



REVIEWS

Harm Reduction in Male Patients Actively Using Anabolic Androgenic Steroids (AAS) and Performance-Enhancing Drugs (PEDs): a Review

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Anabolic androgenic steroid (AAS) and performance-enhancing drug (PED) use is a prevalent medical issue, especially among men, with an estimated 2.9–4 million Americans using AAS in their lifetime. Prior studies of AAS use reveal an association with polycythemia, dyslipidemia, infertility, hypertension, left ventricular hypertrophy, and multiple behavioral disorders. AAS withdrawal syndrome, a state of depression, anhedonia, and sexual dysfunction after discontinuing AAS use, is a common barrier to successful cessation. Clinical resources for these patients and training of physicians on management of the patient using AAS are limited. Many men are hesitant to seek traditional medical care due to fear of judgment and lack of confidence in physician knowledge base regarding AAS. While proposed approaches to weaning patients off AAS are published, guidance on harm reduction for actively using patients remains sparse. Medical education regarding the management of AAS use disorder is paramount to improving care of this currently underserved patient population. Management of these patients must be non-judgmental and focus on patient education, harm reduction, and support for cessation. The approach to harm reduction should be guided by the specific AAS/PEDs used.

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INTRODUCTION

Anabolic androgenic steroids (AAS) and performance-enhancing drugs (PEDs) represent multiple classes of compounds used to enhance one's physique and/or improve physical performance. These include testosterone esters, synthetic androgens, aromatase inhibitors (AIs), selective estrogen receptor modulators (SERMs), selective androgen receptor modulators (SARMs), human growth hormone (hGH), fat-burning compounds, and myriad other compounds. The use of AAS has become widespread in the USA, with an estimated 2.9–4 million Americans using AAS at some point in their lifetime.¹ Worldwide, the lifetime prevalence of AAS use is

estimated at 1–5%.² Several case series of male gym attendees found the prevalence of AAS use to be 15–30% in this population.^{3–5} While AAS use is often associated with professional athletics, the majority of adults using AAS are non-professionals taking these compounds recreationally.^{4,6,7} Despite widely reported cardiovascular, reproductive, hematologic, and neuropsychiatric effects described with these agents, there exist no guidelines or evidence-based harm reduction approaches to men actively using AAS.

It is estimated that over 98% of those using AAS are male.¹ These compounds have become readily available through illicit internet sources.⁸ Men are commonly motivated to use AAS to improve their muscularity and strength.⁷ An increasing societal emphasis on body image is believed to have contributed to increasing AAS use among men.^{9,10} Many of these men may be prone to developing muscle dysmorphia, a pathologic pre-occupation with muscularity and body image that may impair quality of life.^{8,10} AAS use has also been correlated with a history of poor self-esteem, depression, suicidality, and previously experienced physical or sexual abuse.^{11–13}

Common consequences of AAS/PED use include dyslipidemia, hypertension, left ventricular hypertrophy (LVH), arrhythmia, atherosclerosis, polycythemia and thrombosis, infertility, endocrine dysfunction, tendon rupture, and sexual dysfunction.^{6,14–18} Those attempting to discontinue AAS use often experience AAS withdrawal syndrome, a state of depression, anhedonia, and sexual dysfunction which challenges prolonged cessation.⁶ The lack of long-term data, medical education, and national initiatives addressing AAS use is highlighted in several recent reviews, stressing the need for swift action to prevent the worsening of this growing issue.^{2,8} With limited public health resources available to men using AAS,⁶ and general distrust of clinicians among many of these patients,¹⁹ men often rely on other men using AAS and online sources for advice regarding use and procurement.^{7,20}

A major effect of extended AAS use is anabolic steroid-induced hypogonadism (ASIH), which refers to the disruption of the hypothalamic-pituitary-testicular (HPT) axis from prolonged exposure to supraphysiologic doses of testosterone esters, synthetic androgens, and accessory performance-enhancing drugs.²¹ Men using AAS often attempt to prevent

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ASIH by taking various compounds such as SERMs and hCG, an unproven strategy referred to as “post-cycle therapy” or “PCT.” ASIH is proving to be a significant cause of male hypogonadism, with 20.9% of 6033 hypogonadal men reporting prior AAS use in a recent retrospective study.²² The development, degree, and duration of ASIH is highly dependent on factors such as age, dosages used, duration of use, and compounds used.²³

While several authors have addressed the proposed management of men ready to stop AAS use with symptomatic ASIH^{2,23,24} (Table 1), harm reduction guidance for men actively using these agents remains limited. To begin, an example of a common clinical experience for the patient using AAS/PEDs is described to highlight the challenges faced by both clinician and patient. Next, the approach to caring for such patients, review of specific AAS/PED compounds, and strategies for harm reduction are described.

Clinical Example. A 39-year-old man presents to his primary-care clinic to discuss having blood work checked. Vitals are notable for a blood pressure of 142/90 mmHg and a body mass index (BMI) of 31 kg/m². On exam, he has above-average muscularity and mild acne. He hesitantly discloses he has been using steroids to improve his physique and describes his regimen (Table 2). He obtains the steroids from the internet and a friend at the gym helps him plan his “cycle.” He has concerns regarding his use and wants to make sure his liver function and blood counts are “okay.”

The clinician discusses the dangers of AAS use and recommends he discontinue. The patient expresses multiple

concerns with stopping, including concern over losing strength and muscularity. The clinician tells him “it is important for your health that you stop using. Why don’t you stop for a few weeks before we check labs?”

Frustrated with the lack of understanding and lack of assistance from his physician, he resorts to following advice of other men using AAS. Despite multiple attempts to wean his use, he struggles with severe depression from acute AAS withdrawal. Due to his prior experience with his healthcare provider, he continues to self-manage his care and rely on others using AAS rather than seeking medical care.

Initial Approach to Men Using AAS Seeking Healthcare

The presented vignette highlights a common situation: A concerned patient using AAS who is unsure how to best monitor his health, seeking guidance from a well-intentioned clinician with limited experience in assisting such patients. While the patient did not state willingness to cease use, he demonstrated concern for his health by seeking care. His clinician intended to help, but unintentionally promoted preconceived beliefs the patient had regarding the healthcare system, ultimately discouraging him to seek further care.

A recent systematic review of AAS use found common reasons for seeking medical care were overall health concerns, blood test monitoring, and prescription substances. Help with discontinuing AAS use was not a top priority.²⁵ Clinicians should certainly discourage AAS use, but the initial interaction should serve to obtain a better understanding of why the patient is using AAS, what concerns they have, and why they are seeking care. Doing so in a non-judgmental and supportive manner is essential. Open-ended questions may reveal motivations of the patient, such as fertility or side effect avoidance. Identifying these factors creates opportunities to build rapport, minimize harm, and eventually progress to cessation.

Alternatively, no such motivation may be identified. In this situation, harm reduction labs may be even more useful. For example, identifying previously undiagnosed dyslipidemia or cardiac disease may serve as motivation for some patients to consider cessation. The following sections will provide background, side effects, and harm reduction strategies for commonly used AAS/PEDs.

ANABOLIC ANDROGENIC STEROIDS AND PERFORMANCE ENHANCING DRUGS OF MISUSE: (TABLES 3 AND 4)

Injectable Androgenic Anabolic Steroids

Background. Dating back to the 1950s, numerous injectable testosterone compounds were used by elite athletes for strength and muscle gain. By the 1980s, AAS were in use by the general public.⁹ There are three main classes of AAS compounds: testosterone esters, 19-nortestosterone and related derivatives, and dihydrotestosterone (DHT) derivatives^{26,27}

Table 1 Proposed Methods for Transitioning Off AAS

Author	Proposed methods
Anawalt 2019 ²	<ul style="list-style-type: none"> • Method 1: “Immediate discontinuation of AAS with no medical therapy” • Method 2: “Discontinuation of AAS and initiation of a limited course of clomiphene therapy” • Method 3: “Discontinuation of AAS and initiation of a limited course of hCG therapy” • Method 4: “Conversion of nonprescription AAS to prescription testosterone” The author additionally notes “For these patients, the author has prescribed intramuscular dosages of up to twice the typical replacement dosage with a taper to physiologic dosage over several months”
Rahnama et al. 2014 ²³	<ul style="list-style-type: none"> • 4-week testosterone taper with SERM (Clomiphene 25 mg every other day), followed by rechecking testosterone and gonadotrophs. After 4 weeks, the author suggested ending testosterone therapy and continuing SERM use, also adding hCG 1000–3000 IU SQ 3 times weekly if labs suggested a poor response. • After 8 weeks, the authors recommend rechecking testosterone and gonadotrophs. At week 10, SERM dose should be reduced to 50% of starting dosage and continued until the target testosterone level is achieved. • Also mentioned is that some men using chronic high doses of AAS may have direct testicular damage-thus not responding to agents other than testosterone.

Table 2 Example of 12-Week AAS/PED Regimen with 6-Week Post-cycle Therapy

Week	Testosterone (Sustanon 250)	Trenbolone enanthate	Letrozole	Anadrol (Oxymetholone)	Human growth hormone (hGH)	Insulin (Lispro)*	Human chorionic gonadotropin (hCG)	Tamoxifen	Clomiphene
1	500 mg 2x/week	200 mg 3x/week		50 mg/day	6 IU / day	10 units pre-workout			
2	500 mg 2x/week	200 mg 3x/week		50 mg/day	6 IU / day	10 units pre-workout			
3	500 mg 2x/week	200 mg 3x/week	1.25 mg/day	100 mg/day	6 IU / day	10 units pre-workout			
4	500 mg 2x/week	200 mg 3x/week	1.25 mg/day	100 mg/day	6 IU / day	10 units pre-workout			
5	500 mg 2x/week	200 mg 3x/week	1.25 mg/day	100 mg/day	6 IU / day	10 units pre-workout			
6	500 mg 2x/week	200 mg 3x/week	1.25 mg/day	100 mg/day	6 IU / day	10 units pre-workout			
7	500 mg 2x/week	200 mg 3x/week	1.25 mg/day		6 IU / day	10 units pre-workout			
8	500 mg 2x/week	200 mg 3x/week	1.25 mg/day		6 IU / day	10 units pre-workout			
9	500 mg 2x/week	200 mg 3x/week			6 IU / day	10 units pre-workout			
10	500 mg 2x/week	200 mg 3x/week			6 IU / day	10 units pre-workout			
11	500 mg 2x/week	200 mg 3x/week			6 IU / day	10 units pre-workout			
12	500 mg 2x/week	200 mg 3x/week			6 IU / day	10 units pre-workout			
13							2500 IU 3x/week daily	20 mg daily	50 mg 2x/day
14							2500 IU 3x/week daily	20 mg daily	50 mg 2x/day
15							2500 IU 3x/week daily	20 mg daily	50 mg 2x/day
16							20 mg daily	20 mg daily	50 mg 2x/day
17							20 mg daily	20 mg daily	
18							20 mg daily	20 mg daily	

*Taken pre-workout with ~75 g simple carbohydrates

(Table 5). Each class is believed to have somewhat unique anabolic and/or androgenic effects.²⁶

The foundations of most AAS regimens are testosterone esters and synthetic testosterone compounds taken in supraphysiologic doses. Reported doses commonly range between 500 and 1000 mg of testosterone per week,⁷ which is 5–10 times the accepted treatment dose for male hypogonadism.²⁸

It is common for men using AAS to utilize injectable AAS for 8–16 weeks at a time, often referred to as a “cycle”.²⁷ “Stacking” refers to the use of multiple AAS/PEDs during a cycle. A cycle is commonly followed by a period of weeks to months where users either decrease their AAS dose or abstain completely to allow recovery

of their hypothalamic-pituitary-testicular (HPT) axis.²³ Additional AAS nomenclature is available in Table 6.

Adverse Effects. Cardiovascular effects of AAS are the most frequently reported and have the highest quality of data supporting their association. A recent cross-sectional study of 86 males with over 2 years AAS exposure was found to have reduced left ventricular ejection fraction (LVEF), impaired diastolic relaxation, increased left ventricular mass, and higher volumes of coronary artery plaque compared to age-matched non-users.¹⁵ Post-mortem studies revealed increased rates of cardiomegaly, left ventricular hypertrophy, and myocardial fibrosis compared to non-users.^{29–31} Increases in LDL and decreases in HDL were supported by a meta-

Table 3 Overview of AAS/PEDs, Side Effects, and Proposed Harm Reduction Approach

Compound	Common formulations	Users desired effect	Side effects	Harm reduction approach
Injectable AAS	Testosterone esters (cypionate, enanthate, propionate), nandrolone, compounds, trenbolone, boldenone	Increase muscle mass and strength	Dyslipidemia, hypertension, HTN, LVH, arrhythmia, tendon rupture, atherosclerosis	<ul style="list-style-type: none"> • CMP, CBC, lipid profile, PSA (If indicated) • LH, FSH, Testosterone • EKG, Screen for HTN • Consider TTE, CAC scoring • Ensure safe injection practices, discuss history of site infections
Oral AAS	Metandienone (Dianabol), Oxandrolone (Anavar), stanozolol (Winstrol)	Increase muscle mass and strength	All SEs of injectable AAS, hepatotoxicity	<ul style="list-style-type: none"> • Liver function tests in addition to injectable AAS screening recommendation
Aromatase inhibitors (AIs)	Anastrozole, letrozole, exemestane	Block estrogen effects when on high doses of androgens, "reset" HPT-axis	Sexual dysfunction, central adiposity, decreased bone density	<ul style="list-style-type: none"> • Bone densitometry
Selective estrogen receptor modulators (SERMs)	Clomiphene, tamoxifen	Block estrogen effects when on high doses of androgens, "reset" HPT-axis	Visual disturbances, vasomotor symptoms, headaches	<ul style="list-style-type: none"> • No specific testing
Fat-burning compounds	Liothyronine (T3), clenbuterol, dinitrophenol (DNP)	Achieve extremely low body fat levels	Arrhythmia, HTN, hyperthermia (DNP)	<ul style="list-style-type: none"> • ECG, continuous ambulatory ECG adhesive monitoring patch if needed • Screening for HTN • TSH
Insulin	Lispro, Glargine	Increase muscle mass and strength	Hypoglycemic shock, DM	<ul style="list-style-type: none"> • Glucometer • Review treatment of hypoglycemia • Hemoglobin A1c
Human growth hormone (hGH)	Many different brands	Increase muscle mass and strength	HTN, CM, increased risk of malignancy, DM	<ul style="list-style-type: none"> • BMP and magnesium to assess for electrolyte disorders
Diuretics	Furosemide, Torsemide, Hydrochlorothiazide	Reduce subcutaneous water pre-competition. Used with extreme water restriction.	Fatal hypokalemia	
Selective androgen receptor modulators (SARMs)	Ostarine, Andarine, Ligandrol	Increase muscle mass	Unknown, research compounds	<ul style="list-style-type: none"> • Same approach as injectable AAS
Human chronic gonadotropin (hCG)	Many different brands	Preserve testicular volume, increase testicular production of testosterone after AAS cycle	Suppressive to HPT-axis (works on testes), gynecomastia	<ul style="list-style-type: none"> • No specific testing
Site enhancement oil	Synthol, various formulations of water base, oil-based, or silicone-based injections	Increase appearance of muscle size by expanding volume	Infection, fibrosis, CVA, PE, hypercalcemia secondary to granulomas	<ul style="list-style-type: none"> • CMP (to assess for hypercalcemia) • Physical exam of injection sites to assess for abscess/infection

analysis examining 11 studies on dyslipidemia in men using AAS¹⁴; the same study found an association with AAS use and atrial fibrillation and ventricular arrhythmia. Coronary artery calcium (CAC) testing of 14 male professional bodybuilders using AAS found that 7 patients had CAC scores greater than the 90th percentile expected for their age, 3 of which were under 40 years old.³²

AAS use has been shown to cause infertility and ASIH in retrospective studies.¹⁷ Restoration of fertility and endogenous testosterone production is more likely in men who engaged in shorter (generally under a year) and less-extreme AAS use.^{2,23} Estrogenic side effects are common due to the aromatization of exogenous androgens, causing issues such as gynecomastia.³³ Exogenous testosterone is also shown to accelerate the growth of existing metastatic prostate cancer.³⁴

A wide range of behavioral effects are reported with AAS use including impulsivity, hypomanic/manic symptoms, aggression, and anxiety.^{6,35} Multiple retrospective and cross-

sectional studies found an association of AAS use with concurrent illicit substance use disorder, and body image disorders such as muscle dysmorphia.^{10,36,37} AAS withdrawal syndrome is reported in men abruptly stopping AAS use and involves significant symptoms of depression, libido dysfunction, and anhedonia.^{2,6}

Other notable adverse effects include dose-dependent erythropoiesis and polycythemia,³⁸ thrombosis,¹⁶ development of focal segmental glomerular sclerosis (FSGS),³⁹ acute kidney injury (AKI),⁴⁰ and upper extremity tendon rupture.¹⁸

Harm Reduction Strategies. Initial screening should include blood pressure assessment, review of family history of cardiovascular disease, lipid profile testing, a comprehensive metabolic panel, and electrocardiogram (ECG) testing. Hypertension and dyslipidemia should be treated according to national guidelines. Given the increased prevalence of LVH in this population,¹⁴ we favor angiotensin-converting enzyme

Table 4 Initial Treatment of Diagnosed Adverse Effects of AAS/PED Use

Diagnosed AAS/PED adverse effect	Potential treatment if unwilling to discontinue use
Mood disorders, depression, polysubstance abuse	Intensive behavior therapy
Hypertension	ACE inhibitors / ARBs as first line
Sexual dysfunction	Cessation of oral AAS prioritized rather than immediate treatment with PDE-5 inhibitors
Hepatic dysfunction	Cessation of oral AAS, referral to hepatologist
Dyslipidemia	Statins (caution if current oral AAS use)*
Left ventricular hypertrophy	ACE inhibitors or ARBs, referral to cardiologist
Accelerated atherosclerosis	Statins (caution if current oral AAS use)*
Exogenous hyperthyroidism	Education on risk of lethal arrhythmia, EKG if symptomatic palpitation/tachycardia.
Decreased BMD	Bisphosphonates ⁺ or denosumab ⁺ if osteoporosis present
Hypoglycemia	Provide with glucose testing supplies, education on hypoglycemic symptoms and management.
Diabetes mellitus	Dietary control, metformin
Polycythemia	Phlebotomy

*Contraindicated in severe liver disease and unexplained transaminitis. We suggest these agents be avoided in men actively using hepatotoxic oral AAS

+ = Off label for the purpose of treated AI-induced bone loss in men

(ACE) inhibitors or angiotensin receptor blockers (ARBs) for the treatment of hypertension. Obtaining a transthoracic echocardiogram (TTE) is reasonable if there is clinical concern for cardiac dysfunction, chronic AAS use (over 1 year), and/or strong family history of cardiovascular disease. CAC testing should also be considered if additional atherosclerotic cardiovascular disease (ASCVD) risk factors are identified.

We suggest prostate stimulating antigen (PSA) screening in this population the same way it is recommended in men receiving testosterone replacement therapy per Endocrine Society guidelines.²⁸ Screening involves assessing PSA in men aged 55–69 years old (or beginning at age 40 if high risk) in those agreeable to prostate cancer screening. Referral to

Table 6 Commonly Used AAS Nomenclature

Term	Definition
“Gear”, “roids”, “juice”	AAS
“Pinning”	Utilization of injectable intramuscular AAS
“Blast and cruise”	The practice of continually using AAS. “Blast” refers to periods of higher AAS doses. “Cruise” refers to a phase after a “blast” where AAS doses are decreased to slightly supraphysiologic doses
“On cycle”	A period of using AAS several months, usually at high dose
“Off cycle”	A period after using high doses of AAS, where users either stop or decrease their doses. Post-cycle therapy (PCT) is often used during this time
“PCT”	Post-cycle therapy. Refers to multiple drugs used after a period of high dose AAS use. This commonly includes SRMs, AIs, and HCG
“Gyno”	Slang for gynecomastia

urology is recommended in situations of abnormal prostate exam, PSA > 4 ng/mL, sudden worsening of lower urinary tract symptoms, or a confirmed PSA increase of greater than 1.4 ng/mL over a 12-month period. Testosterone levels with gonadotropins may be useful in quantifying the degree of androgen use and HPT-axis suppression, or if AAS use is suspected but uncertain.

Due to the high prevalence of behavior disorders and concurrent substance use,^{13,36,37} we suggest early referral to a behavioral health specialist, ideally having experience regarding substance use disorders and body image disorders. The association between AAS use and increased psychological distress and impaired executive function⁴¹ is one possibility as to why these issues are more frequently seen among this population.

Oral AAS/Pro-hormones

Background. Oral AAS compounds, such as metandienone (Dianabol), oxandrolone (Anavar), and stanozolol (Winstrol) are commonly used in conjunction with injectable AAS during steroid cycles for added muscle size and strength benefits.⁴² These agents gained popularity in the 1970s and continue to be common additions to user-designed AAS cycles.²⁷

Table 5 Classes of Injectable and Oral AAS

Injectable AAS	19-Nortestosterones	Dihydrotestosterone derivatives
Testosterone C-17 esters	Nandrolone compounds (Deca Durabolin, NPPP)	Mesterolone (Proviron)
Testosterone cypionate (Test C)	Trenbolone compounds (“Tren,” “Tren Ace”)	Drostanolone (Masteron)*
Testosterone enanthate (Test E)		Stanozolol (Winstrol, “Winny”)
Testosterone propionate (test prop)		
Testosterone decanoate		
Boldenone undecylenate (Equipose, Test EQ)		
Sustanon 250 (Blend of testosterone esters)		
Oral AAS	Dihydrotestosterone derivatives	Oral androgen pro-hormones
Methylated testosterone derivatives	Oxandrolone (Anavar)	Methasterone (Superdrol)
Methyltestosterone (“MIT”, MethylTest”)	Oxymetholone (Anadrol, “A-bombs”)	1-Androstenedione (Andro)
Metandienone (“Dianabol”, “D-bol”)	Metenolone (Primobolan, “Primo”)*	Dehydroepiandrosterone (DHEA)
Fluoxymesterone (halotestin)	Stanozolol (Winstrol, “Winny”)	
Chlorodehydromethyltestosterone (Turinabol, “CDMT”)		

*Both oral and injectable forms utilized

Adverse Effects. Alkylated oral compounds are associated with hepatotoxicity due to the presence of the 17-methyl group, which prevents degradation by first-pass hepatic metabolism when dosed orally.⁴³

Harm Reduction Strategies. In addition to the approach advised for injectable AAS, obtaining liver function tests is of benefit due to the high prevalence of hepatotoxicity from oral alkylated AAS. Reviewing concurrent substances, medications, or supplements that may cause additional hepatic injury is advised.

Aromatase Inhibitors

Background. AIs, such as anastrozole and letrozole, are used during an AAS cycle to minimize the conversion of testosterone to estradiol. This practice is done to minimize estrogenic side effects such as gynecomastia,²⁰ as well as to maximize the anabolic effects of AAS.

Adverse Effects. Previous randomized control trials of hypogonadal men have shown AI use in men results in decreased sexual function, increased adipose distribution,⁴⁴ and decreased bone mineral density.^{44,45} While no cardiovascular event data exists for men using AIs, a retrospective study of over 13,000 female breast cancer patients using AIs showed an increased risk of valvular dysfunction, pericarditis, and dysrhythmia.⁴⁶

Harm Reduction Strategies. Obtaining yearly bone densitometry in patients using AIs is beneficial to screen for low bone mass; however, it should be discussed that insurance may not cover this cost. In men under 50 with low bone mass, but without an osteoporotic defining fracture, optimization of vitamin D levels and encouraged cessation of AI use are suggested. Bisphosphonates, or denosumab, could be considered in patients found to have osteoporosis. While no strong treatment data in this population exists, and such use would be off-label, these agents have been recommended in a joint position statement regarding management of AI-associated bone loss in post-menopausal women with hormone-sensitive breast cancer.⁴⁷ Discussing the sexual side effects of these agents may also benefit in promoting cessation.

Selective Estrogen Receptor Modulators

Background. Commonly used SERMs include clomiphene citrate and tamoxifen.⁷ Tamoxifen is used with AIs during heavy androgen use to limit estrogenic side effects.^{20,23} Clomiphene citrate is used to assist with recovery of the hypothalamic-pituitary-testicular axis after heavy androgen use.^{2,20,23} It is common for patients to take both clomiphene citrate and tamoxifen together as “post-cycle therapy” (PCT) after a cycle of AAS.²⁷

Adverse Effects. Clomiphene has successfully been used in men for treatment of hypogonadism for up to 7 years with no major adverse effects⁴⁸; however, prior systematic reviews suggested a potential correlation with thrombosis and ocular symptoms due to central retinal vein occlusion (CRVO).^{49,50}

Harm Reduction Strategies. We recommend no specific testing for SERM use; however, gathering user experiences regarding these agents may be useful for future cessation attempts. For example, men using AAS noting previous benefits from clomiphene use may be willing to attempt AAS cessation using such agents in a medically supervised manner.

Human Chorionic Gonadotropin

Background. Human chorionic gonadotropin (hCG) is used to prevent testicular atrophy and preserve some degree of testicular function.²⁷ It is also utilized as PCT to expedite the recovery of testosterone production by Leydig cells.²⁰

Adverse Effects. The primary adverse effects of hCG include potential suppression of the HPT-axis and gynecomastia.²

Harm Reduction Strategies. No specific testing is recommended, although this agent is rarely used in isolation.

Phosphodiesterase-5 Inhibitors

Background. Men using AAS commonly use phosphodiesterase-5 (PDE-5) inhibitors (such as sildenafil or tadalafil) for both erectile dysfunction and improved blood flow to muscles during strength training.⁵¹ Users may also combine these with popular workout supplements containing nitrate donors such as sodium nitrate.⁵²

Adverse Effects. A case series on misuse of these agents described severe hypotension, cardiovascular collapse, and death⁵²; combining PDE-5 inhibitors with nitrates is particularly dangerous given the potential for significant decreases in systolic blood pressure and coronary perfusion.⁵³

Harm Reduction Strategies. A review of the risks of these agents, particularly the danger of combining with nitrate compounds, should be discussed.

Fat Burning Compounds (T3, Clenbuterol, and DNP)

Background. Commonly used compounds to reduce body fat include liothyronine (T3), clenbuterol, ephedrine, and occasionally, dinitrophenol (DNP).^{27,42} T3 is commonly combined with the potent oral beta-2 agonist, clenbuterol. While clenbuterol is primarily used for its fat-burning properties, limited animal data has suggested it may also have an anabolic effect on skeletal muscle.⁵⁴ DNP is an organic uncoupling agent which allows proton leak across the inner mitochondrial membrane, creating heat as

opposed to adenosine triphosphate (ATP). It was originally used in the 1930s as a breakthrough weight loss medication, before being banned in 1938.

Adverse Effects. Clenbuterol and T3 misuse has been associated with hypertension, arrhythmia, and myocardial ischemia in a retrospective review.⁵⁵ Patients using T3 will commonly have markedly suppressed TSH levels, suppressed T4 levels, and significantly elevated T3 levels. DNP has been associated with multiple deaths due to severe hyperthermia.^{56–58}

Harm Reduction Strategies. Screening for hypertension and ECG testing should be performed in all patients using these agents. TSH level with reflexive free T4 and total T3 levels should be obtained in patients using thyroid hormone as a PED.

Site Enhancement Oils

Background. The use of injectable intramuscular oil (also called “site enhancement”) is utilized by some men using AAS, especially elite bodybuilders.⁵⁹ Site enhancement oil adds volume to the injected muscle, creating a “fuller” appearance. A popular formulation, known as synthol, consists of 85% oil suspended in an alcohol and lidocaine.⁵⁹ An additional compound, polymethylmethacrylate (PMMA), has been misused for cosmetic body sculpting.⁶⁰

Adverse Effects. Various complications, including injection site abscesses, systemic infection, cerebrovascular accident (CVA), intramuscular cystic disease, muscular fibrosis, vasculitis, and pulmonary emboli, have been described in case series.^{59,61} Case reports of hypercalcemia secondary to 1,25-dihydroxyvitamin D production from granulomas formed at the areas of injection have also been described.^{62,63}

Harm Reduction Strategies. A CMP should be obtained to assess for hypercalcemia. Physical exam of injection sites should assess for potential infection, abscesses, or masses.

Insulin

Background. Insulin is used during phases of attempted weight gain due to insulin’s anabolic effects on protein and glycogen synthesis. Short-acting insulin is commonly administered pre-workout, post-workout, or both with simultaneous ingestion of simple carbohydrates.⁴²

Adverse Effects. Multiple cases of hypoglycemia in non-diabetic bodybuilders misusing insulin are reported, including one case of hypoglycemic coma.^{64–66}

Harm Reduction Strategies. A reasonable approach includes educating the patient on potential life-threatening hypoglycemic events, assessing a hemoglobin A1c, as well as providing

glucometer and testing supplies to those who decline to stop using insulin. A hypoglycemia treatment plan should be provided.

Diuretics

Background. Diuretics, such as furosemide and torsemide, are used 1–2 days prior to a physique competition to minimize subcutaneous water retention. Diuretic use occurs concurrently with extreme water and salt restriction, followed by a period of “salt loading.” Prior to competition, some competitors attempt to completely restrict sodium in addition to lowering water intake to less than 250 cc during the day of competition.⁶⁷

Adverse Effects. The combination of high-dose diuretics and electrolyte/water manipulation increases the risk of lethal electrolyte derangements such as hypokalemia. A case of hypokalemic paralysis during a bodybuilding competition was recently reported, in which the patient took 160 mg oral furosemide while restricting water intake.⁶⁸

Harm Reduction Strategies. Patients using diuretics while manipulating water and food intake are at the greatest risk of life-threatening electrolyte derangements. Potassium and magnesium levels should be assessed.

Human Growth Hormone and Related Peptides

Background. Human growth hormone (hGH) is used during AAS cycles to enhance muscle hypertrophy and strength.^{42,69} Doses vary significantly and generally range between 2 and 12 international units (IUs) daily.^{27,42} Synthetic growth hormone-releasing hormone (GhRH) analogues, such as sermorelin, and IGF-1 are also used as a PEDs and sometimes prescribed by anti-aging clinics via compounding pharmacies.²⁷

Adverse Effects. Growth hormone excess has physiologic sequelae including hypertension, cardiomyopathy, increased malignancy risk, entrapment syndromes, and diabetes mellitus among many others, as is seen in patients with acromegaly.⁷⁰

Harm Reduction Strategies. Initial assessment should include screening for hypertension, hemoglobin alc, assessment of cardiovascular risk factors, and ensuring patients are up to date with age-appropriate cancer screenings.

Dopamine Agonists

Background. Dopamine agonists (DAs), such as cabergoline and bromocriptine, are occasionally taken by men using AAS to mitigate potential hyperprolactinemia.²⁷ While somewhat controversial, one animal study demonstrated that the use of the progestin-derived synthetic androgens nandrolone decanoate resulted in significant prolactin elevation.⁷¹

Cabergoline is also used for enhanced sexual function and reduction of refractory period, which has been demonstrated in several randomized control studies.^{72,73}

Adverse Effects. Side effects of DAs include headaches, orthostasis, nausea, increased impulsivity, and occasionally cardiac valvular disease in chronic use.⁷⁴

Harm Reduction Strategies. Screening for and treating behavioral disorders are of importance given AAS alone has the potential to cause these issues. In rare situations patients have taken high-dose DAs for more than several years, a screening TTE is reasonable to exclude valvulopathy.

Selective Androgen Receptor Modulators

Background. Selective androgen receptor modulators (SARMs) represent a relatively new class of non-steroidal compounds with tissue-specific agonist or antagonist activity at the androgen receptor. While the first SARM was originally developed in 1998, none has been FDA-approved.⁷⁵ Multiple professional athletes have been found using these compounds illegally in the past several years.^{76,77} SARMs are typically purchased online as “research chemicals”.⁷⁸

Adverse Effects. While long-term data on these agents are not yet available, a clinical trial of one SARM was found to cause HDL suppression and abnormal liver function tests.⁷⁹ In a recent study involving chemical analysis of 44 products marketed online as SARMS, only 23 (52%) were found to contain SARMs, while many contained alkylated AAS compounds.⁷⁸

Harm Reduction Strategies. Given the substantial lack of data on these agents, we suggest a similar approach to patients using injectable AAS. Patients using SARMs should be educated on the lack of safety data.

DISCUSSION

AAS use among men continues to be a major healthcare issue that has not been adequately addressed by the medical community. The combination of easily procurable AAS/PEDs via internet sources and increased societal emphasis on idealistic muscular physiques across social media-fueled this health crisis. As with any substance use disorder, it is our duty as clinicians to provide empathetic, ethical, and supportive care to minimize self-harm until successful cessation is achieved. Limited formal undergraduate and graduate medical education on AAS use, distrust of clinicians among men using AAS,¹⁹ and lack of evidence-based harm reduction approaches to this population have resulted in suboptimal care. It is a concerning disconnect between patients and clinicians which has yet to improve.

Many clinicians request these patients immediately stop AAS use; however, multiple physiologic and environmental

factors challenge patients attempting to do so. Symptoms of depression, anhedonia, and sexual dysfunction due to AAS withdrawal syndrome increase the rate of recidivism in this population.⁶ A recent case-controlled study suggested most men discontinuing AAS eventually recover endogenous testosterone production and spermatogenesis⁸⁰; however, being able to successfully abstain for long enough (months to years) to allow for HPT-axis recovery is a separate challenge altogether. Those using AAS likely associate with other men who use AAS and prioritize muscularity, strength, and body image. These ongoing environmental exposures and temptations in themselves serve as risk factors for recurring use. Given the many challenges of successful AAS cessation, it is paramount that harm minimization is prioritized to reduce the development of devastating health effects.

Harm reduction strategies are needed to assist the millions of men using these compounds who are currently unable or without the desire to quit. A recent review by de Ronde et al.⁸¹ emphasizes the need for improved healthcare of men using AAS, but notes “It is the policy of our clinic not to offer routine health and blood checks to active users *without* health problems.” The authors discuss that reassuring results might encourage patients to continue using AAS. We believe this approach further propagates distrust of physicians, encourages continued reliance on other men using AAS for guidance, and reduces the likelihood of eventual cessation. A harm minimization approach to active AAS use is analogous to widely accepted public health practices such as screening active smokers for lung cancer and intravenous drug users for blood-borne viruses.

Compassionate care is paramount. It is essential that cessation of AAS use is routinely discussed with the patient. These regular discussions should be non-judgmental and caring, much like with smoking cessation. The authors strongly oppose the prescribing of medications with potential anabolic uses in patients who are currently using illicit AAS/PEDs. For example, we discourage prescribing an AI or SERM to a patient on illicit AAS who wishes to decrease his estrogen levels. In men who present with sexual dysfunction, not ready to work towards discontinuing AAS use, we discourage the use of PDE-5 inhibitors or other related treatments because clinician-supervised cessation of AAS improves/resolves this issue. We strongly support the screening and treatment of AAS-related cardiovascular conditions, behavioral disorders, and hematologic disorders to further reduce self-harm during AAS use. Once a patient acknowledges he is ready to discontinue AAS use, we currently favor a personalized approach as outlined in reviews by Anawalt² and Rahnema et al.,²³ as no randomized control trials on this subject have been conducted.

We believe harm minimization would not only reduce adverse effects of AAS but also serve as a bridge to cessation. For example, many men using AAS are relatively young and have no prior health issues. A medical assessment revealing hypertension, dyslipidemia, and LVH may serve to have such a patient reconsider further use and consider cessation. In some men, the

desire to continue AAS use will predominate despite the diagnosis of serious adverse effects. In these cases, the authors recommend continued close clinical surveillance in addition to prompt referral to appropriate behavioral health specialists. This will allow for continued health monitoring and management of adverse effects, while further building rapport and presenting ongoing opportunities to reconsider cessation.

LIMITATIONS

Most of the reviewed literature consisted of cross-control studies, retrospective reviews, and case series. The lack of randomized controlled data and limited prospective data are significant limitations. The guidance provided is based upon the current literature and the clinical experience of the authors.

CONCLUSIONS

A harm reduction approach, with a strong emphasis on reducing cardiovascular risk, should be taken with men actively using AAS who decline current cessation.

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Declarations:

Conflict of interest: Thomas O'Connor owns and operates a private practice internal medicine clinic based out of Essex, CT, and has written a book on the adverse effects of AAS misuse. The authors have no other disclosures to declare.

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