however, the predominant area of AAS usage has now expanded into clinical scenarios, persons undergoing sexual

reassignment, and by those interested in AAS for purely aesthetic enhancement. Thus, it is not only athletes who are using AAS to gain performance advantages but also other individuals for various reasons. Use for AAS to enhance athletic performance is banned, and coaches, trainers, and medical staff should monitor for signs of use. The use/abuse of AAS has several notable side effects with various consequences that are, in some cases, reversible. Coaches, parents, trainers, and medical staff need to understand why athletes might use AAS and provide educational programming in a preventive capacity. The position of the ACSM is that the illicit use of AAS for athletic and recreational purposes is, in many cases, illegal, unethical and also poses a substantial health risk. Nonetheless, TRT is used in treating various conditions, and clinicians may elect to use this therapy when medically necessary. The ACSM acknowledges the lawful and ethical use of AAS for clinical purposes and supports the physicians' ability to provide androgen therapy to patients when deemed medically necessary.

This article is published as an official pronouncement of the American College of Sports Medicine and is an update of the 1987 ACSM position stand on the use of anabolic-androgenic steroids. Click here <http://links.lww.com/MSS/C362> to download a slide deck that summarizes this ACSM pronouncement on anabolic-androgenic steroid use. This pronouncement was reviewed for the American College of Sports Medicine by members-at-large and the Pronouncements Committee.

Care has been taken to confirm the accuracy of the information present and to describe generally accepted practices. However, the authors, editors, and publisher are not responsible for errors or omissions or for any consequences from the application of the information in this publication and make no warranty, expressed or implied, with respect to the currency, completeness, or accuracy of the contents of the publication. The application of this information in a particular situation remains the professional responsibility of the practitioner; the clinical treatments described and recommended may not be considered absolute and universal recommendations.

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