Opinion Article

Possiblescenariosoftestosteroneandanabolicandrogenic steroids use in and outside medicine

Abstract:

Anabolic hormones, particularly testosterone and anabolic androgenic steroids (AAS), serve a range of applications with distinct goals, benefits, and risks. This article aims to clarify four primary scenarios in which these hormones are used, to aid in reducing misunderstandings and promoting more evidence-based discussions. The first scenario, testosterone replacement therapy (TRT), is well-documented as a treatment for hypogonadism, offering improvements in body composition, metabolic health, and cardiovascular outcomes with proper supervision. The second scenario involves therapeutic use of AAS in cases of significant catabolism, muscle loss, or other clinical conditions requiring anabolic support. Here, controlled studies underscore the potential of AAS to improve muscle mass, bone density, and physical function, though clinical practice underutilizes these therapies.

A third, more debated scenario covers the controlled use of supraphysiological doses of testosterone and AAS for performance and aesthetics. Research, including randomized controlled trials (RCTs), has shown measurable benefits in body composition and physical strength with minimal adverse effects when appropriately monitored. However, such uses remain controversial and are not widely endorsed by medical organizations due to ethical and safety concerns.

The final scenario contrasts sharply with the others, detailing the risks associated with unregulated AAS abuse. This includes prolonged use, high dosages, poor-quality products from the underground market, and polypharmacy, which collectively heighten the risk of severe health consequences. This chaotic pattern of abuse complicates the assessment of AAS's specific impact on health due to numerous confounding factors.

A clearer distinction between these scenarios could enhance academic and clinical discourse, leading to more precise recommendations. By acknowledging the varied contexts in which AAS and testosterone are used, healthcare providers and researchers may make better-informed decisions, advancing safer practices and more effective guidelines.

Keywords: Anabolic steroids, ergogenic aid, testosterone, hypogonadism, androgens

Introduction:

The topic of anabolic hormone use, particularly testosterone and anabolic androgenic steroids (AAS), encompasses diverse applications, each with unique goals, benefits, and potential risks [1]. These uses range widely, from treating hormonal deficiencies like hypogonadism to enhancing physical performance and aesthetics [1,2]. However, the varied applications of these substances are often misunderstood or even conflated, complicating discussions in both clinical and academic settings [3]. A clearer, more nuanced perspective on these scenarios is needed to reduce confusion and guide evidence-based dialogue in medicine and public health [3].

Thus, in this context, the central aim of this scientific article is based on the idea that differentiating these scenarios is essential for advancing informed discussions and aiding clinicians in making appropriate, individualized decisions for patients. Additionally,by understanding these contexts more fully, we think that professionals can better evaluate the various benefits and risks, moving toward more targeted guidance and policies in both clinical and athletic domains.

The following sections will discuss the division into four scenarios: hypogonadism and testosterone replacement, therapeutic use of anabolic steroids, controlled supraphysiological testosterone use for aesthetics, and anabolic steroids and PEDs (performance enhancing drugs) abuse.

First scenario: hypogonadism and testosterone replacement

Current knowledge indicates clearly that levels of anabolic hormones, including testosterone, progressively decrease with age, leading to an increased prevalence of hypogonadism and testosterone deficiency in older adults [4,5]. This hormonal decline contributes to a worsening profile of cardiovascular risk factors (such as diabetes, hypertension, metabolic syndrome, and obesity) and results in reduced physical fitness and adverse body composition changes [4,5]. These changes include loss of muscle

mass and strength (sarcopenia and dynapenia), decreased bone mass (osteopenia and osteoporosis), and increased body fat accumulation (obesity) [1,4,5].

In contrast, testosterone replacement therapy (TRT) has been shown to partially or fully reverse these metabolic deteriorations without increasing cardiovascular risk and outcomes, as demonstrated in a recent Androgen Society Position paper [6]. Additionally, numerous longitudinal studies have linked hypogonadism to heightened cardiovascular events, while testosterone therapy appears to reduce these adverse outcomes [7], as reviewed by Corona G, et al (2018) in a meta-analysis including 37 observational studies.

Regarding body composition, as seen in a comprehensive literature review, by Traish A. (2021), that included predominantly randomized controlled trials, TRT in hypogonadal individuals promotes gains in muscle mass, increases in bone mass, reductions in body fat, and improvements across various physical fitness parameters (exercise capacity, muscle strength), as well as enhanced well-being and quality of life [8].

Therefore, we think that with appropriate clinical indication and adherence to contraindications, testosterone replacement therapy should be considered a valuable component of the therapeutic arsenal due to its substantial potential health benefits for individuals with testosterone deficiency.

Second scenario: therapeutic use of anabolic steroids

The search for therapeutic benefits of Anabolic Androgenic Steroids (AAS) dates back to the 1940s, with early observations of their capacity to increase muscular nitrogen retention and exhibit anti-catabolic effects [9]. Over the subsequent decades, numerous studies were published in scientific databases and compiled in collections (books), as seen in the *Handbook of Experimental Pharmacology 43: Anabolic Androgenic Steroids* (1976), edited by Professor Charles Kochakian, considered one of the pioneers in therapeutic use research [9]. More recently, other academic works have been published, such as *Anabolic Therapy in Modern Medicine* (2001) by Dr. William Taylor [10].

Together, these references present a compelling rationale, addressing how specific diseases alter anabolic capacity and increase catabolism, the prevalence of associated testosterone deficiency, deteriorations in body composition, the depletion of biological materials (bones and muscles), and studies that have documented the beneficial clinical outcomes linked to AAS replacement therapy in these contexts [9,10]. Some of the diseases mapped in this scenario, where AAS have been applied therapeutically, are listed in the table 1 below.

Table 1: Therapeutic use of testosterone and AAS in clinical setting

Kochackian CD - Handbook of Experimental Pharmacology 43: Anabolic Androgenic Steroids (1976) Taylor WN - Anabolic Therapy in Modern Medicine (2001)	
1. Sarcopenia and Frailty	15. Cancer
2. Corticosteroid-Induced Osteoporosis	16. Cardiovascular Diseases and Cardiac Rehabilitation
3. Postmenopausal Osteoporosis and Hormone Replacement Therapy in Women	17. Chronic Obstructive Pulmonary Disease
4. Osteoporosis and Male Andropause	18. Stroke
5. Autoimmune Diseases	19. Diabetes Mellitus
6. Amyotrophic Lateral Sclerosis	20. Chronic Kidney Disease
7. Chronic Fatigue	21. Muscular Dystrophies and Myopathies
8. Multiple Sclerosis	22. Spinal Cord Injury
9. Rheumatoid Arthritis	23. Alzheimer's Disease and Cognitive Deficit
10. Sjögren's Syndrome	24. Osteoarthritis
11. Systemic Lupus Erythematosus	25. Immobility and Gravity-Related Changes
12. Systemic/Multiple-Sclerosis	26. Nutritional / Nutrologyc Therapy
13. AIDS and HIV Infection	27. Dermatological Diseases and Wound Healing
14. Thermal Injury / Burn Patients	

As with testosterone replacement scenario, the therapeutic use of AAS, although still largely underutilized in clinical practice, should be considered, as we think, a viable option in the medical therapeutic toolkit due to its potential benefits in mitigating body depletion, preserving physical fitness, and improving clinical outcomes.

Third scenario: controlled supraphysiological testosterone and aesthetics

For over 50 years, testosterone and AAS have been used for aesthetic purposes and athletic performance enhancement [11]. Given the undeniable effects of these substances, the International Olympic Committee (IOC) banned the use of testosterone, its derivatives, and other anabolic hormones in competitions, classifying them as doping agents [11]. However, since then, numerous academic studies have been conducted on healthy young individuals (e.g., strength training practitioners) using supraphysiological doses of testosterone and AAS, providing significant insight into both their positive effects and potential risks [11, 12].

In this context, several rigorous randomized controlled trials (RCTs) have administered doses up to six times the standard therapeutic replacement dose (Testosterone Enanthate, 600 mg/week, for 20 weeks), showing marked improvements in body composition (fat reduction, lean mass increase) and physical fitness (muscle strength), with adverse effects considered clinically acceptable (that is, adverse effects were observed, particularly metabolic changes, but they were transient and not clinically significant during the period of supraphysiological use, with no severe health-related adverse outcomes reported) [12].

Other RCTs have examined cardiovascular effects with the supraphysiological use of testosterone mixed esters and nandrolone decanoate (200 mg/week), either in isolation or in combination, over 4 to 8 weeks, using echocardiography [13,14]. These studies found no significant changes across various hemodynamic and morphological parameters. According to authors, these cardiovascular findings associated with short-term supraphysiological AAS use are supported by earlier uncontrolled studies that similarly found no alterations in echocardiographic and arterial dynamics [13,14].

In a controlled study by Anderson RA et al. (1992), no changes in mood or sexual function were observed with the use of 200 mg/week of testosterone enanthate over 8 weeks [15], and Pope HG et al. (1994) reported only rare behavioral changes in a controlled trial involving 160 athletes, in those who used up to three times the therapeutic dose (300 mg/week) [16].

According to logic, an essential factor to consider when discussing AAS use is that the beneficial and adverse effects are dose- and duration-dependent, rather than related to the purpose of use; thus, effects are observed regardless of whether the purpose is therapeutic or recreational (aesthetic and performance) [2,3, 9-12]. As such, many therapeutic studies have provided “proof of concept” for the appropriate clinical safety (not the complete absence of adverse effects, but clinically acceptable ones) of dosages that could also produce aesthetic effects (e.g., 200 mg per week of nandrolone decanoate for patients with renal anemia or 20-80 mg of oxandrolone for individuals with HIV) [17,18]. Therefore, by employing evidence-based scientific reasoning, proof of concept (internal validity) from therapeutic RCTs can allow for extrapolation (external validity) to other settings, including recreational use.

Thus, the literature includes a substantial, although not fully comprehensive, body of research on the controlled use of AAS and testosterone at supraphysiological doses that can produce aesthetic effects [2,3]. Many professional societies and medical

councils, however, do not recommend non-therapeutic use (for aesthetics or performance) due to a "lack of evidence of safety and efficacy," a stance that is, at least partially, contradictory to various studies already published, particularly for short-term, cyclic use (as opposed to continuous supraphysiological dosing) [12-18].

Finally, we think that this third scenario could be considered "debatable"—that is, a cautious prescription wherein, on one hand, there is evidence of efficacy (for aesthetics and performance) with adequate clinical safety when used in a controlled, short-term manner and at moderate doses (up to six times the physiological replacement dose). On the other hand, medical and sports organizations do not endorse this use and may impose ethical and professional penalties on practitioners who engage in it.

Fourth scenario: anabolic steroids and PEDs abuse

From our point of view, this is a highly chaotic scenario that should be avoided by users, rigorously countered by healthcare professionals, and thoroughly understood by researchers. Also, it should not be compared to the third scenario due to the entirely inappropriate nature of comparing isolated supraphysiological use in a controlled setting with the uncontrolled and excessive abuse seen in this context.

There is no doubt that the abusive use of AAS can lead to a range of side effects, from mild to severe, in most users, as documented by Parkinson AB.& Evans NA. in a survey of 500 users, where only 0.8% reported no side effects [19]. Among the commonly reported effects are increased skin oiliness and acne, gynecomastia, mood and behavioral changes, sexual dysfunction and testicular atrophy, water retention, insomnia, injection site pain, skin striae, increased body hair, hair loss, voice deepening, clitoral enlargement, elevated blood pressure, and alterations in cholesterol profile and liver enzymes [19,20].

However, as proposed by Goldman A.&Basaria S [20], the more severe effects, particularly cardiovascular ones, stem from low-quality methodological evidence that is insufficient for establishing causality, such as case reports, case series, retrospective case-control studies, cross-sectional studies, and uncontrolled cohorts. Additionally, according to Fanaroff AC et al. (2020), evidence without proper randomization is inadequate for accurately discerning the true benefits and risks, which can compromise the validity of a true proof-of-concept approach [21].

Indeed, numerous potential confounders exist in this context and should always be considered in academic discussions. These include the use of poor-quality drugs from the underground market (with adulteration rates exceeding 30%) [22], extremely high doses (10–30 times the therapeutic dose), continuous use over years, concurrent use of multiple drugs (polypharmacy, whether of AAS or ancillary drugs, which significantly raises the risk of clinical emergencies with substances such as GH, diuretics, beta-agonists, insulin, stimulants, etc.), different drug combinations, pre-existing behavioral or mood alterations, inadequate assessment of prior clinical or laboratory outcomes, lack of understanding of personal and family health history for risk prediction, and absence of medical oversight aimed at advising discontinuation or reducing severe health risks that could potentially be avoided, among others [2,3,16,19,20,23].

Certain questions that can be proposed may assist professionals and researchers in gaining a clearer and more accurate perspective on adverse health outcomes when dealing with non-randomized studies, as presented in the following table 2.

Table 2: Proposed investigative questions in uncontrolled studies

Uncontrolled studies	Questions
Case report Case series Case-control Survey Cross sectional Cohort	1- What was the patient's personal and family health history prior to use/abuse? 2- What was the source of the drug used? 3- Was the quantity moderate, slightly supraphysiological, or abusive? 4- Were AAS or testosterone used alone, or in combination with other legal and illegal substances? 5- How long was the supraphysiological dose used? (total lifetime duration and time in continuous use) 6- Was there any health monitoring or professional supervision aimed at reducing potential harms?

Therefore, based on rational thinking, abusive, high-dose, uninterrupted AAS use with concurrent polypharmacy [24], along with the abuse of other legal (e.g., alcohol and tobacco) and illegal drugs (such as cocaine, marijuana, methamphetamine, LSD, ecstasy, etc.), without professional oversight and health monitoring, has led to

severe health consequences for users, including fatalities, and must be avoided [19,20]. While it is clear that this scenario is dangerous, the exact and specific contribution of AAS to such outcomes remains obscure due to the numerous confounders present in this chaotic and uncontrolled context [20].

Conclusions:

As proposed, certain distinctions can be relevant and useful for consideration in academic discussions and clinical practice. Furthermore, a thorough understanding of each scenario by professionals and researchers may help mitigate misunderstandings surrounding this controversial topic—the use of anabolic hormones, particularly testosterone and AAS—from therapeutic applications to aesthetic and performance-enhancing purposes.

Disclaimer (Artificial intelligence)

The authors declare that generative AI was used only at the final stage of manuscript preparation and exclusively for linguistic refinement in English (Name: ChatGPT; Version: GPT-4; Model: OpenAI's Large Language Model; Source: OpenAI - https://openai.com). No original text was generated or substantively edited by the AI.

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