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Public Health Impact of Androgens

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Abstract

Purpose of review—To summarize recent findings regarding the public health impact of androgen abuse.

Recent findings—Abuse of androgens (also called "anabolic-androgenic steroids") has grown into a major worldwide substance abuse problem involving tens of millions of individuals, of whom about 98% are male. Most androgen abusers are still under age 50 today, and thus the long-term effects of these drugs are only beginning to be understood. Recent studies confirm that long-term supraphysiologic androgen exposure produces cardiovascular toxicity, characterized especially by cardiomyopathy and atherosclerotic disease. Withdrawal from androgens after long-term use may produce prolonged and sometimes irreversible hypogonadism in men. Supraphysiologic androgen levels may sometimes cause irritability, aggressiveness, and violence, whereas androgen withdrawal may cause depression. However, these psychiatric effects are idiosyncratic, affecting only a minority of users. Emerging evidence now also suggests that long-term androgen exposure may cause neurotoxicity, raising the possibility that aging androgen abusers may be at increased risk for dementia. Several recent studies have also described androgen-induced hepatotoxicity, nephrotoxicity, and adverse musculoskeletal effects.

Summary—Recent studies have demonstrated marked adverse effects of long-term androgen abuse. As increasing numbers of androgen abusers reach middle age, these effects will likely represent an emerging public health problem.

Keywords

androgens; anabolic-androgenic steroids; cardiovascular disease; neurotoxicity; hypogonadism

Introduction

Testosterone was first isolated in the 1930s, and hundreds of synthetic androgens were synthesized in the following years [1]. By the 1950s, elite athletes had discovered that these hormones could greatly improve muscle mass and athletic performance. However, it was not until the 1980s and 1990s that androgen use began to spread from elite athletics to the general population. Today, about 80% of these general-population androgen abusers take

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Conflicts of interest

Drs. Kanayama and Kaufman report no conflicts of interest. During the last three years, Dr. Pope has received research grant support from Shire and Sunovion, and has testified as an expert witness in two cases involving illicit androgen use.

these drugs simply to “get big,” for personal appearance or other purposes, rather than for any athletic competition [2]. Notably, even the oldest members of this general-population group – men who first took androgens as youths in the 1980s – are only now reaching middle age and entering the age of risk for adverse effects of long-term supraphysiologic androgen exposure. This large pool of non-athlete androgen abusers will likely account for the majority of the future public health problems associated with androgen abuse. Below, we review recent evidence on the nature and extent of these problems. We begin with a discussion of the number of at-risk individuals, followed by recent evidence of the cardiovascular, neuroendocrine, psychiatric, and possible neurotoxic effects of long-term androgen exposure.

Epidemiology

How many individuals are at risk for long-term androgen toxicity? Unfortunately, it is difficult to estimate the prevalence of androgen abuse worldwide because of the markedly disparate results of surveys. On the one hand, a recent review has suggested that androgen use may occur in children before their 10th birthday [3]. By contrast, another recent review [4] examined pooled data from nine studies of androgen users published worldwide since the year 2000 in which age of onset of androgen use was assessed. In these studies, comprising more than 3000 AAS users, fewer than 1% reported having initiated androgen use prior to age 15 and only about 13% had initiated AAS prior to age 18. Similarly, Sagoe and colleagues [5] found that only 0.3% of 2055 Norwegian adolescents (0.5% of males and 0.1% of females) reported use of androgens by age 17. In light of these data, why would some studies suggest that androgen abuse is common in adolescents? A possible reason for this discrepancy is that many prevalence studies, extending as far back as the 1980s [6], have relied upon anonymous surveys – and it appears likely many adolescents misinterpreted questions about “steroids” on these surveys and gave false-positive responses, when they had in fact not used a genuine androgen [7]. This problem is particularly likely in studies that have relied on questionnaires asking simply whether the respondent had “used steroids,” without distinguishing between anabolic steroids and corticosteroids, and without distinguishing between genuine anabolic steroids and commercial dietary supplements (e.g., [8–10]). Nevertheless, despite the possibly inflated figures generated by such surveys, a recent best estimate suggests that about 3 million men have used AAS in the United States alone [4]. The annual number of new American androgen users has remained stable over the last 20 years, leading to a steadily increasing population prevalence, as young new users enter the cohort, while existing users – almost all of whom are still under age 60 today – grow older. Worldwide, the number of androgen users likely reaches into the tens of millions, as suggested by a comprehensive review of 271 prevalence studies which reported a mean lifetime prevalence of androgen use of 3.3% [11]. Notably, however this mean was derived from pooled studies of disparate populations, with lifetime prevalence estimates ranging from 0% in some studies (e.g., among 118 Chinese graduate students [12]) to 86% in another (among 395 British men specifically chosen because they injected image- and performance-enhancing drugs [13]). Sports participation, body image disorders, psychiatric disorders such as depression, and higher levels of aggression have all been posited as potential risk factors for androgen use [14, 15]. Numerous studies have also found that

androgen use is associated with use of other performance- and image-enhancing drugs, as well as with classical drugs of abuse, although the causal pathways between androgen use and other drug use are not well delineated [2, 16, 17].

Cardiovascular effects

Although animal data and anecdotal evidence from humans have long suggested that androgens may cause premature cardiovascular morbidity and mortality [4], it is only recently that these effects have been rigorously demonstrated. In the largest study to date, Baggish and colleagues [18*] compared 86 men age 34–54 years reporting at least two years of cumulative supraphysiologic androgen exposure and 54 comparable experienced weightlifters reporting no androgen abuse, using echocardiography and computed tomography coronary angiography. On echocardiography, androgen users, as compared to non-users, displayed significantly impaired systolic and diastolic function as evidenced by reduced left ventricular ejection fraction and decreased diastolic tissue velocity, respectively. These deficits were pronounced in men currently using androgens at the time of evaluation, and appeared to partially, but not completely, resolve after androgen use was discontinued. Androgen users also displayed significantly greater coronary artery plaque volume than nonusers, and the degree of plaque volume was significantly associated with the total burden of lifetime androgen exposure. Three (3.5%) of the 86 androgen users had experienced documented myocardial infarctions at age 46 or earlier and a fourth man had required stenting for congestive heart failure. None of the non-users showed a history of myocardial infarction or stenting. Several recent smaller studies have produced results generally congruent with the above findings (e.g., [19–22]).

Neuroendocrine effects

It is well recognized that exogenous androgen administration leads to suppression of the hypothalamic-pituitary-testicular axis, leading to testicular atrophy, decreased endogenous production of testosterone, and reduced spermatogenesis [23, 24]. Importantly, long-term androgen users will often exhibit protracted androgen-withdrawal hypogonadism upon discontinuing androgen use. Although there have been scattered reports over the last two decades describing prolonged hypogonadism following discontinuation of supraphysiologic androgen use [25*], it is only recently that the frequency and severity of this problem have been recognized. For example, Kanayama and colleagues [25] described 24 men, recruited in the course of two ongoing studies of androgen abuse, who reported at least two years of lifetime supraphysiologic androgen use, and who had discontinued androgens at least three months prior to the time of evaluation. Five of these men were receiving physiological replacement doses of testosterone (physician-prescribed in four cases and illicitly obtained in one), leaving 19 untreated men. The investigators compared this latter group with 36 comparable non-androgen-using weightlifters recruited in the course of the same studies. The former users displayed significantly reduced testicular volumes and lower serum testosterone levels than nonusers, with 5 users showing testosterone levels less than 200 ng/ml despite abstinence from androgens for 3, 7, 8, 16, and 24 months, respectively. On the Sexual Desire subscale of the International Index of Erectile Function [26], the 19 former androgen users reported strikingly reduced libido compared to nonusers (mean [SD]: 5.6

[2.5] versus 7.4 [1.4]; $p < 0.001$). Notably, among the 5 former androgen uses receiving replacement testosterone, two had failed to regain normal libidinal and erectile function despite adequate replacement doses. Of the total group of 24 former androgen users, 7 (29%] were found to have met DSM-IV criteria [27] for a major depressive episode during androgen withdrawal; 4 of these 7 men had never experienced a major depressive episode at any other time in their lives.

Very similar results were reported by Rasmussen and colleagues [28*], who compared 37 current androgen abusers, 33 former abusers with a mean [95% confidence interval] abstinence period of 2.5 [1.7, 3.7] years, and 30 comparable non-androgen-using weightlifters. Nine (27.2%) of the former androgen users, but none of the androgen non-users, exhibited serum testosterone levels below the lower limit of normal (12.1 nmol/dl) ($p = 0.002$ by Fisher's exact test, two-tailed). Nine (27.2%) former users as opposed to 2 (6.7%) non-users reported erectile dysfunction ($p = 0.046$); 14 (42.4%) former users versus 3 (10.0%) non-users reported decreased libido ($p = 0.005$), and 10 (30.3%) former users versus 1 (3.3%) non-user reported depressive symptoms ($p = 0.007$).

Another recent study assessed a database of 6033 men who sought treatment for hypogonadism between 2005 and 2010 [29]. Of these, 97 (1.6%) displayed profound hypogonadism, with testosterone levels of 50 ng/dL or less, and 42 (43%) of these men reported prior androgen abuse. The investigators subsequently surveyed 382 men in their current hypogonadal population and found that 80 (21%) reported prior androgen abuse. Hypogonadal men in this cohort aged 50 or younger were 10 times as likely to report prior androgen use compared to men older than age 50 – suggesting that prior androgen use represented an important factor to assess in younger men presenting with unexplained hypogonadism.

The mechanisms of prolonged androgen-withdrawal hypogonadism remain incompletely understood [23, 25]. Some cases may be attributable to incomplete recovery of gonadotropin function, leading to hypogonadotrophic hypogonadism. However, other individuals may display hypogonadism despite normal or elevated levels of luteinizing and follicle-stimulating hormones, suggesting that they may have experienced direct testicular toxicity (i.e., damage to Leydig cells). Still others may display normal pituitary hormones and testosterone levels, yet still display functional symptoms of hypogonadism, suggesting possible development of end-organ resistance due to down-regulation of androgen receptors. Thus, men with androgen-withdrawal hypogonadism may require multiple treatment strategies to normalize testosterone levels. Unfortunately, in the authors' experience, few physicians are familiar with treating such individuals.[23] Aggressive treatment appears important in such cases, since these men may otherwise resume supraphysiologic androgen use in order to self-treat their dysphoric symptoms.

Physicians evaluating hypogonadism should also consider the possibility of surreptitious androgen use. For example, couples might present with complaints of infertility when the male has used androgens without disclosing his use to his partner. Similarly, individuals experiencing androgen-withdrawal hypogonadism might surreptitiously resume androgen use for periods of time without informing their treaters.

Neuropsychiatric effects

It has been recognized for decades that in a small portion of users, supraphysiologic androgen doses may induce hypomanic or manic symptoms, and that androgen withdrawal may lead to major depressive episodes [4]. These effects are not uniform, with a majority of users showing few psychiatric changes and a small minority showing severe pathology. Several placebo-controlled studies suggest that these phenomena cannot be explained purely by psychosocial factors or suggestive influences, but the underlying biological mechanism remains unknown. Studies in hamsters administered androgens during adolescence suggest a role for the vasopressin and serotonin systems in creating increased offensive aggression and decreased anxious behaviors during the exposure period [30, 31], but it is unclear whether these findings can be extrapolated to humans.

In addition to acute psychiatric effects, early evidence suggests that supraphysiologic doses of androgens – together with hypogonadism following androgen withdrawal – may produce neurotoxic effects. This possibility was first suggested by *in vitro* findings that supraphysiologic levels of testosterone produced apoptotic effects in neuronal cells, leading the investigators to speculate that individuals chronically abusing markedly supraphysiologic doses of androgens might be at risk for cognitive deficits [32]. Subsequently, a pilot study in humans found deficits in visuospatial memory among androgen users, and the degree of these deficits was significantly associated with the total lifetime burden of androgen exposure [33].

Recent evidence from our group has amplified these concerns. Using proton magnetic resonance spectroscopy of the anterior cingulate cortex, we detected deficits in levels of the myo-inositol epimer scyllo-inositol in androgen users compared to a non-using weightlifter control population [34]. Because scyllo-inositol prevents clumping and deposition of β amyloid, a recognized culprit in Alzheimer's-type dementia (AD), a scyllo-inositol deficit could reflect high levels of β amyloid and could increase the probability of β amyloid clumping, possibly leading to cognitive deficits. In the same sample of individuals, we also demonstrated that users displayed enlargement of the right amygdala, decreased functional connectivity between the right amygdala and other cortical structures, and higher fractional anisotropy in the inferior-fronto-orbital fasciculus, which structurally connects amygdala to other brain areas, as compared to non-users [34, 35]. These anatomical abnormalities may be related to the scyllo-inositol deficit, as the amygdala is considered part of an axis of early β amyloid pathology [36].

A Norwegian group has also demonstrated decreased functional connectivity between the amygdala and the default mode network, together with other nodes involved in emotional and cognitive regulation, in 50 current androgen users as compared to 59 non-androgen-using comparison men [37]. These same investigators also demonstrated widespread thinning of the cortex and smaller neuroanatomical volumes, including total gray matter, cerebral cortex, and putamen, in androgen-using weightlifters as compared to non-users [38*]. These differences could not be attributed to verbal IQ, intracranial volume, levels of anxiety and depression, or measures of attention and behavioral problems. Moreover, the

magnitude of these differences appeared to be associated with total lifetime exposure to androgens.

In some sports where androgen abuse is frequent, such as American football, athletes are also vulnerable to concussions – raising the question of whether androgen exposure may amplify the brain effects of concussive injury. Although we are not aware of human data in this regard, a recent laboratory study found that mice exposed to high-dose androgens and subsequently subjected to two mild traumatic brain injuries exhibited significantly greater axonal injury and microgliosis than mice receiving brain injuries in the absence of androgen exposure [39].

Notably, androgen abusers typically use these drugs in courses or so called “cycles,” lasting weeks or months, separated by drug-free intervals. Thus, they experience grossly supraphysiologic androgen levels while on-cycle, frequently followed by protracted hypogonadal androgen levels after stopping a cycle, so that only rarely do they experience normal (eugonadal) androgen levels. Prolonged departures from the eugonadal range may increase the risk for neurotoxicity, as both supraphysiologic *and* hypogonadal androgen levels increase oxidative stress [40–43], which in turn can increase β amyloid levels, amyloid plaque formation, and cognitive dysfunction [44, 45].

In short, both androgen exposure and androgen withdrawal may lead to a variety of neurotoxic effects, which are only beginning to be explored. If these effects are real, one might ask why they have not already been reported to be clinically evident among long-term androgen abusers. One plausible explanation is that the great majority of the world’s androgen abusers are still in middle age or younger, as explained above in this paper. Therefore, some androgen abusers may have already developed subtle cognitive deficits, but still be too young to exhibit visible impairment. As these millions of individuals move beyond middle age, more serious effects might become apparent.

Effects on other organ systems

Recent papers continue to document that supraphysiologic doses of androgens may also occasionally produce adverse effects on other organ systems such as the liver [46] and kidney [47]. Some cases of liver injury may arise as a result of androgens surreptitiously included in so-called dietary supplements frequently used by weightlifters, although these supplements may contain other hepatotoxic ingredients, so that the offending agent is often uncertain [48, 49]. Another recent paper has reported a markedly elevated prevalence of tendon ruptures, especially involving upper-body muscles such as the pectoralis, biceps, and triceps, among 88 long-term androgen abusers as compared to 54 otherwise similar weightlifters [50].

Conclusion

Some tens of millions of individuals, almost all of whom are male, abuse supraphysiologic doses of androgens to enhance personal appearance and in some cases to improve athletic performance. The great majority of androgen abusers did not begin using these drugs until at least the 1980s or 1990s. Thus, even the oldest members of this population are only now

reaching middle age, and hence it is only recently that large-scale studies of the long-term adverse effects androgen abuse are beginning to appear. It has become clear that long-term exposure to supraphysiologic levels of androgens frequently causes cardiomyopathy (although this is apparently partially reversible when androgens are discontinued), atherosclerotic disease, often prolonged androgen-withdrawal hypogonadism, occasional toxicity to liver and kidney, and a variety of neurotoxic effects that are only beginning to be assessed.

It is difficult to predict the full magnitude of the public health problem that will evolve as the older members of this large population of androgen abusers pass beyond middle age and begin to experience an increasing risk of these effects. At the least, it appears that the full magnitude of this problem is still ahead of us, and that over the next decade or two, the adverse effects of androgen abuse will become increasingly evident, especially in countries such as the United States, British Commonwealth countries, and Scandinavia, where androgen abuse has now been widespread for 20 to 30 years.

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Key points

Widespread abuse of supraphysiologic doses of androgens did not arise until the 1980s and 1990s, and thus the great majority of the world's androgen abusers are still under age 50 today.

The best-documented and probably most concerning long-term adverse effects of androgen abuse are cardiovascular disorders, including cardiomyopathy and atherosclerotic disease.

Increasing evidence suggests that prolonged androgen-withdrawal hypogonadism is common among androgen abusers, and deserves aggressive treatment to deter individuals from resuming androgen abuse in an effort to self-treat dysphoric withdrawal symptoms.

Several lines of evidence suggest that long-term exposure to supraphysiologic androgens produces neurotoxic effects, raising the possibility that androgen abusers might develop early-onset cognitive deficits as they age.

It is still difficult to predict the full public health impact of androgen abuse because the oldest androgen abusers are only now entering the age of risk for long-term adverse effects. It seems likely that these effects will become increasingly prevalent in the next decade or two as abusers age.