

The Public Health Consequences of Performance-Enhancing Substances

Who Bears Responsibility?

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The nonmedical use of performance-enhancing substances, particularly androgens and related drugs, has been a global public health problem for several decades.^{1,2} A meta-analysis of 271 studies published between 1970 and 2013 estimated lifetime prevalence rates of 6.4% among males and 1.6% among females.¹ The use of banned performance-enhancing drugs in elite sports has received much attention but is merely the tip of the iceberg.

The self-administration of androgens to enhance physique and self-esteem by recreational bodybuilders and others desiring larger muscles (eg, some members of the military, police, bodyguards) affects many more men but has received little attention from the medical community and government. Testosterone and androgen preparations approved by the US Food and Drug Administration (FDA) for medical uses originally were obtained by some athletes secretly (eg, through coaches, trainers, and other athletes) in the closed environment of the locker room. With the advent of the internet, androgens have become widely available for purchase from home,³ including veterinary and untested “designer steroids” with known or uncharacterized toxic effects in humans.

The myoactive effects of androgenic substances primarily drive the use of these drugs.⁴ Larger muscles can power performance, but the desire for a larger physique commonly is secondary to a distorted body image termed *muscle dysmorphia*.⁵ Physiological doses of androgens do not achieve the effects of larger muscles, so some individuals will take 10 to 100 times the amount prescribed for medical indications and perceive that the benefits outweigh the potential for adverse consequences. Over time, individuals with high-dose use can develop a withdrawal syndrome when they try to stop due to suppression of the hypothalamic-pituitary-gonadal axis and consequent androgen deficiency.^{4,6} Withdrawal symptoms include muscle loss, fatigue, decreased sex drive and function, and suicidal depression. One estimate suggests that up to one-third of individuals with nonmedical use of androgenic substances will develop a full dependence syndrome or moderate to severe substance use disorder.⁴

Although androgenic substances are not acutely intoxicating, they have neuropsychotropic effects due to a wide distribution of androgen receptors in the brain, including regions associated with addiction. Consequently, long-term use of high doses has hedonic or reinforcing effects, and in some users can induce manic-like symptoms and aggression.⁷

The neurological basis for cognitive dysfunction in individuals with nonmedical androgen use has been demonstrated with functional magnetic resonance imaging.⁸ In addition, a high prevalence of cardiomyopathy has been detected among users. In one study, echocardiography showed depressed left ventricular ejection fraction (<52%) in 41 of 58 (71%) current users of anabolic-androgenic steroids and early left ventricular relaxation velocity (<8.5 cm/s) in 29 of 58 (50%) current users.⁹ However, as with many structural cardiac conditions, the full health consequences will not be realized until current users progress into middle age.

In this issue of *JAMA*, Van Wagoner and colleagues¹⁰ explored the availability of a new class of performance-enhancing substances through the internet, selective androgen receptor modulators, which are nonsteroidal ligands for the androgen receptor. These compounds have been shown to have anabolic properties in rodents, and early clinical trials showed anabolic activity in older persons.¹¹ However, the pivotal phase 3 trial in patients with cachexia and cancer (NCT00467844) failed to meet prespecified end points for improvements in lean body mass. Long-term cardiovascular safety data were not collected in that trial.

Even though these drugs have not received FDA approval, Van Wagoner et al¹⁰ found that, of 44 products purchased from internet sites advertising selective androgen receptor modulators, 52% contained these unapproved drugs. More concerning, 91% of these products contained various combinations of unapproved drugs such as selective androgen receptor modulators, anabolic steroids, growth-hormone secretagogues, and other nuclear hormone receptor modulators. Furthermore, 11 products (25%) contained active ingredients not listed on the label and 26 products (59%) contained different amounts of the compound than that listed on the label.

How can these pharmaceutical agents be widely available to the public without FDA approval, prescription, or manufacturing oversight? The increasing use of these agents illustrates the complex interplay of rapid developments in information technology, consumerism, medicine, and public policy. The origins may be traced back to the 1994 Dietary Supplement Health and Education Act, which exempted products considered “dietary supplements” from rigorous studies to demonstrate safety and efficacy as required for FDA approval of drugs prior to marketing. The result was a flood of unregulated dietary supplements with clever advertising schemes encouraging the public to pursue an easy solution to



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deeper medical problems. Androgens and androgen precursors as chemical entities were aggressively marketed as supplements, even though these compounds are drugs and not food. Androstenedione was specifically excluded as a dietary supplement when the consequences of its widespread use became known; however, many of these so-called dietary supplements still contain hormones, drugs, and known toxins often not listed on the label.

Whose responsibility is it to police the illicit sale of androgens and selective androgen receptor modulators or similar violations of federal laws and public safety? The medical profession has no authority in this area. Consumers are unlikely to become involved because nonmedical androgen users, like other individuals with substance use disorders, often conceal and deny their use. The FDA is responsible for taking action against any adulterated or misbranded dietary supplement product after it reaches the market. However, unlike drugs, the vendor (not the FDA) is responsible for evaluating the safety and labeling of its products and there is little incentive to do so. Flagrant violations of these statutes abound, and the FDA does not have the resources to address all of these cases in enough detail to take corrective legal action.

The US Drug Enforcement Administration (DEA) shares responsibility because androgens are schedule III drugs. However, the DEA is overwhelmed with the opioid epidemic, and industry-sponsored legislation last year seriously impaired efforts of the DEA to thwart complicit narcotic distributors. It is unrealistic to think that the DEA will turn its attention to androgens when opioid addiction remains a major concern. Without major changes in the laws to regulate

putative dietary supplements and internet sales (along with substantial resources for enforcement), the unrestricted abuse of androgens and related drugs among the general public will continue.

In addition to the availability of androgens from the internet, prescription of androgens has contributed to the public health problem. Some physicians overdiagnose idiopathic hypogonadotropic hypogonadism, especially in older men, to legitimize their use of these products despite findings that improvements in fatigue or vitality are neither statistically nor clinically different from placebo.¹² Androgen misuse by patients, misprescribing by physicians, and illicit sales contribute to the use of these substances and their risk of the related health effects. Physicians should be encouraged to examine their prescribing practices, including avoiding use of testosterone outside FDA and professional society guidelines¹³ for men with low levels of testosterone who lack a medical indication.

The paucity of reliable data on androgen abuse and the lack of training for physicians about the acute or long-term management of patients with nonmedical androgen use¹⁴ make dealing with the current situation more difficult. Physicians should ask patients about their use of dietary supplements when taking a medication history, and also inquire about muscle-strengthening routines when exercise is discussed.

As Van Wagoner and colleagues¹⁰ showed, access to androgens and now selective androgen receptor modulators has never been easier. Now is the time for the medical community to rally government authorities to take action to prevent the ready access of these potent drugs.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Auchus reported receiving consulting fees from the US Anti-Doping Agency, Major League Baseball, and the National Football League. No other disclosures were reported.

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