Androgenic Steroids Use and Abuse

Past, Present, and Future

Arthi Thirumalai, MBBS*, Bradley D. Anawalt, MD

KEYWORDS

• Anabolic steroid abuse • Androgens • Doping • Performance-enhancing drugs

KEY POINTS

- Elite athletes commonly abuse androgenic steroids as performance-enhancing drugs and use a variety of tactics to avoid discovery but methods and processes to detect abuse of these performance-enhancing drugs have evolved.
- Among the general population, long-term abuse of androgenic steroids seems to be uncommon but the highest risk groups are teenage boys and young men who are in competitive sports or who are bodybuilders and weightlifters.
- When used at high doses for prolonged periods, there are detrimental effects on the reproductive axis and potentially on the cardiovascular, hepatic, hematologic, neuropsychiatric, and dermatologic systems.
- Androgenic steroid abuse must be distinguished from the use of physiologic dosages for male hypogonadism.
- Androgens at physiologic or near physiologic dosages are generally safe and might also be useful in the chronic catabolic states, sarcopenia, hypoproliferative anemia, and as a component of male hormonal contraceptives.

INTRODUCTION

The effects of androgens have been an area of great interest ever since Charles Edouard Brown reported marked improvements in energy and vigor after self-administering an aqueous extract of canine and bovine testes in the 1870s. In 1935, Ernst Laqueur isolated and Adolf Butenandt and Leopold Ruzicka synthesized testosterone.[1] Subsequently, from the 1950s onwards, athletes started using various chemical derivatives of testosterone for competitive advantage. Although scientists remained skeptical of the effects of these chemicals, athletes continued their widespread use until these drugs were officially banned from use by the International Olympics Committee in 1974.[2] The effects of supraphysiologic testosterone on muscle size and strength were convincingly demonstrated in 1996 by Bhasin and colleagues.[3] It is noteworthy that all androgens have anabolic action at the muscle but the ratio of androgenic to anabolic effects vary by agent (refer to "Muscle-Wasting Conditions" section). Therefore, the term "anabolic androgenic steroids (AASs)" can be condensed to "androgenic steroids,"; however, we have chosen to use "AAS" in this review because readers are likely more familiar with that. AAS abuse spans a wide array of products with the principal goal of increasing systemic androgenic action, by either providing exogenous androgens or their precursors, or by increasing endogenous androgen concentrations (**Fig. 1**). The World Anti-Doping Agency (WADA) was established in 1999 to combat abuse of AASs and performance-enhancing drugs. Despite these measures, androgen abuse remains a

Department of Medicine, University of Washington, 1959 Northeast Pacific Street, HSB C-209, UW Box # 357138, Seattle, WA 98195, USA
* Corresponding author.
E-mail address: arthidoc@uw.edu

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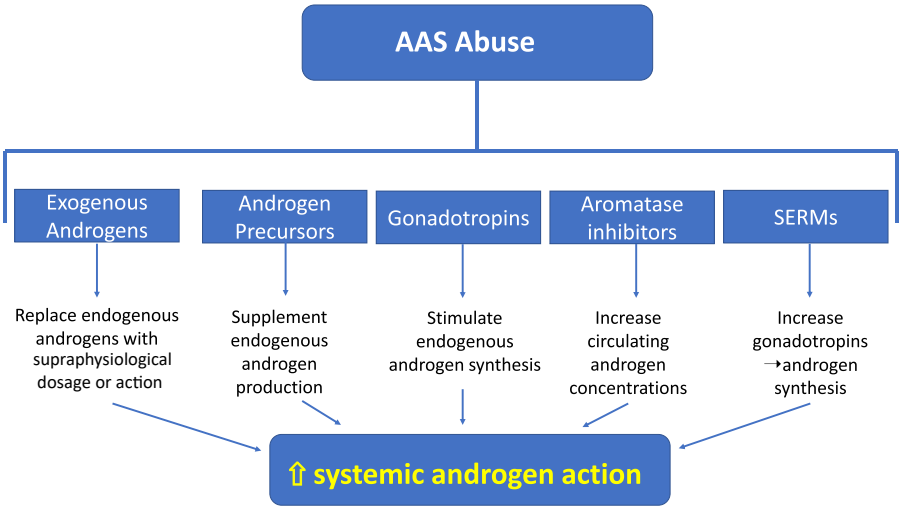

Fig. 1. Mechanisms behind AAS abuse. This figure outlines the various classes of drugs and their mechanisms of increasing systemic androgen effects. AAS, anabolic androgenic steroids; SERMs, selective estrogen receptor modulators.

problem in international sports, and the detection of performance-enhancing chemicals has needed to constantly evolve. Furthermore, the use of AASs has also spilled over into the general population in men aiming to achieve a "desired" appearance and boost self-esteem. There can be adverse consequences of the long-term abuse of AASs. In this review, we will outline the current state of AAS abuse among the general population and in the world of sports, provide guidance on how to diagnose AAS abuse, and offer strategies to manage patients wishing to discontinue their use and attend to their fertility goals during this process. We will also review the consequences of chronic AAS abuse and explore the data behind the therapeutic use of AAS in certain disease states. For this review, we will focus on AAS abuse in men because the prevalence among women is significantly lower[4] and data on long-term consequences and management is of insufficient quality to make strong recommendations.

EPIDEMIOLOGY OF ANABOLIC ANDROGENIC STEROID ABUSE

Estimating the prevalence of AAS use is challenging. Sources of this information include self-reported surveys, results of doping tests, investigative journalism, and government hearings.[5] Limitations of surveys include underreporting due to unwillingness to report,[6,7] small sample sizes, and confusion regarding exact AAS agents used.[8] Using results of doping tests to define the prevalence of AAS use are fraught with issues of variability in lists of banned substances and methodologies of drug testing, and they likely underestimate drug use in elite athletes by 8-fold.[7] Anabolic agents comprise most atypical findings (87%) reported by WADA and all adverse analytical findings (46%) reported by the International Amateur Athletics Foundation per the 2017 Anti-Doping Testing Figures Report.

Among the various studies, prevalence rates of AAS abuse among elite athletes and gym attendees have ranged from 9% to 67% and from 3.5% to 80%, respectively.[9] Weightlifters, powerlifters, and bodybuilders are also at higher risk for chronic AAS abuse, and rates as high as 33% to 80% have been reported.[10,11] Studies looking at these higher risk populations skew the overall prevalence estimates of AAS abuse because these are several-fold higher than in the general population.[4]

It has been estimated that the lifetime prevalence of "ever use" of AAS in the United States is between 1.3 and 4 million with ~100,000 new users annually.[12,13] However, most data do not clearly distinguish among lifetime, one-time, or sporadic use from chronic, sustained use of AAS. A study using mathematical modeling suggests that 30% to 35% of AAS users have used them at doses high enough and durations long enough to cause dependence.[13] The prevalence in the United States might be higher than other parts of the world: lifetime prevalence of AAS use of 0.7% in men and 0.002% in women was reported in a 2012 Swedish national survey of the general population.[14] Men have much higher prevalent use than women in all regions of the world, with a 2014 meta-analysis of worldwide studies of

AAS use indicating a lifetime prevalent use of 6.4% in men and 1.4% in women.[4] However, this study did not distinguish between sporadic use versus chronic abuse of AAS.

Despite the easier access to AAS through the Internet, the overall prevalence of AAS use seems to be declining among adolescents after a peak in the early 2000s.[15] Surveys such as Monitoring the Future and the Youth Risk Behavior Survey showed peaks of 3% to 5% around 2001 and rates around 1% to 3% in 2017 to 2018.[5,16] In summary, although AAS abuse exists in the context of performance-enhancement, there is no epidemic of their use among the general population.

BEHAVIORS AMONG ANABOLIC ANDROGENIC STEROID ABUSERS

AAS abusers tend to have a variety of motivating factors that can include performance-enhancement in athletics and sports, change in bodily appearance with fat-burning and muscle-building or an interest in looking and feeling "better."[17,18] The agents can be procured from multiple sources, with the most commonly reported ones being the Internet (71%), from a gym dealer (24%), foreign mail-order (19%), or prescription (11%).[19,20] Most users overwhelmingly report using (91%–95%) and preferring (77%) injectable options.[19,20] Users often "stack" multiple agents together or "pyramid" by progressively increasing drug intake, plateau, and then taper down during a median cycle length of 11 weeks (average 4–20 weeks) and repeat these patterns for a variable number of cycles (cycling).[5,19,20] The rationale of stacking or pyramiding is based on the incorrect belief that these patterns of use might mitigate against long-term adverse effects. During the "off-cycle" periods, many will consume ancillary drugs: (1) aromatase inhibitors to reduce side effects such as gynecomastia or (2) selective estrogen receptor modulators (SERMs) or gonadotropins (human chorionic gonadotropin [hCG]) to preserve testicular size and enhance testosterone levels, thereby preventing withdrawal symptoms. They may also consume a considerable number of nutraceuticals. An exhaustive list of all these agents and AASs is published elsewhere,[5] and a concise list of commonly abused AASs is presented in **Table 1**. Unfortunately, an overwhelming 92% of AAS users reported that they did not think their physicians were knowledgeable about AAS use.[19] The burden lies with the medical community to bridge this lack of trust, highlight the potential negative effects of prolonged AAS use, identify, and assist those who might be motivated to stop AAS abuse.

DETECTION OF ANABOLIC ANDROGENIC STEROID USE

Due to concerns for the rampant use of AASs among elite athletes, WADA and other antidoping agencies have been updating their testing practices and expanding the list of banned substances. A longitudinal monitoring program called the biological passport has recently been developed to prevent and detect the use of performance-enhancing drugs. The basic premise is to establish a "baseline" profile of various urinary androgen precursors and metabolites and then evaluating for changes in these urinary compounds over time. WADA has outlined detailed methodologies on how testing of elite athletes should be performed, and these are well-outlined in a prior publication.[21] Assays for various androgens and their metabolites have been continually modified over time to improve sensitivity and accuracy. Athletes tend to use many evasive techniques such as dilution, using someone else's urine sample or providing a sample from a time when they are not using AAS to avoid detection. To circumvent this, strict guidelines have been implemented for testing athletes, including testing at random times, and even observed micturition.

The approach to detecting AAS abuse in clinical practice differs (**Fig. 2**). Clinicians should suspect AAS abuse in a muscular man who presents with concerns of infertility, gynecomastia, or evaluation for testosterone supplementation. These men might report a decline or plateau in their strength or muscle bulk when training with weights and usually have "bigorexia" or muscular dysmorphia, a distorted body image that they are not muscular enough.[22] Physical examination reveals a normal virilization and large or hypertrophic muscles. When serum luteinizing hormone (LH) is suppressed to the lower limit of detection, testicular volumes are usually reduced by 25% to 35%.[23] However, if the baseline testicular volumes were 25 cc or greater, then the AAS abuser will not have "small testes." Testicular texture (softness) is not useful. Gynecomastia or breast tenderness can be another clinical finding in men who use aromatizable nontestosterone androgens or androgen precursors that disproportionately raise serum estradiol concentrations compared with testosterone.

Initial hormonal evaluation should include the measurement of serum testosterone, follicle-stimulating hormone (FSH), and LH. Interpretation of these laboratories is summarized in **Table 2**. It is not useful to measure urinary precursors or metabolites of androgens in clinical practice. First, these assays are not widely available in commercial

Table 1
Agents that are commonly used for anabolic androgenic steroid abuse

Exogenous Androgens (Generic/Common Name)	
"Designer Androgens"	*Endogenous Androgens Used as Drugs*
Bolandiol	Testosterone
Clostebol (Steranobol)	Dihydrotestosterone
Danazol	Boldenone (Equipoise)
Drostanolone (Masteron)	Nandrolone (Durabolin)
Gestrinone	
Metandienone (Dianabol)	
Metenolone (Primabolan)	
Oxandrolone (Anavar)	
Oxymetholone (Anadrol)	
Stanozolol (Winstrol)	
Tetrahydrogestrinone (The Clear)	
Trenbolone (Trenabol)	
Androgen Precursors	
Androstenedione (Andro)	
Androsterone	
Dehydroepiandrostenedione (DHEA)	
Gonadotropins	
hCG	
Recombinant human LH	
Aromatase inhibitors	
Anastrozole	
Letrozole	
Exemestane	
Selective estrogen receptor modulators	
Clomiphene	
Raloxifene	

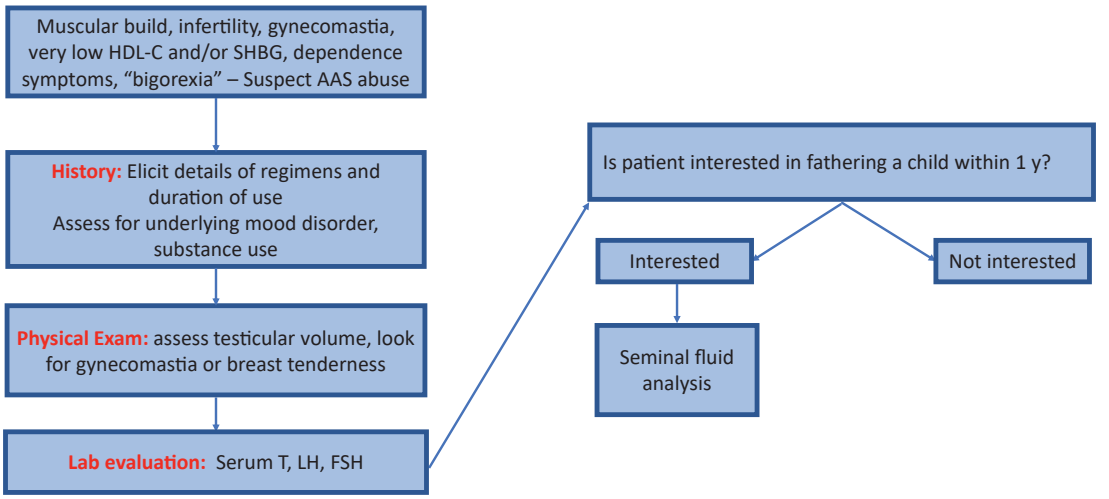

Fig. 2. Proposed initial evaluation when AAS abuse is suspected. This figure depicts an approach to the initial evaluation of a patient with AAS abuse or suspected AAS abuse. AASs, anabolic androgenic steroids; HDL-C, high density lipoprotein cholesterol; SHBG, sex-hormone binding globulin.

Table 2
Clinical signs and serum hormone concentrations during anabolic androgenic steroid use

Agent Used	New Onset or Tender Gynecomastia	Testes <15 cc	Serum Testosterone	Serum FSH	Serum LH
Testosterone	More common	More common	↑	↓	↓
Nontestosterone androgenic steroids	More common[a]	More common	↓	↓	↓
Testosterone precursors[b]	More common	More common	↑	↓	↓
Gonadotropins (eg, hCG)	Common	No	↑	↓	↓
Aromatase inhibitor alone	Uncommon	No	↑	↑	↑
SERM (eg, clomiphene)	?	No	↑	↑	↑

Abbreviations: FSH, follicle stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; SERM, selective estrogen receptor modulator.
[a] If agent is aromatizable.
[b] Symptoms manifest only at very high dosages.

laboratories for individual patients. Second, it is not possible to prevent submission of a urine sample during a time of nonuse or substitute a urine sample from a nonuser. Subsequent discussion with patients entails a discussion about the potential for adverse effects with a long-term AAS use and possible options to taper off.

ADVERSE EFFECTS OF ANABOLIC ANDROGENIC STEROID ABUSE

Is the use of AAS harmful? This question cannot be answered simply because it depends on the agent used, route of administration, dose and duration of use, use of adjunctive therapies and substances, and a person's age and underlying physical and mental health. Some adverse effects are class effects of androgens, such as suppressive effects on the hypothalamic-pituitary-testicular axis and erythrocytosis but other effects are specific such as hepatotoxicity with oral alkylated testosterone derivatives. Use of nonaromatizable androgens and aromatase inhibitors might have a higher likelihood of causing reductions in libido or erectile function due to the decreased estradiol production.[24] Changes in high-density lipoprotein-cholesterol (HDL-C) are more notable with oral formulations. Sporadic or transient use of AAS is less likely to have lasting adverse impacts on health; however, there are some data to support long-term effects of chronic high dose AAS use. Unfortunately, the data are weak and derived from case reports and series, case-control studies, and cross-sectional studies. In the following sections, we will review the potential adverse effects (Fig. 3) and the strength of the data for causation for each adverse effect (Table 3).

Reproductive Function

The use of an exogenous androgen exerts negative feedback inhibition at the hypothalamus and pituitary glands via the androgen and estrogen receptors and results in suppression of endogenous testosterone and sperm production.[25,26] Although using an AAS, its androgen action is sufficient to prevent hypogonadal symptoms (fatigue, decreased libido, erectile dysfunction) but these symptoms can develop in between cycles of use when the hypothalamic-pituitary-testicular axis is still suppressed. Aromatizable androgens, particularly at high doses, and hCG therapy (that stimulates aromatase) can cause tender gynecomastia. Some AASs are not aromatized; otherwise, men might use aromatase inhibitors (to avoid gynecomastia) that can lower estradiol concentrations considerably. In this setting, low serum estradiol concentrations can result in decrease in libido or erectile dysfunction despite androgenic effects of the AASs.[24] Many AAS abusers will detect testicular shrinkage over time but not men who use hCG. The timeline of recovery for the hypothalamic-pituitary-gonadal axis can be months[27] or years,[28,29] depending on duration and dosage of AAS use. In some men who have abused high dosages for years, the suppression of the gonadal axis may persist for many years (or indefinitely).[30] Additionally, in men who

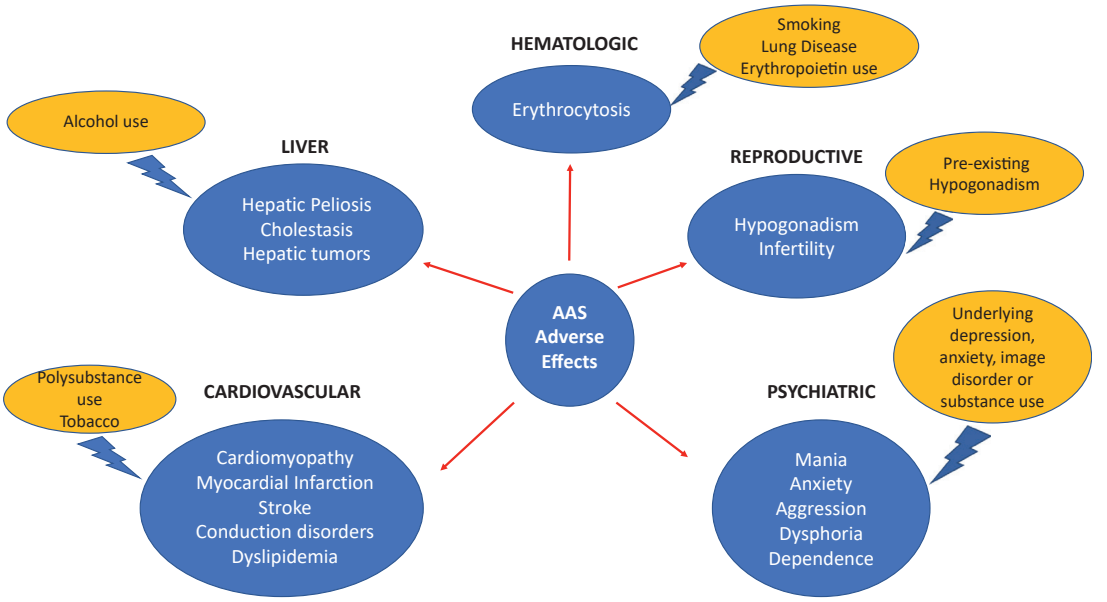

Fig. 3. Adverse effects of AAS abuse by system. This figure outlines the various known or suspected adverse effects of AAS use (in blue) and the potential confounding factors (in orange) that could exacerbate or be the primary cause of the adverse effect. AAS, anabolic androgenic steroids.

do not recover their gonadal function within 1 year after cessation of AAS use, the possibility of underlying classic causes of hypogonadism should be considered (eg, pituitary macroadenoma or Klinefelter syndrome). Men can present with infertility due to the inhibition of spermatogenesis, during or long after AAS abuse. Therefore, the abuse of AAS can cause variable presentations (see **Table 2**).[31–35] Depending on the regimen used, symptoms may develop during a cycle, in between cycles (for short-acting AASs), or persist after cessation of use.

Psychiatric Disturbances

Several psychiatric symptoms have been reported with AAS use, with certain symptoms developing during use while others constitute a "withdrawal syndrome." In studies of the psychiatric impact of AASs, investigators have interviewed AAS users about their psychiatric history "on" and "off" drug,[36–39] whereas other investigators have compared AAS users with nonusers using structured interviews and psychological scales[40–45] or followed AAS users longitudinally with

Table 3
Studies on adverse systemic effects of anabolic androgenic steroid use

Adverse Effect	Case Report/Series	Cohort Study or Case-Control Study	Cross-Sectional Study	Clinical Trials	Other (Meta-Analyses)
Reproductive function	212,213,28,29,30	27	31,32		33,34
Psychiatric disturbances	37,38,43,46,49	36,39,40,41,42,44,45,47		3,54,55,56,57	
Cardiovascular Effects	60,61,62,63,64,65,66,67,68,69,70, 71,72,73,74,75,76,77,78,79,80, 81,82,83,84,85,86,87,88,89,91,104	90,92,93,94,95,96,97, 98,100,105,106		101,102	
Hepatic Effects	110,114,115,118,119,120		113,117		109
Erythrocytosis	77,133,134	105		125,126,127, 129,131,132	128,130

The numbers in the various cells represent the reference number of the study demonstrating each adverse effect.

assessments during "on" and "off" cycles.[46,47] There seems to be a dose-related effect of AASs on mood disorders, particularly at doses equivalent or higher than 1000 mg testosterone per week.[5,48] There are also numerous observational reports that describe uncharacteristically aggressive or violent behaviors in previously normal individuals[5,49] who are using AASs. There have also been studies of supraphysiologic androgen exposure in healthy men using 300 mg of testosterone enanthate per week that demonstrated no adverse psychiatric effects[50–53] but this dosage is not comparable with those used by many chronic AAS abusers (500–1000 mg or greater per week). Placebo-controlled studies of the effects of 500 mg per week of testosterone[3,54–57] showed that 4.6% of men had hypomanic or manic symptoms compared with none on placebo. Based on the observational data from AAS abusers and experimental studies of high doses of testosterone in healthy men, there seems to be biological plausibility for a causal role of androgens in the reported psychiatric manifestations in a minority of AAS users. Symptoms that have been described during AAS abuse encompass issues with impulse control, aggression, anxiety, hypomania, and mania. When "off" the AAS agents, mainly depressive symptoms can develop—depressed mood, apathy, hypersomnia, anorexia, loss of libido, suicidality—that are likely due to a combination of sudden withdrawal of supraphysiologic androgen action as well as clinical hypogonadism. Potential confounders in all these presentations include underlying psychiatric disorders such as anxiety and depression[58,59] and concurrent use and abuse of alcohol and/or illicit drugs.

Cardiovascular Effects

Various adverse cardiovascular effects have been described in case reports and series from AAS use. These comprise cardiomyopathy,[60–65] myocardial infarction,[66–77] cerebrovascular accidents,[78–80] conduction abnormalities,[81–84] and coagulation abnormalities.[70,85–89] Evidence of cardiomyopathy has also been shown from postmortem studies showing greater cardiac mass[90] and ventricular hypertrophy with fibrosis[91] in AAS users; echocardiography[92–99] and cardiac MRI[100] have demonstrated decreased ventricular ejection fractions and reduced diastolic tissue velocities.

The best-defined adverse effect of AAS use on cardiovascular risk is a reduction in HDL-C, particularly with oral formulations.[101–103] However, whether this dyslipidemia increases atherosclerotic events is unclear although one study did report considerably higher coronary artery calcium scores than expected for men of that age in 14 professional weightlifters with long-term AAS use history.[104] A 2022 cohort study of 100 AAS abusers demonstrated reductions in HDL-C, apoprotein A and lipoprotein (a) and an increase in low-density lipoprotein-cholesterol, and apoprotein B.[105] Another cohort study of 86 weightlifters with a long-term AAS use showed myocardial dysfunction and accelerated atherosclerosis.[106] A limitation of these data is confounding from the high prevalence of tobacco and illicit substance use (cocaine, amphetamines) among these populations[107,108] but a sensitivity analysis looking at the contribution of these factors did not change their outcomes significantly.[106]

Hepatic System

A common misconception is that AAS use causes hepatotoxicity; however, this adverse effect is seen only with oral 17α-alkylated androgens.[109–112] The main consequences that have been described include hepatic peliosis[113–115] (a condition in which blood-filled cysts accumulate in the liver), cholestasis,[113] and various types of hepatic tumors.[109,115–120] One potential confounding factor is the development of transaminase elevations from excessive exercise in AAS users can be mistaken for hepatotoxicity.[121]

Erythrocytosis

Androgens have a stimulating effect on erythropoiesis through multiple possible mechanisms: increasing sensitivity to erythropoietin, suppressing hepcidin transcription and increasing iron availability to erythrocytes.[122–124] The use of AASs has been associated with dose-related increases in hemoglobin and hematocrit. This has been shown in clinical trials of healthy men treated with supraphysiologic doses of testosterone,[125–129] hypogonadal older men,[130–132] and in case reports of AAS abusers.[77,133,134] A recent cohort study of AAS abusers (n = 100) that followed them around the time of use as well as thereafter, showed a mean absolute increase in hematocrit of 3%, which was transient and normalized shortly after cessation of use (at 3 months and 1 year).[105] Potential confounders could include the use of other performance-enhancing techniques (abuse of erythropoietin or blood transfusions) or concurrent long-standing smoking history resulting in chronic obstructive pulmonary disease and hypoxemia. The concern with increasing red blood cell mass is the potential risk of increased viscosity of blood and its effects on cardiovascular disease. Studies have linked an elevated hematocrit to a higher rate of

cardiovascular death,[135] cerebral infarction,[136–138] and coronary heart disease.[139–143] However, the data linking AAS-use-induced erythrocytosis to adverse cardiovascular events is anecdotal.

Other Adverse Effects

Several other adverse effects of AAS abuse have also been described. Among musculoskeletal effects, tendon ruptures[144,145] and rhabdomyolysis[146,147] have been noted. The evidence of increased risk of tendon ruptures is based on case reports, and proposed mechanisms include disproportionate strength of hypertrophied muscles[148] as well as deleterious effects of AAS on the architecture of tendons,[149,150] as seen in preclinical models. Similarly, multiple case reports of rhabdomyolysis exist and is likely related to the excessive exercise that AAS abusers tend to engage in. Chronic effects of high doses of androgens on the pilosebaceous units can result in acne and androgenic alopecia.[151] Chronic kidney disease[152,153] has been described in a case report and case series with AAS abuse. There is an expected increase in serum creatinine in these users due to muscle hypertrophy. However, proteinuria and glomerulosclerosis have been described[153] and hypothesized to be due to a combination of postadaptive glomerular changes secondary to increased lean body mass and direct nephrotoxic effects of AAS. Finally, AAS abuse is associated with higher risk for various infections.[19,154,155] These include blood-borne infections such as HIV, hepatitis B and C, as well as skin and soft-tissue infections from unclean injection practices. In an Internet survey, 13% of AAS abusers admitted to unsafe needle practices.[12] Other risk factors that predispose AAS abusers to infections such as HIV, hepatitis B and C, include the high rate of use of these agents among homosexual[156] and incarcerated men.[157–159]

To summarize, in men, AAS abuse leads to suppression of testosterone and sperm production that is generally reversible within 1 to 2 years but the recovery time depends on duration, dose, and half-life of the AAS. There is also a dose-dependent increase in hematocrit that might lead to frank erythrocytosis. In some men, high dosages of AASs might cause psychiatric disturbances. Cessation after prolonged abuse of AAS is associated with a withdrawal syndrome that includes depression and fatigue and can be difficult to distinguish from persistent suppression of the hypothalamic-pituitary-testicular axis. There is an association between AAS abuse and cardiovascular disease that is concerning but this association is influenced by confounders such as a high prevalence of tobacco use, cocaine, amphetamines, and poor health habits in AAS abusers.

MANAGEMENT OF ANABOLIC ANDROGENIC STEROID USE AMONG THE GENERAL POPULATION

As reviewed before, some people use AAS fleetingly in their lifetime and can escape any lasting consequences of such an exposure. However, among those who develop dependence to these agents, clinical pathways for management are not well established. The initial assessment by medical professionals (see **Fig. 2**) should include evaluating whether the patient has dependence symptoms such as dysphoria, depression, fatigue, loss of libido or body (muscular) dysmorphia when not using AAS. Eliciting what the patient's motivations for ongoing use are and the presence of any associated history of depression, anxiety, and substance use issues are extremely important. Having a frank discussion about the duration and nature of AAS use and assessing the patient's readiness to stop using are the essential first steps in building trust with the patient and laying the framework to make any recommendations in the future (**Fig. 4**). It is also important to assess their near-term goals for their health and fertility (see **Fig. 4**).

Men Unwilling to Stop Anabolic Androgenic Steroid Use

For men who are not ready to quit AAS use, offering the option of prescription testosterone therapy, sometimes at supraphysiologic dose (such as testosterone cypionate 150 mg intramuscularly every week or more) can help build a physician–patient relationship that opens the door to closer monitoring for side effects and facilitates tapered discontinuation of AAS use.[22] Prescription testosterone therapy is safer than continued nonprescription AAS abuse because unregulated sources of androgens are often contaminated with miscellaneous compounds.

Men Willing to Stop Anabolic Androgenic Steroid Use

When men are interested in quitting AAS use, there are no FDA-approved treatment options, and the management approach largely depends on the person's fertility goals and duration of use.

Men desiring to father a pregnancy within 1 year

For men who wish to conceive within the next ~12 months, a seminal fluid analysis should be performed. Ideally, 2 seminal fluid samples

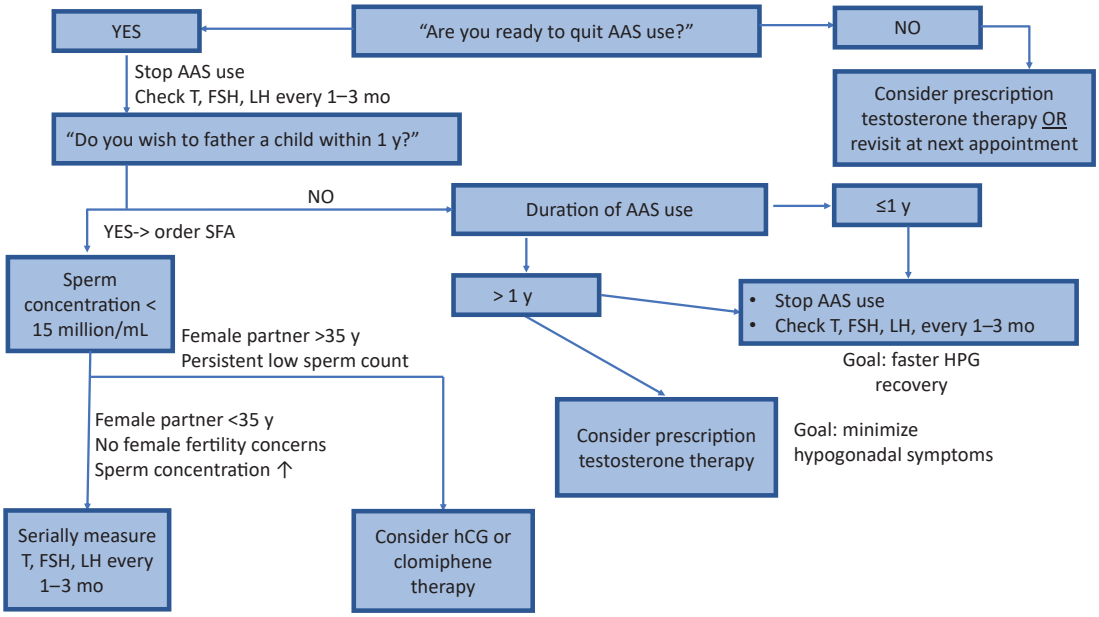

Fig. 4. Proposed discussion of cessation of AAS use, fertility needs and treatment options with patient. This figure outlines a suggested algorithm to assess a patient's readiness to quit AAS abuse and to assess their fertility goals. AASs, anabolic androgenic steroids; FSH, follicle stimulating hormone; hCG, human chorionic gonadotropin; HPG, hypothalamic-pituitary-gonadal; LH, luteinizing hormone; SFA, seminal fluid analysis; T, testosterone.

obtained after 2 to 7 days of ejaculatory abstinence should be analyzed. The time to recovery of the hypothalamic-pituitary-gonadal axis varies based on duration and route of AAS use, and it can be months[27] or years.[28,29] For those who have been using AAS for considerably longer than 1 to 2 years, the recovery is slower and requires longer term monitoring. This unpredictable recovery time of the hypothalamic-pituitary-gonadal axis may not align with their reproductive timeline and goals. This becomes particularly relevant if the female partner in the relationship is older (35 years or above) or also has infertility issues. In such men, the use of agents such as hCG[29] or clomiphene[160,161] have been described (**Table 4**), if their semen concentration is low. There are very little data to support effectiveness of hCG or clomiphene in men who have stopped AAS abuse. It is our recommendation to consider hCG therapy over clomiphene due to the lack of any safety concerns. Clomiphene is a SERM, which increases serum gonadotropins and testosterone concentrations within 2 to 4 weeks in men with intact hypothalamic-pituitary-gonadal function.[162–164] Although doses up to 100 mg every other day have not revealed adverse events in men aged younger than 50 years in these short-term studies, there are case reports of venous thromboembolism associated with clomiphene use by men.[165,166] hCG has the biological activity of LH and stimulated the Leydig cells in the testes to make testosterone. The increase in intratesticular testosterone drives spermatogenesis.[167] On hCG therapy, serum testosterone is monitored every 1 to 2 months, with the goal of achieving concentrations of 400 to 800 ng/dL. Subsequently, sperm concentrations are assessed every 1 to 3 months, with the goal of achieving at least 5 to 10 million sperm/mL of ejaculate and/or pregnancy. However, hCG increases testosterone while keeping gonadotropins suppressed. So, if after 6 months of hCG therapy, there has been an insufficient sperm response or lack of pregnancy, addition of FSH (either as human menopausal gonadotropin, or recombinant human FSH) can be considered to stimulated spermatogenesis. There are no safety concerns with hCG when used at dosages that maintain serum testosterone concentrations in the normal range. New onset of gynecomastia occurs in some men because the LH activity of hCG increases aromatization of testosterone to estradiol. A discussion with the patient is required, outlining a treatment plan of a 12 to 24-month trial (see **Table 4**) of these options, to increase serum testosterone in the upper half of normal range to see if it stimulates spermatogenesis, while acknowledging the unknown risks and likelihood of success.

Table 4
Proposed trial for induction of spermatogenesis in infertile men with prior anabolic androgenic steroid use with near-term fertility goals

Agent	Clomiphene	Human Chorionic Gonadotropin
Starting Dose	25 mg orally every other day	1000–2000 IU subcutaneously 2–3 times a week
Dose escalation	Increase by 12.5–25 mg every other day on monthly basis if serum testosterone less than the lower limit of normal	Increase weekly dosage by 1000–2000 IU on monthly basis if serum testosterone less than the lower limit of normal
Maximum	100 mg every other day	4000–6000 IU 2–3 times a week
Monitoring	Serum T, FSH and LH every month Once T in 400–800 ng/dL range for 3–6 mo, measure sperm concentration	Serum T every month Once T in 400–800 ng/dL range for 3–6 mo, measure sperm concentration
Side Effects	Venous thromboembolism	Injection site discomfort, cost
Outcomes	Anecdotal success in case reports	Anecdotal success in case reports

Abbreviations: AAS, anabolic androgenic steroids; IU, international units; ng/dL, nanograms per deciliter; T, testosterone.

No immediate desire for fertility

For men who have used AASs for less than a year duration, AAS can be stopped, and they can be monitored approximately every 3 months with assessment of serum testosterone and gonadotropins. Assessment of a seminal fluid analysis might never be required or can at least be deferred until after serum testosterone return to the normal range for 3 to 6 months. While waiting for the hypothalamic-pituitary-gonadal axis to recover, prescription testosterone therapy can be considered to ameliorate severe symptoms of hypogonadism but men should be counseled that this will maintain the suppression of serum endogenous gonadotropins, testosterone, and spermatogenesis.

POTENTIAL CLINICAL USES OF PRESCRIPTION ANDROGENS

AAS abuse is distinct from testosterone pharmacotherapy in men with hypogonadism. Diagnosing hypogonadism (primary or secondary) in a symptomatic patient with unequivocally low serum testosterone concentrations and appropriate treatment with testosterone therapy is not controversial and is the accepted standard of care.[168] Treating middle-aged to older men with borderline serum testosterone concentrations without convincing hypogonadal symptoms with physiologic doses of testosterone has been increasing. Reviewing the risks and benefits of such therapy and its appropriateness is not the aim of our current article, and we direct the readers to recent reviews.[169–171] There might be a role of AAS beyond testosterone replacement therapy for hypogonadism. In this section, we will summarize studies that have explored nontraditional uses of AAS.

Muscle-Wasting Conditions

Androgens are anabolic. Historically, these were measured in animal models by calculating the ratio of the change in levator ani weight (muscle-building or anabolic effect) to change in ventral prostate weight (androgenic effect).[172] Agents such as testosterone, dihydrotestosterone, and methyltestosterone have an anabolic to androgenic action ratio of about 1:1. However, other androgens, such as oxandrolone and nandrolone, have a ratio that is closer to 10:1[173,174] and have significant myotrophic effects. As such, these and other androgens have been used in severe catabolic states that cause muscle-wasting such as severe burns,[175,176] HIV/acquired immunodeficiency syndrome-associated wasting,[177–180] hemodialysis,[181] neuromuscular diseases such as Duchenne muscular dystrophy,[182–184] amyotrophic lateral sclerosis,[185] chronic obstructive pulmonary disease (COPD),[186–189] and protein catabolism from chronic corticosteroid therapy.[190] These studies have demonstrated measurable improvements in bone mineral content, total body weight, and lean body mass as well as reduction in hospital and rehabilitation facility lengths of stay. One important consideration is the possibility of coexisting hypogonadism in these chronic disease states and the need to evaluate such patients appropriately and treat when indicated.

Hypoproliferative Anemias

As previously mentioned, androgens have a stimulant effect on erythropoiesis.[122–124] This action has been used to treat a variety of anemias. In patients with aplastic anemia, various androgens have been investigated with and without corticosteroids[191–193] and response rates have varied from 40% to 100%.[194–196] Among patients with anemia due to chronic kidney disease, various androgens have been investigated with and without erythropoietin therapy[197–199] and have shown an increase in erythropoietin levels[200] and hemoglobin,[201] as well as reduction[201] or even elimination[202] of transfusion needs. Androgens have also been studied in treatment of other anemias including refractory anemias, anemia from chronic lymphocytic leukemia and hemolytic anemia with success.[193] Despite their clear beneficial effects on erythropoiesis in various anemic states, their use remains controversial due to concerns for development of androgenic side effects, polycythemia, and concerns for cardiovascular risks. Therefore, at this time, androgen therapy is considered second-line therapy or adjunctive to erythropoietin.

Male Hormonal Contraception

Androgens have been studied as hormonal contraceptive methods in men for many decades now. Studies using testosterone have proven effective at preventing pregnancies with greater than 95% efficacy, alone or in combination with progestins in various contraceptive efficacy trials.[203–208] These regimens have faced challenges such as inconvenient dosing regimens (weekly injections) and notable adverse effects (acne, modest weight gain, reduction in HDL-C, mood changes), which have hampered any product from coming to market. Novel androgens such as dimethandrolone undecanoate[209] and 11β-methyl-19-nortestosterone dodecylcarbonate[210] are being studied as potential daily oral or long-acting injectable formulations for male contraception. Another regimen that is currently undergoing an efficacy trial is a daily topical novel progestin, nestorone, formulated as a combined gel with testosterone.[211] If these agents move forward in drug development, they could revolutionize the world of contraception, distributing the burden more evenly among the sexes.

SUMMARY

The use of AASs is prevalent among the international athletic community. Although young male body builders are more likely to use AASs, it is unclear how common chronic AAS abuse is in the general population. Among those who abuse high dosages, infertility, erythrocytosis, neuropsychiatric adverse effects are the most common adverse effects. AAS abuse might also increase cardiovascular risk. There are no established care pathways to detect and treat patients who have abused AASs. Frank, respectful discussion with the patient is the best approach. The main approved indication for therapeutic use of AASs is for male hypogonadism. However, other novel uses of these agents include muscle-wasting conditions, anemias, and male hormonal contraception. A better understanding of the breadth and magnitude of the long-term effects of AAS on various organ systems by means of clinical trials will further our ability to manage their use among athletes and the public, as well as optimize their use in various disease states.

CLINICS CARE POINTS

- The possibility of androgenic steroid use should be considered in men who exhibit muscle hypertrophy, particularly if associated with infertility.
- Laboratory clues include elevated hemoglobin/hematocrit, low high-density lipoprotein-cholesterol (HDL-C) and low sex-hormone binding globulin (SHBG).
- Hormone assessment demonstrates suppressed serum gonadotropins (follicle-stimulating hormone and luteinizing hormone) and low serum testosterone, if abusing non-testosterone androgens, or high-normal to high serum testosterone, if abusing testosterone precursors or drugs with luteinizing hormone activity such as human chorionic gonadotropin (hCG).
- Clomiphene use results in a distinct pattern of high-normal to high gonadotropins and high serum testosterone without suppression of HDL-C or low SHBG.
- The topic of discontinuation of use is best approached in a nonjudgmental manner by educating them about long-term adverse consequences.
- There is not any recommended approach to helping men wean off anabolic androgenic steroid regimens but prescription of modestly higher than replacement dosages of testosterone followed by a tapering of the dosage might be effective and prevent loss to follow-up. If duration of abuse was less than 1 year, it is reasonable to recommend discontinuation of androgenic steroid abuse

without prescription of testosterone therapy. Most men who have abused androgenic steroids for less than 1 year will recover serum testosterone and gonadotropins to normal within 1 to 2 months.

DISCLOSURE

A. Thirumalai and B.D. Anawalt: Nothing to disclose.

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