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Illicit Use of Androgens and Other Hormones: Recent Advances

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Abstract

Purpose of review—To summarize recent advances in studies of illicit use of androgens and other hormones.

Recent findings—Androgens and other appearance- and performance-enhancing substances are widely abused worldwide. Three notable clusters of findings have emerged in this field in recent years. First, studies almost unanimously find that androgen users engage in *polypharmacy*, often ingesting other hormones (e.g., human growth hormone, thyroid hormones, and insulin), ergo/ thermogenic drugs (e.g., caffeine, ephedrine, clenbuterol), and classical drugs of abuse (e.g., cannabis, opiates, and cocaine). Second, reports of long-term psychiatric and medical *adverse effects* of androgens continue to accumulate. In cardiovascular research particularly, controlled studies have begun to supersede anecdotal evidence, strengthening the case that androgens (possibly acting synergistically with other abused drugs) may cause significant morbidity and even mortality. Third, it is increasingly recognized that androgen use may lead to a *dependence syndrome* with both psychological and physiological origins. Androgen dependence likely affects some millions of individuals worldwide, and arguably represents the least studied major class of illicit drug dependence.

Summary—Given mounting evidence of the adverse effects of androgens and associated polypharmacy, this topic will likely represent an expanding area of research and an issue of growing public-health concern.

Keywords

androgens; anabolic-androgenic steroids; testosterone; human growth hormone; substance abuse

Introduction

The androgens are a family of hormones that includes testosterone, the prototype natural androgen, together with its naturally occurring relatives, plus numerous synthetic derivatives of testosterone, created over the last 70 years [1]. These hormones are also often called “anabolic-androgenic steroids,” but in this review we will use the more proper term “androgens” [2]. Androgens are widely used under non-medical conditions by individuals wanting to gain muscle or lose body fat. This practice is illegal in much of the industrialized world, although in some countries androgens are available over the counter without

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prescription. For simplicity here, we will refer to non-medical androgen use as “illicit androgen use,” while recognizing that in some localities this practice is not actually illicit.

In earlier decades, androgen use was largely confined to elite athletes, but since the 1980s, this form of substance use has spread out of the elite athletic community and into the general population [3]. Nowadays, most androgen users are not competitive athletes at all, but simply individuals who want to look leaner and more muscular [4–7]. The great majority of users are male, since women rarely aspire to be highly muscular, and are also vulnerable to the masculinizing effects of androgens, such as beard growth and masculinization of secondary sexual characteristics. Although some anonymous student surveys have reported seemingly high rates of androgen use among girls, these estimates are likely grossly inflated by false-positive responses due to misinterpretation of the “steroid” questions, as we have explained previously [8]. A recent epidemiologic study in Sweden [9] has reinforced the conclusion that androgen use is very rare among women, even when looking specifically at women who attend gymnasiums [10]. Similarly, a recent large American web-based survey [11] identified 518 androgen users, comprising 506 men and 12 women – a male/female ratio of 42 to 1. In this paper, therefore, we will consistently speak of androgen use among men, though we acknowledge that occasional women may also use these drugs [12–15].

The present review is restricted primarily to papers from the last 2–3 years on illicit androgen use; the literature prior to this interval is already well summarized in prior reviews [1, 3, 16]. Our search for recent papers was conducted using the United States National Library of Medicine PubMed search engine, using the search terms “anabolic-androgenic steroids,” “anabolic steroids,” and “androgen abuse.” We also obtained additional recent references through articles cited in current papers and through discussions with colleagues currently involved in research on illicit human androgen use. In the last few years, three major themes emerge: 1) increasing documentation of polypharmacy by androgen users; 2) increasing reports of adverse medical and psychiatric effects from long-term androgen exposure; and 3) increasing recognition of an androgen dependence syndrome. We note in passing that the last 2–3 years have also seen important studies of other aspects of androgens that were generated by our search terms above. These studies include, for example, investigations of androgen effects in animal models, including several new studies of mechanisms for androgen-induced aggression [17–20] and possible androgen-related depression [21]. Recent animal studies have also pursued mechanisms of the performance-enhancing effects of androgens (for review see [22]), as well as androgen-induced adverse effects, including cardiac [23], neuronal [24], and possible carcinogenic effects [25]. We will not attempt a complete review of these animal studies here, since this review is focused primarily on illicit human androgen use, but important animal studies of immediate relevance to human androgen abuse are mentioned in the text that follows. We would also note in passing that many recent papers have also examined topics such the use and/or detection of veterinary androgens [26–29], and biochemical detection of androgens for doping control in human athletes. For example recent papers have described methods for detection of androgens in fingernail clippings [30], and hair [31], as well as advances in doping control methods overall (for reviews see [32, 33]). Again, however, we will not attempt a full coverage of these topics here, and will focus primarily on illicit human androgen use.

Polypharmacy

Recent studies have consistently shown that androgen users typically ingest a wide variety of additional drugs. These include other performance- or appearance-enhancing drugs and also “classical” drugs of abuse. For example, in one series of recent papers [34–37], Hildebrandt and colleagues have suggested that androgen users might be better characterized

more generally as appearance- and performance-enhancing drug (APED) users, where androgens are complemented by use of nonsteroidal anabolic hormones (e.g. human growth hormone and insulin) and by ergo/thermogenic drugs (e.g. caffeine, ephedrine, clenbuterol, and thyroid hormones). Ancillary drug use is typically influenced by the particular performance and body-image concerns of individual users. Specifically, in an Internet survey of 1000 male Internet APED users, these authors classed respondents in four groups, focused respectively on “lean hypermuscularity, primarily leanness, primarily mass building, or a common nonspecific muscularity” [35]. The first class, composed primarily of bodybuilders, exhibited the highest levels of overall APED use and likely the greatest risk of adverse effects; the second class appeared primarily focused on leanness; the third appeared to be primarily composed of powerlifters with less focus on leanness; and the fourth exhibited the least overall body-image pathology. In a subsequent review [36], the authors built on these findings to postulate three core elements to APED use: polypharmacy, body image disturbance, and disturbances in dieting and exercise.

Several other recent papers have described use of other APEDs among androgen users. For example, our group [38] examined 100 American androgen users age 18–40 and found that 27 (27%) reported some use of human growth hormone (HGH); within the subgroup of 31 androgen users diagnosed with androgen dependence [39], 22 (70%) had used HGH and/or its daughter compound, insulin-like growth factor-1 (IGF-1). We noted that the prevalence of HGH use among American androgen users has risen steadily over the last two decades in successive studies from our laboratory – a trend likely due in part to the dramatic decline in street prices for illicit HGH. Indeed, in constant 2011 United States dollars, the street price of HGH has declined from about \$50 per international unit in 1980 [40] to only about \$3 per unit today. Widespread polypharmacy involving HGH and other drugs has also recently been documented among androgen users in other countries [41–43]. This is a matter of concern, since both androgens [44, 45] and HGH [46–49] exhibit cardiac toxicity, raising the specter of synergistic cardiotoxic effects in individuals combining these hormones. Synergistic effects might influence other organ systems as well; one new report suggests that androgens might interact with IGF-1 to enhance Leydig cell proliferation, with a possible increased risk of testicular cancer [25].

It should also be noted that androgen users frequently ingest a variety of “dietary supplements” or “nutraceuticals” in addition to the drugs enumerated above. Although these supplements are typically sold over the counter without regulation, numerous recent studies have shown that certain supplements actually contain potent androgens [50–53] or other APEDs such as clenbuterol [54]. Conversely, a sizable proportion of drugs sold on the street or over the Internet as supposedly genuine androgens may be mislabeled, impure, or simply counterfeit [55–57]. Thus an individual’s actual total burden of APED exposure may differ substantially from what he believes that he has ingested.

Recent studies also continue to show that androgen users ingest numerous classical drugs of abuse in addition to APEDs. Our group has particularly noted the high levels of opioid use among American androgen users [7, 58]. In an analysis of 134 American weightlifters, we diagnosed lifetime opioid abuse or dependence in 5 (7%) of 72 androgen nonusers, 8 (19%) of 42 androgen users not meeting criteria for lifetime androgen dependence, and a remarkable 10 (50%) of 20 users showing lifetime androgen dependence. These findings are consistent with earlier papers suggesting a particular overlap between androgen and opioid use [59–61], and with animal studies suggesting similar mechanisms in androgen and opioid dependence [62–67], thus raising the possibility that human androgen users may be particularly vulnerable to problems with opioid abuse [68]. Indeed, in earlier papers, our group had conjectured that androgen use might represent a gateway to opioid use [59, 60], but subsequent studies both from our center [58] and from Sweden [69] have suggested that

initiation of opioid and other illicit drug use is at least as likely to precede androgen use as to follow it.

Illicit androgen users abuse numerous classical drugs other than opiates. For example, a recent Internet survey found that 11.3% of 506 male self-reported androgen users reported cocaine use within the past month, as compared to 4.7% of 771 nonusers [4]. In recent studies in Sweden [69] and the United Kingdom [70], a history of cocaine use was more common than history of opioid use among androgen users. An Australian survey of secondary school students found androgen users six times as likely as nonusers to report past-year use of cannabis and 30 times as likely to report past-year cocaine or heroin [71]. A 2011 review analyzed 18 peer-reviewed English-language studies from 1995–2010 assessing both androgen and other drug use in various populations [72]. In general, the studies found a strong relationship between androgen use and use of both classical illicit drugs and alcohol, but a more mixed relationship between androgen use and use of tobacco and cannabis.

In closing, it should be noted that there are certainly some individuals who perceive their illicit androgen use as part of a “healthy” program of proper diet, weightlifting, and other athletic activity [73]. Such individuals may eschew other forms of illicit drug use and regard themselves as quite different from ordinary drug abusers. Although we have periodically encountered such individuals in settings such as needle exchange programs (for example, see [70]), the weight of evidence suggest that in most settings, these cases represent a minority of the population of illicit androgen users.

Adverse Effects of Androgen Use

Although some scientific [73, 74] and popular [75–77] writers still question the dangers of androgen use, evidence of adverse medical and psychiatric effects has continued to mount in the last 2–3 years [78].

Cardiovascular effects

Perhaps most worrisome are recent studies of cardiovascular function in long-term androgen users. For years, individual case reports and small case series have reported cardiomyopathy, arrhythmias, myocardial infarction, cerebrovascular accidents, and coagulation abnormalities in known or suspected androgen users – and these are summarized in several recent reviews [3, 45, 79–82]. Now, larger controlled studies have begun reinforce these anecdotal impressions. Far and colleagues [83] have just reported pathological findings in 87 consecutive deceased men testing positive for illicit androgens versus 173 age-adjusted deceased control men; the androgen users showed markedly greater cardiac mass even after adjusting for body mass and other variables. D’Andrea et al. [84], comparing 20 androgen-using and 25 non-using athletes, found that users showed significantly lower early and late diastolic tissue velocities, together with reduced peak systolic strain. Similar evidence of systolic and diastolic myocardial dysfunction has subsequently emerged from another Italian group comparing 11 androgen users, 17 non-using weightlifters, and 20 sedentary control men [85]. These authors speculated that their findings reflected increased myocardial collagen content arising from a repair process against androgen-induced direct cellular injury – an impression supported by recent pathological observations by the same group in four deceased androgen users [86]. Hassan and colleagues reported impaired diastolic function in 15 androgen-using weightlifters compared to 5 non-androgen-using weightlifters and 5 sedentary men [87], and Kasikcioglu et al. have demonstrated impaired right ventricular function in 12 androgen-using weightlifters versus 14 non-using weightlifters and 15 non-weightlifting controls [88]. In a comparison of 12 long-term androgen users and seven age-matched non-using weightlifters [44], our group found showed strikingly lower left ventricular ejection fractions and strain measures. Indeed 10 (83%) of the androgen

users, but only one nonuser, displayed ejection fractions below 55%, the usual limit of normal ($p = 0.003$ by Fisher's exact test, 2-tailed). The androgen users also showed diastolic impairment, illustrated especially by markedly lower E' velocity and E/A ratios.

The literature also continues to show that androgens, especially orally active androgen preparations, increase low-density lipoprotein cholesterol and decrease high-density lipoprotein cholesterol in both humans [45, 89] and animal models [90]. This lipid profile is recognized as a major risk factor for coronary heart disease [91], leading to the speculation that androgens promote premature atherosclerotic disease [45, 92, 93] – even though direct evidence of this phenomenon remains limited. However, one recent imaging study of 14 professional bodybuilders has found an apparent association between early coronary-artery calcium and long-term androgen use [94].

It should be noted that the above studies, like most studies reviewed this paper, focused primarily on illicit androgen users – typically younger individuals taking supraphysiologic doses of androgens for performance enhancement or body image. However, even when androgens are administered at physiologic doses to hypogonadal men under medical supervision, adverse cardiovascular effects may occur. Notably, one recent study of physiologic testosterone replacement, in 209 hypogonadal men over age 65 with mobility limitations, was terminated prematurely because of a significantly elevated rate of adverse cardiovascular events in the testosterone group versus the placebo group [95]. However, a similar recent study of testosterone in 274 frail or near-frail men over age 65 failed to find such an association [96]. In any event, one must be cautious in extrapolating from these results to cardiovascular effects in younger illicit androgen users, since these men may ingest combinations of androgens equivalent to 10–50 times normal physiologic replacement doses [1] – and they may superimpose various other drugs as well, as described above.

Neuroendocrine effects

The last several years have also witnessed increasing recognition of the problem of androgen-induced hypogonadism. This phenomenon appears primarily attributable to androgen-induced negative feedback on the hypothalamic-pituitary-testicular (HPT) axis [97, 98], but may also reflect direct effects on the testis [99]. Although short courses of androgens (say, 6–10 weeks in duration) rarely cause prolonged suppression of HPT activity [100, 101], longer courses may suppress HPT function for months [89], and sometimes more than a year after androgens are discontinued [102, 103]. Further, even when hypothalamic-pituitary function has normalized, primary hypogonadism may persist as a result of apparent direct androgen effects on the testicle [104]. Although androgen-induced hypogonadism can sometimes be successfully treated with human chorionic gonadotropin [103], clomiphene [105, 106], or combinations of these agents [98], these measures are not always successful [104, 107]. Hypogonadism is frequently associated with infertility [99, 108], loss of libido and sexual dysfunction [109], and depression [109, 110]. Interestingly, hypogonadism induced by androgen withdrawal [1, 111] or by other pharmacological means [109, 110] seems to produce few depressive symptoms in most men, but severe depression in occasional men. The reasons for this idiosyncratic pattern remain poorly understood.

Effects on other organ systems

Elevated creatinine and decreased glomerular filtration rate may occur as a result of rhabdomyolysis in highly muscular androgen users engaged in heavy resistance training [112, 113], but the degree to which this may progress to frank renal disease is less clear [114]. However, one ominous recent report has described 10 cases of focal segmental glomerulonephritis in long-term androgen users [115].

Another ominous recent finding is that supraphysiological levels of testosterone can induce apoptosis in human neuronal cells in vitro [116], raising the possibility that long-term high-dose androgen use might lead to neuronal damage in human users. Similar findings have now just emerged from another in vitro study using the androgens nandrolone and methandrostenolone (methandienone) [24]. Although we are unaware of observations of dementia or other neurodegenerative diseases in long-term androgen users, it may be important to watch for this possible phenomenon.

Finally, it should be remembered that a substantial literature has documented androgen effects on other organ systems, including the liver [117], immune system [118], and musculoskeletal system [119], among others [1, 120]. However, we have found few major studies in these areas within the 2–3 year time window of the current review. In one of these few studies, Swingel et al. [121] reported evidence of increased toxicant-associated fatty liver disease in 95 androgen users as compared to 85 control weightlifters. However, this conclusion was based partially on elevated transaminase levels among the androgen users – and transaminases are also present in muscle, so that rhabdomyolysis from heavy workouts can greatly elevate transaminases in muscular individuals with no liver disease at all [122, 123]. Notably, Swingel et al. found virtually no difference between users and nonusers in gamma glutamyl transpeptidase (GGT) – an enzyme present exclusively in the liver and not in muscle. This observation would suggest caution in attributing the users' transaminase elevations to liver disease.

Psychiatric effects

A substantial past literature has documented that androgens can cause hypomania, aggression, or violence in occasional users [1, 124]. These effects have been demonstrated in several placebo-controlled double-blind investigations [125–127], indicating that they cannot be ascribed purely to psychosocial factors, and hence likely reflect a biological effect of androgen themselves. Although we have found no major new studies of this specific topic within our 2–3 year time window, several recent Swedish epidemiologic studies have explored associations between androgen use and violent or criminal behavior. Three studies of prisoners found various associations between androgen use and violent crime, likely attributable to multiple paths of causality, in that androgens were not necessarily a proximal trigger to violence [128–130]. For example, as noted in another recent Swedish study, some androgen users report deliberate use of these drugs in preparation for committing a crime [131]. A recent example of this latter practice is the terrorist Anders Breivik, charged with killing 77 civilians in Oslo and Utøya, Norway, on July 22, 2011. In his 1500-page manifesto [132], Breivik details his use of Winstrol (stanozolol) and DBOL (presumably methandrostenolone) in systematic preparation for his terrorist attacks.

Possible mechanisms of androgen-induced behavioral effects continue to be explored in animal models. Although the details of this research are beyond the scope of the present review, accumulating evidence shows that chronic androgen administration influences a variety of monoaminergic and peptidergic neurotransmitter systems that are likely involved in modulating behavior [20, 133–135].

Androgen Dependence

It has been recognized for more than two decades that androgen use may lead to a dependence syndrome in perhaps 30% of users [68], and possible psychiatric [136, 137] and neuroendocrine [138] mechanisms for this syndrome have been proposed. In the last 2–3 years, research has cast new light on this problem, which likely affects on millions of individuals worldwide, and arguably remains the least studied of all major forms of illicit substance dependence [68].

One stimulus for this growing interest is accumulating evidence for androgen dependence in laboratory animals [66]. For example, male hamsters will self-administer testosterone to the point of death, and they develop an intoxication syndrome with opioid-like features [139]. Interestingly, pretreatment with the opioid antagonist naltrexone will prevent testosterone self-administration in this model [65]. Further, a variety of animal studies suggest that androgen can modify brain opioid systems, as well as other neurotransmitter systems as mentioned above [133–135, 140].

These animal studies suggest that androgens possess some hedonic properties, perhaps mediated by binding to plasma membrane receptors as opposed to androgen genomic effects [66, 140]. However, humans typically report few hedonic or intoxicating effects from androgens [39, 68] – suggesting that human mechanisms of androgen dependence are more complex. Acknowledging these issues, our group has proposed formal diagnostic criteria for androgen dependence [39], based on the nine standard criteria for substance dependence of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV), appropriately adapted to decrease emphasis on intoxication *per se* and to acknowledge other aspects of the androgen dependence syndrome. In a subsequent psychometric study [70], we developed an interview module based on these criteria, and showed that this module yielded very good interrater reliability ($\kappa = 0.76$) and strong internal consistency (Cronbach's $\alpha = 0.77$ – 0.87).

By contrast Hildebrandt and colleagues, as discussed earlier, have suggested that it may be overly simplistic to diagnose androgen dependence using traditional substance use criteria, since androgen use occurs in a larger context of polypharmacy, body image disturbance, and disturbances in dieting and exercise [36]. Accordingly, these authors propose a more complex diagnostic structure where an "appearance and performance enhancing drug use disorder" is diagnosed on the basis of 3 of 8 possible "A" criteria covering recurrent polydrug use, together with either 3 of 6 "B" criteria for body image disturbance, or 2 of 6 "C" criteria for pathological dieting or exercise behavior. The authors have recently complemented this proposal with a psychometrically validated Appearance and Performance-Enhancing Drug Use Schedule (APEDUS) [37], which includes 10 modules comprising some 200 individual items tapping the various domains of pathology just discussed.

Both of the above two research groups have speculated further on possible mechanisms of androgen dependence. Building upon a recent study of risk factors for androgen use among 233 American weightlifters [7], we have explored factors that may potentiate the subsequent progression from initial androgen use to outright androgen dependence. We suggest that this progression may develop via any or all of three etiologic mechanisms [111]. First, individuals with body-image disorders may become "addicted" to androgens for their *anabolic effects*, in that these individuals become pathologically concerned that they will lose muscle and gain body fat if they stop the drugs. Second, as discussed above, androgens suppress HPT function via their *androgenic effects*, causing potential androgen-withdrawal hypogonadism. Men experiencing dysphoric effects of hypogonadism may resume androgens to alleviate this dysphoria, again contributing to dependence. Third, androgens possess at least some *hedonic effects*, as suggested by the animal studies above, and these effects may contribute to androgen dependence via mechanisms shared with classical addictive drugs, especially opioids. The relative contributions of these three mechanisms vary among individuals, and also vary with the stage of androgen dependence, with psychological aspects dominating in early stages and more physiological aspects in later stages. We suggest that one must be conscious of all three pathways to fully address androgen dependence, and propose a range of consequent treatment options [111].

Hildebrandt and colleagues [141] propose an allostatic model of androgen “addiction” that shares many features with our model above. In particular, these authors agree that classical models of drug dependence, which emphasize hedonic effects, account poorly for androgen dependence, and that a broader focus is necessary. Like our group, they emphasize that psychological features such as body-image disturbance, plus neuroendocrine factors such as regulation of the HPT and hypothalamic-pituitary-adrenal axes must be incorporated into any model of androgen dependence. They then propose a model whereby exercise and androgen use initially produce desirable secondary gains, but put pressure on the homeostatic system as a result of increased metabolic/musculoskeletal allostatic load. This combines with increased hormonal allostatic load to contribute to physiological addiction, marked by the use of ancillary substances to reduce the side effects of allostatic load. Using this model, the authors discuss factors that may modulate individual risk for dependence and its consequences.

Conclusion

Androgen abuse first spread from elite athletics and into the general population in the 1980s, and thus the oldest users – those who began androgens as youths in the 1980s – are only now reaching middle age, with consequently increasing risk of long-term adverse effects from these drugs [3]. By analogy, imagine that widespread cigarette smoking began only in the 1980s and that the oldest smokers were only now reaching age 50. In that scenario, we might be first glimpsing the potential dangers of cigarettes, but full-scale studies would still be years away. An analogous situation might now exist for androgens. Mounting evidence in the last few years suggests that long-term androgen abuse, together with associated polypharmacy, may cause greater toxicity – especially to the cardiovascular, neuroendocrine, and central nervous systems – than previously reported, although larger controlled studies are still required. In particular, with growing recognition of androgen dependence syndromes, is becoming increasingly important to understand the origins and consequences of androgen dependence as a potentially major issue for public health.

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Bullet points

- Illicit androgen use is frequently accompanied by use of other appearance- and performance-enhancing drugs, such as human growth hormone, insulin, and thermogenic/stimulant agents, together with classical drugs of abuse such as cannabis, opioids, and cocaine.
- A growing literature has documented substantial long-term adverse effects of androgen use, including especially cardiomyopathy, dyslipidemia with potential atherosclerotic disease, prolonged suppression of the hypothalamic-pituitary-testicular axis, and major mood disorders.
- It is increasingly recognized that illicit androgen users may develop a dependence syndrome, which appears to be mediated by a combination of psychological, neuroendocrine, and hedonic factors.