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Dear Colleague:

Abuse of anabolic-androgenic steroids (AAS) and performance-enhancing drugs is a major public health concern for men worldwide yet is often interchangeably labeled by the media as “testosterone abuse,” “steroid abuse,” or “doping.” This has led to confusion among patients, and even some physicians, who have difficulty discussing inappropriate use of anabolic androgens and performance-enhancing drugs as

distinct from appropriate testosterone therapy in patients with hypogonadism.

The current climate of negative public perception about abuse of AAS and performance-enhancing drugs presents an excellent opportunity for patient education. In this issue of *TU Times*, we will consider the types of AAS being abused—including exogenous and endogenous AAS, gonadotropins, and androgen modulators—and dissect the patterns of androgen abuse.

Our goal is to bring clarity to the discussion about the appropriate use of testosterone for the treatment of hypogonadism. It is also imperative for patients and physicians to be able to have an informed conversation about safety concerns, discriminating between the dangers of illicit “street use” of AAS and the potential adverse effects of testosterone therapy.

To this end, in the feature article, we review the prevalence, history, and difficulty of assessing the impact of AAS abuse. In the interview, my distinguished colleague Wayne J.G. Hellstrom, MD, offers his clinical insights on recognizing AAS abuse, supporting patients in adopting lifestyle changes to ensure overall health, and educating patients about safe and appropriate treatment of hypogonadism with testosterone therapy.

We hope that you find this newsletter informative and applicable in your clinical practice to improve patient care. Please provide us with feedback by completing the [evaluation and posttest](#).

Sincerely,

Feature Article

Ronald S. Swerdloff, MD

Abuse of anabolic-androgenic steroids (AAS) is a significant public health issue.^{1,2} According to worldwide surveys conducted in the late 1980s and early 1990s, millions of boys and men have abused AAS to enhance athletic performance or personal appearance,^{1,3,4} and US surveys have estimated abuse of AAS by male high school students to be between 3% and 11%.^{2,3}

From the 1930s through the 1980s, AAS (including testosterone and related compounds) were primarily used to treat hypogonadism.⁵ The first documented use of testosterone as a performance-enhancing drug in competitive sports occurred in the 1950s, when elite athletes began using AAS at supraphysiologic doses, leading to the recognition by some and suspicion by others of their potential for enhancing muscle mass growth.^{4,6} In 1974, AAS use was banned by the International Olympic Committee,¹

however, its use had already begun to spread beyond weightlifters to other sports, such as baseball and swimming.^{1,5,7}

In 1996, landmark findings published in *New England Journal of Medicine* provided evidence that supraphysiologic doses of testosterone enhance athletic performance, providing scientific evidence of what elite athletes had known for 40 years.^{1,4,6} This study of 40 healthy men aged 19 to 40 years demonstrated that intramuscular testosterone enanthate 600 mg per week increased muscle mass, size, and strength over a 10-week period, especially for the group of men enrolled in a strength-training program.⁴

Today, a variety of factors complicate discussing the impact and dangers of AAS abuse. Many types of androgens and androgen modulators are being abused, including exogenous and

endogenous AAS, gonadotropins, and androgen modulators.¹ To boost testosterone levels, many “street users” are taking multiple agents, including accessory drugs, such as androgen-receptor stimulating agents or their surrogates, eg, human chorionic gonadotropin, aromatase inhibitors, or clomiphene-like products.^{1,7} Physicians should be aware of the wide array of androgens and androgen modulators being abused, including those that the World Anti-Doping Agency (WADA) has designated as prohibited.¹

In the case of “street use,” androgens are acquired illicitly, often through unconventional sources, even from physicians prescribing therapy without due diligence or prescribing outside existing safety guidelines (which contributes to the problem of androgen misuse)^{8,9} or from the Internet.¹⁰ Frequently with illicit androgen abuse, the type of androgen is unknown, and the surreptitious nature of abuse challenges any systematic investigation.¹¹ Furthermore, the patterns of androgen abuse differ widely, confounding safety discussions. Two common patterns of AAS abuse are “stacking” and “cycling.” Two or more androgens are “stacked” when taken simultaneously while doses are progressively increased over a short period.^{1,3,7} “Cycling” is alternating periods of AAS use with drug holidays.^{1,3,7} Illicit users may take multiple medications never designed for humans, and some stack huge doses of up to 25 medications.

Much of the discussion about uncontrolled AAS is anecdotal, because of the private and personal nature of the abuse of this class of drug.^{7,10} The literature in this area relies heavily on case reports, and safety reports have not been systematically accumulated.^{7,10} It is critical to consider as a growing public health concern both the adverse effects (AEs) of current androgen abuse in young men and the chronic health concerns caused by past long-term abuse in a population of now middle-aged or older men.⁸

AEs of AAS are potentially serious and underreported and include severe acne, infertility due to suppression of spermatogenesis, long-term disturbance of the hypothalamic-pituitary-gonadal axis, sexual dysfunction, hepatotoxicity (predominantly, if not exclusively, with the use of 17-alkylated agents), and psychiatric and behavioral issues.^{1,3,5} Taken in supraphysiologic doses, AAS show various long-term, serious AEs.⁵ After prolonged, chronic use of AAS, some AEs often are irreversible, such as gynecomastia, caused by increased

estrogen levels from aromatization of testosterone, and atherosclerosis, resulting from elevated low-density lipoprotein and depressed high-density lipoprotein levels.³

The effect of testosterone therapy at physiologic levels is being studied, and its effect on cardiovascular parameters is being evaluated.¹² This topic is discussed in detail in [Issue 1](#) of *TU Times*, in which we carefully reviewed current knowledge about the relationship between testosterone and cardiovascular disease (CVD) and explored the safety concerns associated with testosterone therapy administered at physiologic levels. Because of the relatively short history of unregulated use, the long-term negative effects of AAS, such as AAS-induced CVD, have not yet been fully ascribed in the population.⁵ Furthermore, concomitant use of other drugs, such as human growth hormone (HGH) and erythropoietin, confounds risk assessment in this population.³

Reported behavioral effects of AAS include hypomanic or manic symptoms, sometimes accompanied by aggression or violence, and depressive symptoms, which may occur during AAS withdrawal.^{5,7} The mechanism for these idiosyncratic and unpredictable symptoms remains unclear: Many of the reported AEs may be due to co-administration of multiple drugs.^{5,7} The possible causality of AAS is difficult to study under laboratory conditions because of ethical and practical considerations.^{5,7}

WADA-Prohibited Androgens and Androgen Receptors

Exogenous AAS	Endogenous AAS	Gonadotropins	Androgen Modulators	Other
Androstenediol	Androstenediol	hCG (men)	Androstenedione	SARMs
Androstenedione	Androstenedione	LH (men)	Antiandrogens	
Bolandiol	Dihydrotestosterone		Aromatase inhibitors	
Bolasterone	Epitestosterone		DHEA	
Calusterone	Testosterone			
Desoxymethyltestosterone				
Fluoxymesterone				
Mestanolone				
Mesterolone				
Methandienone				
Methylnortestosterone				
Methyltestosterone				
Nandrolone				
Oxandrolone				
Oxymesterone				
Oxymetholone				
Stanozolol				
Testosterone				
Tetrahydrogestrinone				
Tibolone				
Trenbolone				

AAS, anabolic-androgenic steroids; DHEA, dehydroepiandrosterone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; SARM, selective androgen receptor modulator; WADA, World Anti-Doping Agency.

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Some “street users” are attracted to AAS abuse simply based on the belief that AAS will enhance behavior or competitiveness. AAS abuse may be linked to underlying personality and psychological traits of the user, such as low self-esteem, low self-confidence, and poor body image; histrionic manner; narcissism; antisocial behavior, violence, and aggression; and, among adolescents, a tendency toward high-risk behavior.^{3,7} It has been suggested that preexisting psychiatric disorders or behavioral traits of AAS abusers may predispose them to violent or aggressive behavior while taking extremely high doses of AAS.^{3,5,7}

According to results of a 2-year program in Sweden, steroid abuse among adolescents can be prevented by health-promoting activities, such as group discussions among adolescents, and by building self-confidence.² Boys aged 16 to 17 years are responsive to discussions about appearance and societal perceptions of male appearance.² They are not persuaded by discussion of risk, because risk-taking is

desirable in that demographic, but are persuaded by peer pressure.² As in this study from Sweden, similar success has been achieved elsewhere by using peer pressure to educate high school athletes about behaviors designed to reduce their intent to use androgens, but it has not had the far-reaching effect desired.¹¹ The effort evidently needs more support, through public education as well as through clinicians and the wider healthcare community.

Various surveys indicate that the prevalence of androgen use among adolescents has decreased over the past 10 to 15 years.¹¹ This decrease may be attributed to education and to the availability of alternatives (eg, nutritional sports supplements) to illicit drug use.¹¹ In addition, the National Strength and Conditioning Association (NSCA) has emphasized education to help athletes, coaches, and fitness trainers become more knowledgeable, highly skilled, and technically educated in their approach to exercise program design and implementation, including setting realistic goals and recognizing athletes' response to training as drug-free versus drug-enhanced.¹¹ Negative attention in the media about steroids provides the impetus to educate athletes, the general population, and our patients about the health consequences of AAS abuse.¹

Patients regularly hear conflicting reports about steroid use and abuse in the news, and may be confused by loose use of the terms "steroid" and "testosterone" by the media. There is a clear need for patient and public education about AAS and testosterone therapy.^{1,9} Responding to a survey conducted by the American Association of Clinical Endocrinologists (AACE),

more than 200 physicians related feeling pressured by their patients to prescribe testosterone when it is not medically necessary.¹³ Ninety percent of endocrinologists were concerned that publicity about the wide availability of testosterone in a more accessible form and HGH therapy have created false expectations among patients.¹³

AACE and Endocrine Society clinical practice guidelines recommend testosterone therapy only for appropriate patient populations, ie, men with documented cases of hypogonadism according to serum evaluation in the presence of signs and symptoms.^{14,15} "Patients should be taking this type of replacement medication only when there is a proven deficiency state," emphasized Paul S. Jellinger, MD, President of AACE, "and that should be determined by a physician."¹³

Patients need education about the dangerous AEs of AAS abuse¹³ as well as how to best ensure appropriate and safe administration of testosterone therapy when prescribed for hypogonadism.⁹ Most importantly, physicians need to effectively and accurately communicate to

patients the safety record for medically appropriate testosterone therapy. Despite major advances in understanding, optimal use of testosterone in cases of documented hypogonadism and eliminating androgen abuse remain challenges.⁹

Though preliminary studies have highlighted the potential benefits of testosterone therapy, large-scale, long-term studies may provide the clinical endpoint data needed to establish chronic testosterone therapy safety and investigate whether testosterone therapy confers the benefit or risk of CVD-caused or all-cause mortality.¹⁶

Critical Points to Keep in Mind When Evaluating the Impact and Dangers of Androgens

- Which medication or drug?
- Was it acquired from conventional (ie, medical professional after thorough evaluation) or unconventional source (eg, Internet)
- Route of administration
- "Street use" of anabolic-androgenic steroids often involves large doses or unknown quantities acquired from unconventional sources
- Specific dose
 - ◆ Physiologic or supraphysiologic range
- Age of recipient (younger vs older)
- Very few studies conducted with the regimens used in androgen abuse

Courtesy, Ronald S. Swerdloff, MD.

An Interview With Dr Hellstrom



Wayne J.G. Hellstrom, MD
 Professor of Urology
 Chief, Section of Andrology
 Tulane University Medical Center
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Dr Hellstrom, there is growing recognition of the problem with androgen abuse in the United States. What caused the problem, and what are the implications?



The medical dangers to young girls starving themselves under pressure to emulate the tall, bony models who walk down the fashion catwalks have been documented. Similarly, young men are under pressure to be sexually

attractive and athletic. Reports of androgen abuse by high-level sports figures—Olympic athletes, baseball players, cyclists, body builders, and so on—are widespread. However, the message about the dangers of androgen abuse is, unfortunately, not as far-reaching. Beginning at a young age, many boys are influenced by images they see in the media of the "ideal" body type: large and muscular, with low body fat.

Q What makes it difficult to discuss “testosterone abuse,” “steroid abuse,” or “doping”?

A “Testosterone abuse,” “steroid abuse,” and “doping” are terms often used indiscriminately to refer to a wide range of problems, particularly by the media (newspapers, Internet, television, radio). They are used almost interchangeably, without distinguishing blood doping or abuse of HGH, testosterone, or some other androgen. For example, the term “steroid abuse” has been used to describe blood doping, transfusion of erythrocytes, or treatment with the hormone erythropoietin. In the course of this interview, I will use “androgen abuse” to mean inappropriate use of androgens, which may or may not include testosterone.

Q Men, throughout their lifespan, are under great pressure to appear manly. How do you think this affects the overall health of your patients?

A At an early age, young men may feel peer pressure to use performance-enhancing drugs or AAS, despite not understanding the consequences of such choices. When I suspect androgen abuse in my practice, I am direct with my patients to educate them about the long-term health consequences, including testicular atrophy, gynecomastia, hepatotoxicity, hypogonadism, and infertility.

Q What problems compound the challenges of treating men for androgen abuse?

A Men tend to be more reluctant to seek medical care than women are. A growing body of evidence suggests that men are less likely to seek help, particularly for conditions they perceive will make them appear vulnerable or weak, such as depression or substance abuse. It is often an acute condition or a complaint of sexual dysfunction that brings a man into my clinic. I seize every opportunity to speak frankly about sexual health and lifestyle changes that may affect the patient’s sexual health.

Unfortunately, many men do not overcome the initial barrier to visit a healthcare provider to discuss sexual health matters. A study by Rich and Ro published in 2002 suggested that men aged 15 to 24 years have lower physician-visit rates than any other gender or age group.¹⁷ Because young men rarely received professional medical counseling during this period, they are at undue risk for sexually transmitted diseases and health conditions that may affect their sexual health in both the short and long term.

Q How does androgen abuse present in your office, and what is its relationship to hypogonadism?

A Sometimes it is the adolescent patient who presents with symptoms that suggest androgen abuse. However, more commonly, it is older patients—in their 30s, 40s, or even older—who present with symptoms of infertility, azoospermia, or hypogonadism (eg, loss of libido, erectile dysfunction) that may have resulted from previous androgen abuse.

Q Do you think the Internet has influenced patient’s misuse of androgens and misunderstanding of appropriate use of testosterone therapy?

A Yes, there’s a lot of unauthoritative and incorrect information on the Internet. In addition, the Internet gives patients unprecedented access to purchase drugs. Patients often do not understand that drugs purchased over the Internet are being distributed illegally and are not regulated to ensure safety. That androgens are drugs men may abuse in silence further exacerbates the challenges we face as healthcare providers.

Q Based on your clinical experience, what variables do you consider when deciding whether to initiate treatment with testosterone therapy? Have you encountered patients with hypogonadism who are concerned about initiating testosterone therapy because of publicity surrounding androgen abuse?

A In cases of suspected hypogonadism, I perform a thorough evaluation of the patient. This includes a medical and sexual history, physical examination, and laboratory evaluation. I carefully assess whether the patient is truly symptomatically hypogonadal—has a combination of low serum testosterone levels and symptoms—and whether testosterone therapy is appropriate.

Some of my patients do express concern about “steroids” and are confused about corticosteroid, AAS, or HGH use versus appropriate use of testosterone in the treatment of hypogonadism.

Q Do you have any suggestions for how to help stop androgen abuse and how to properly treat hypogonadism?

A Patient education via distribution of educational materials is key in informing patients about hypogonadism and treatment appropriate for affected patients. Having a central, nonjudgmental, online resource to refer patients to that discusses androgen abuse and medically indicated testosterone therapy for hypogonadism is a necessary step in winning patient confidence.

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