Anabolic steroid–induced hypogonadism: diagnosis and treatment

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Objective: To develop an understanding of hypogonadal men with a history of anabolic-androgenic steroid (AAS) use and to outline recommendations for management.
Design: Review of published literature and expert opinions. Intended as a meta-analysis, but no quality studies met the inclusion criteria.
Setting: Not applicable.
Patient(s): Men seeking treatment for symptomatic hypogonadism who have used nonprescribed AAS.
Intervention(s): History and physical examination followed by medical intervention if necessary.
Main Outcome Measures(s): Serum testosterone and gonadotropin levels, symptoms, and fertility restoration.
Result(s): Symptomatic hypogonadism is a potential consequence of AAS use and may depend on dose, duration, and type of AAS used. Complete endocrine and metabolic assessment should be conducted. Management strategies for anabolic steroid–associated hypogonadism (ASIH) include judicious use of testosterone replacement therapy, hCG, and selective estrogen receptor modulators.
Conclusion(s): Although complications of AAS use are variable and patient specific, they can be successfully managed. Treatment of ASIH depends on the type and duration of AAS use. Specific details regarding a patient's AAS cycle are important in medical management. (Fertil Steril® 2014;101:1271–9. ©2014 by American Society for Reproductive Medicine.)
Key Words: Anabolic-androgenic steroids, androgens, hypogonadotropic hypogonadism, gynecomastia, testicular atrophy, erectile dysfunction, clomiphene citrate, tamoxifen, human chorionic gonadotropin

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Anabolic-androgenic steroid (AAS) users have come a long way since the end of the 19th century, when an aging Dr. Brown-Séquard eagerly reported "a decided gain in strength" after injecting himself with the "orchitic fluid" of laboratory animals. This discovery created enthusiasm and controversy alike while laying the foundation for the field of andrology (1–3). Synthetic androgens were born in the 1930s when Foss first described the medical use of orally bioavailable methyltestosterone (4, 5). Since that time, androgens have been approved for the treatment of a variety of conditions, including testosterone (T) deficiency, osteoporosis, cachexia, delayed puberty, and breast cancer (6). Derivatives of T have varying degrees of relative anabolic and androgenic activity—exerting their ergogenic and cosmetic effects by targeting the androgen receptor to increase lean muscle mass, burn fat, and boost athletic performance (7–10).

Unfortunately the use of androgens is not without significant side effects, including hepatotoxicity, cardiotoxicity, polycythemia, dyslipidemia, hypertension, depression, gynecomastia, testicular atrophy, and infertility—all well described but poorly understood sequelae (7, 11–14). Additionally, for men who have previously used AAS, a unique condition known as anabolic steroid–induced hypogonadism (ASIH) becomes a real concern. Clearly described in 1990 by Jarow and Lipshultz (15), ASIH has recently been identified as a potentially underrecognized cause of hypogonadism in young men (16). Demographics and usage patterns vary among AAS users, who report different motivations for

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use. The present review focuses on the nonprescribed use of AAS. At present, there is a lack of information in the peer-reviewed literature describing the demographics, characteristics, and psychologic make-up of AAS users. Furthermore, there are no comprehensive management recommendations available for the treatment of AAS-induced complications such as infertility and ASIH. Understanding has been hindered by a lack of publications, with only a few case series and very few large-volume studies existing—making meta-analysis impossible. Most physicians are uncomfortable addressing AAS use and are hesitant to broach the topic with patients. To effectively manage these patients, a basic understanding of the AAS user's self-treatment strategy is required. With the present review, we provide a summary of the pathophysiology underlying AAS use and provide management recommendations for symptomatic patients who have previous used, or are currently using, AAS.

MATERIALS AND METHODS

A Pubmed literature search was conducted for the time period of 1965–2013. There were insignificant published quality data for meta-analysis, so a systematic review was performed. Key terms included "anabolic-androgenic steroids," "androgens," "hypogonadotropic hypogonadism," "gynecomastia," "testicular atrophy," "erectile dysfunction," "infertility," "clomiphene citrate," "tamoxifen," "human chorionic gonadotropin," "selective estrogen receptor modulators," and "aromatase inhibitors."

Data collection for common treatment strategies was based on in-depth unsolicited discussions with users who had taken AAS for primarily bodybuilding purposes. Additionally, an Internet search strategy for AAS user blogs and discussion sites was used to describe the demographics and usage patterns of the modern AAS user (17). The external validity of these techniques is supported by earlier studies that used similar methods of Internet data mining to report consistent findings (9, 18–26).

RESULTS

The Modern Anabolic Steroid User: An Evolving Portrait

Since the early ergogenic use of AAS by Olympic athletes of the 1950s and 60s, nonmedical use of AAS has evolved from an ethical issue of fairness in sport to a very real public health concern (27, 28). The lifetime prevalence of AAS use for men is estimated to be from 3.0% to 4.2% (12) and is increasing (29). Use among male gym attendees is estimated to be as high as 15%–30% (9, 19, 25). Furthermore, the growing trend of androgen replacement in rejuvenation clinics was recently acknowledged by Moss et al. (6). As such, the prototype of an AAS user is rapidly shifting to encompass a spectrum from the competitive body builder/athlete to men seeking to optimize their physical appearance.

Historically, media coverage concerning AAS has focused disproportionately on athletes (from elite professionals to high school students) seeking a competitive edge. In reality, at least four out of five AAS users are not competitive athletes but rather men who desire what they perceive to be an "enhanced" appearance (9, 17, 21, 25). Recently, however, data from the "Monitoring the Future" study (30) found that illicit AAS use was declining among adolescents—potentially due to the success of education and numerous prevention campaigns targeting high school athletes (31).

Consistent with these data, Cohen et al. (17) found that 94% of the 1,955 adult AAS users began after the age of 18 years with an overwhelming number being whites in their late 20s–30s with a slightly above-average socioeconomic status. These men were self-reported perfectionists and highly goal-oriented. Data from a recent retrospective study found that 20.9% of 382 hypogonadal patients seeking T replacement therapy (TRT) had earlier AAS exposure (16). Therefore, physicians treating hypogonadism should be aware of potential etiologies such as ASIH and understand where AAS are obtained, the regimens that users follow, and the adverse events that should be monitored.

AAS Availability and Procurement

It has previously been suggested that the Internet is the most common source for men to obtain AAS as well as ancillary drugs (9, 17, 21, 32, 33). Access to these suppliers can vary from open access to special invitations offered by Internet forum members or via word of mouth at local gymnasiums. Internet suppliers offer bundled packages that commonly include T and synthetic androgens as well as selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), human chorionic gonadotropin (hCG), and phosphodiesterase-5 inhibitors (PDE5i) (33–35). Beyond nonphysician sources, nutritional supplements sold legally online or in retail stores have been found to contain AAS or other ancillary drugs that may or may not be listed as ingredients on the product label (33, 34, 36–41). Indeed, >20% of legally sold nutritional supplements have been found to be contaminated with AAS (39). With global sales of nutritional supplements exceeding $32 billion in 2012 and rapidly rising, this ubiquitous impurity poses significant public health problems (42). Therefore, when counseling and developing a treatment plan for the hypogonadal patient with ASIH, it is critical to have an understanding of what supplements the patient is on and where they were obtained.

Users' Sources of Information and Medical Advice

When developing a self-designed treatment plan, AAS users spend considerable time researching and seeking advice from more experienced associates (43). Historically, AAS use was developed by a gym subculture whereby novice bodybuilders interested in performance-enhancing substance use would obtain the drugs and information from more experienced users at the gym, often establishing a mentor-mentee relationship (19, 25). Now the most easily accessible source for information regarding the details of illicit AAS use is the Internet (9, 17, 44). Numerous blogs and forums exist (e.g., www.steroid.com, www.steroidology.com) where AAS users around the world can anonymously offer or request advice, share drug sources, chronicle results, and collaborate on dosing schedules. Another source of information involves