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

specific "nutritionists" who, for a fee, usually yearly, give advice to these men about AAS, dietary supplements, and nutritional plans.

The AAS user's rationale for choosing various drugs and protocols is typically based on anecdotal evidence and interpretations of quasiscientific literature propagated via Internet forums. It is also apparent that some users achieve popular authority within the Internet bodybuilding community and are often consulted for medical advice via forums. Indeed, given the minimal exposure that physicians have to AAS, coupled with the fact that many "expert" users have experimented with the majority of available AAS and their companion medications, it is not too far-fetched to consider first-hand experience of achievable gains, side effects, and "optimal" self-treatment regiments by seasoned AAS users to be of perceived "greater value" than an average physician's recommendation. Indeed, it is the general consensus within the AAS community that experienced AAS users are more educated than their physicians on AAS use, a sentiment that may contribute to the AAS user's hesitancy to approach his physician for advice when adverse symptoms occur (17, 43).

Motivations for Use and Dependence: A Challenge for Clinicians

Results from large surveys sampling AAS users on Internet bodybuilding forums have reported that the most common reason for beginning AAS use was to increase muscle mass and decrease body fat (9, 17). These users also reported feeling compelled to continue their regimens for a fear of the withdrawal that would result in excessive hypogonadal symptoms and the loss of muscle mass (6, 17).

When considering the concept of ASIH, the aggregate AAS dose and duration likely portends the extent of the condition; however, it must be recognized that there are substantial variations in types and amounts of AAS used (45). A subset of aggressive users may develop a dependence syndrome of combined physiologic and psychologic etiology, subjecting themselves to long-term or permanent endocrine dysfunction (9, 12, 14, 15, 17, 31, 44–46). Given these case reports as well as the known AAS side effects, one might wonder whether AAS users experience regret over their decision to use AAS. If these suspicions are correct, then determining the reasons for regret would be a valuable tool in educating current patients previously on AAS who are seeking TRT for hypogonadism.

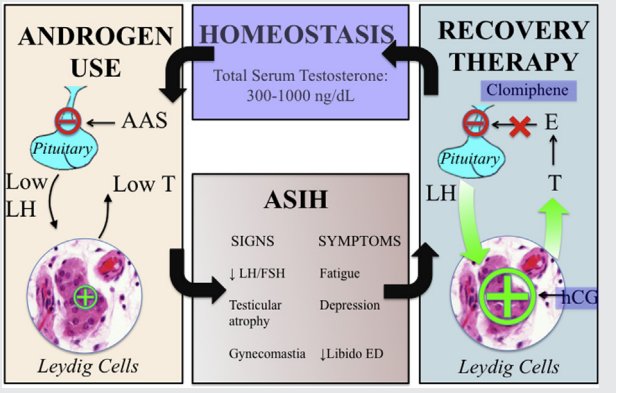
In stark contrast to the classic drug abusers, most AAS users show considerable forethought in their illicit substance use (47). Users typically obtain all of the necessary medications before beginning their self-determined "treatment" cycle and follow calculated dosing schedules (9, 17, 25, 48, 49). AAS users are often hesitant to stop their regimens and often present to physicians with requests for diagnostics or unwarranted therapies without the intent of stopping illicit AAS use. It is also common for AAS users to want to cycle off all TRT, feeling that this enhances their responsiveness and improves safety. As such, the treatment of AAS users poses a unique challenge for physicians. It may be helpful to gauge the patient's knowledge of AAS-associated complications while working to address misconceptions that often stem from Internet forum trends and popular anecdotal evidence. Central to this is the need for physicians to become more educated about the psychology and pathophysiology underlying AAS use.

Pathophysiology

Feedback suppression. Use of AAS results in hypogonadotropic hypogonadism by feedback suppression of the hypothalamic-pituitary-gonadal (HPG) axis via inhibition of pulsatile GnRH release and a subsequent decrease in LH and FSH (Fig. 1). The duration of suppression and the resultant symptomatic ASIH is highly variable and due to multiple factors, including differences in the choices of drugs, amounts used, and durations of use. Based on our experience, there may be differences between individual users regarding the response kinetics of the HPG axis. Our experience and that of other investigators suggests that younger men may have a more "elastic axis" capable of recovering GnRH pulsation and gonadotropin secretion faster and more completely than older AAS users (50). It is possible that shorter durations, lower doses, younger ages, and higher T levels at baseline are associated with a quicker recovery of HPG axis function after AAS use.

ASIH: a unique pathophysiology. Considerable variation exists regarding drug combinations, dosing, and duration of use. Up to 90% of AAS users combine or "stack" multiple androgens, a practice that users believe provides the greatest results while minimizing unwanted side effects (19, 48). Traditionally, a typical bodybuilding cycle includes a stack of multiple AAS at a combined dose of 500–1,500 mg/wk and lasts on average 4-12 weeks (17, 19, 25, 32, 48, 51) (Table 1). The most commonly used androgens reported by multiple surveys are single-ester T, nandrolone, stanazolol, metandienone, and trenbolone (16, 17, 32). In contrast,

FIGURE 1



Illustrates the pathophysiology of anabolic-androgenic steroid (AAS)–induced hypogonadism (ASIH) and the mechanism of action of selected treatment strategies. Recovery therapy focuses on estrogen blockade at the level of the hypothalamus to encourage GnRH pulsation and gonadotropin release to restart the hypothalamic-pituitary-gonadal axis and increase testosterone production.

Rahnema. Anabolic steroid–induced hypogonadism. Fertil Steril 2014.

TABLE 1

Commonly reported user-reported side effects and concerns, user strategies for management, and physician recommendations.

Side effect	User strategies for management	What should physicians recommend?
Low endogenous T	SERMs to restart axis	Discontinue AAS Start recovery protocol with TRT, SERMs, or hCG
Gynecomastia	Tamoxifen Aromatase inhibitors Cabergoline and bromocriptine for galactorrhea	Chronic gynecomastia likely unresponsive to medical management Surgical management is best option for chronic gynecomastia Acute gynecomastia may be treated with tamoxifen per SERM recovery protocol Avoid hCG use if possible. Use of aromatase inhibitors is discouraged because of possible sexual side effects
Testicular atrophy	hCG injections	Testicular atrophy will resolve discontinuation of AAS and recovery of HPG axis function hCG should be reserved for cases unresponsive to first line SERM treatment
Sexual dysfunction	PDE5 inhibitors Herbal aphrodisiacs Cabergoline Mesterolone for added androgenic effects Dapoxetine	PDE5 inhibitors should be first-line treatment Herbal aphrodisiacs should be discouraged owing to contamination concerns Dapoxetine not yet approved for sexual dysfunction
Hepatic dysfunction	Users of oral AAS concerned with hepatic function may take herbal supplements such as milk thistle extract for liver protection	Encourage discontinuation of oral AAS and herbal supplementation Perform complete metabolic panel to assess liver function
Alopecia	Users often prophylactically take finasteride to prevent hair loss	Although AAS use may worsen existing alopecia, 5-alpha-reductase inhibitor use should be discouraged because it may worsen symptoms of ASIH

Note: AAS = anabolic-androgenic steroid; ASIH = anabolic-androgenic steroid–induced hypogonadism; HPG = hypothalamic-pituitary-gonadal; PDE5 = phosphodiesterase-5; SERM = selective estrogen receptor modulator; TRT = testosterone replacement therapy.

Rahnema. Anabolic steroid–induced hypogonadism. Fertil Steril 2014.

medical TRT is given at fixed replacement doses and may not be a good model to describe pharmacodynamics in the AAS user. Although some evidence exists describing the recovery period after exogenous T used as a hormone replacement (52, 53), it is likely that a more complex and global endocrine disruption exists for the AAS user because of the stacking and cycling of multiple high-dose synthetic androgens and other ancillary drugs, culminating in a unique pharmacologic milieu (48). Beyond the systemic consequences of hypogonadotropic hypogonadism, nonhuman animal studies suggest direct testicular toxicity results from synthetic androgen use (29, 50, 54–58). However, the significance of these findings is not well established, and the extent to which heavy AAS use might contribute to primary gonadal failure remains unclear and warrants further study.

Adverse Effects and Treatment Recommendations

AAS users commonly report side effects that they consider to be esthetically unpleasing, such as testicular atrophy, fluid retention, acne, gynecomastia, and alopecia (9, 16). Sexual dysfunction was reported by 25% of users, and symptoms of androgen deficiency, including fatigue and depression, are common complaints, especially during a post-cycle period. Polycythemia also is a common adverse event, occurring in ~40% of patients. Long-term AAS users may have serious underlying hepatic, renal, and cardiovascular disease, with hypertension and dyslipidemia common among chronic users.

ASIH arises from the combination of hyperandrogenism, resulting from the supraphysiologic supplementation of AAS, and subsequent hypogonadism. This T deficiency occurs because typical AAS users alternate between "on-cycle" supraphysiologic plasma androgen levels and periods of androgen deficiency where ancillary drugs such as SERMs, AIs, and hCG are used in attempts to recover the HPG axis (7, 9, 17, 19, 25, 32, 48, 59). Via suppression of estrogen and thus its negative feedback, the hypothalamus can restart the HPG axis (Fig. 1).

Diagnostic and treatment recommendations. Initial testing typically consists of a hormonal panel (LH, FSH, E_2, T, free T, SHBG, and PRL), complete blood cell count, lipid profile, prostate-specific antigen, and a comprehensive metabolic profile. Common post-cycle complaints include depressive mood alterations, fatigue, lethargy, insomnia, and decreased libido, and any such symptoms should be addressed. Physical examination should include height, weight, blood pressure, and body mass index, and common signs consistent with AAS use, such as acne, gynecomastia, testicular atrophy, skin striations, and alopecia should be noted if present.

For AAS users seeking treatment and assistance in permanently discontinuing AAS, certain steps should be taken. Following establishment of a nonjudgmental, healthy, and trusting physician-patient relationship, the patient should be counseled to discontinue all AAS as well as any self-administered ancillary drugs and supplements. For the severely symptomatic patients, a 4-week tapered course of transdermal or injectable TRT may provide immediate symptom improvement. Simultaneous administration of a SERM (such as clomiphene citrate, 25 mg every other day) will interact at the hypothalamus causing stimulation of LH and ultimately increase intratesticular T (Fig. 1). For patients with ASIH-induced gynecomastia, 20 mg tamoxifen daily will block the breast estrogen receptors and stimulate HPG axis recovery (60–65).

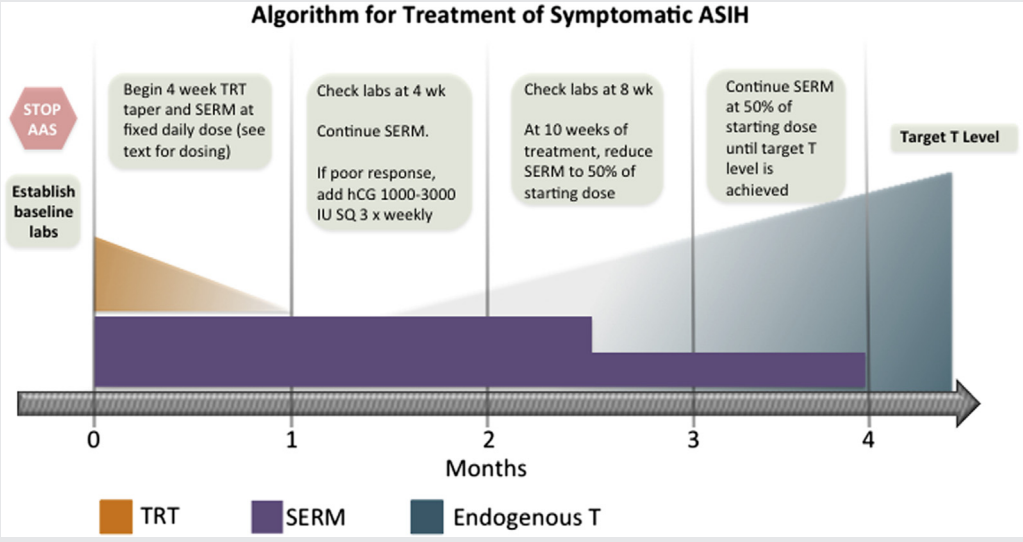
After 4 weeks of treatment with TRT and/or a SERM, repeated hormone panels should be obtained. If the patient has had either a poor gonadotropin response or a poor T response, the authors commence a 4-week course of hCG (1,000–3,000 IU, 3 times per week) while continuing daily treatment with a SERM at the initial starting dose (66–69). If a patient develops gynecomastia while on hCG, tamoxifen (10 mg b.i.d.) or anastrazole may be commenced. After 8 weeks of hCG and adjunctive treatment, hormone levels should once again be assessed. At this point, if the total serum T remains low and the patient continues to be symptomatic, primary testicular failure is likely (46). These patients will require a longer duration of TRT to avoid permanent ASIH. If appropriately increased serum T and gonadotropin levels are observed, the SERM may be reduced to 50% of its starting dose at 10 weeks of treatment and continued through weeks 12–16 or until target serum T level is achieved (70) (Fig. 2). Recovery of hormonal function may be limited in men with testicular failure, and close monitoring is recommended.

Management of gynecomastia. Gynecomastia, or painful breast enlargement, is a common and distressing complication of AAS use occurring in as many as one-half of all users (71). Partially due to an imbalance of T/E_2 signaling in breast tissue (72), symptoms may arise in the post-cycle period because of profound ASIH or administration of hCG (and subsequent elevations in E_2 secondary to aromatization) along with a systemwide decline of endogenous androgen signaling. Alternatively, it may occur while on-cycle, depending on the relative anabolic-to-androgenic effects as well as any progestin-like effects of medications used. AAS compounds that are susceptible to aromatization are more likely to cause gynecomastia (72). Finasteride, used by as many as 10% of AAS users for alopecia (17), may potentiate this effect and should be discontinued in ASIH users with gynecomastia (73–76). Herbal supplements such as tribulus terrestris and saw palmetto extract have no proven benefit and might cause worsening gynecomastia. As such, AAS users should be advised to discontinue these supplements (77, 78). The use of hCG has been reported in >40% of AAS users (17) and may cause, or exacerbate, gynecomastia (72).

Symptom duration is likely the best prognostic indicator for response to therapy (72, 79, 80) with acutely tender gynecomastia being the most amenable to medical treatment. Gynecomastia that has persisted for >1 year is more likely to involve significant fibrosis and typically responds poorly to drug therapy (72, 80–82). In such nonpainful chronic cases, surgical treatment is the best option for cosmetic improvement (73, 83, 84). Although large trials are lacking, tamoxifen appears to be the most safe and effective agent for the medical management of AAS-associated gynecomastia (63, 81, 82, 85–87). Because tamoxifen has been used effectively to increase gonadotropin secretion and restart the HPG axis in the setting of ASIH as well as idiopathic hypogondotropic hypogonadism (15, 88–93), the authors recommend tamoxifen for the medical treatment of ASIH with concomitant AAS-associated gynecomastia (Fig. 2).

Evidence that AIs are effective in the treatment of gynecomastia exists, and the authors have used them previously with good success and minimal side effects. However, Finkelstein et al. (94) recently reported findings suggesting that suppression of circulating estrogen levels with AIs decreases libido, worsens erectile dysfunction, and increases percentage body fat in men with a chemically repressed HPG axis despite the administration of TRT. Given that men with symptomatic

FIGURE 2



Suggested treatment algorithm for symptomatic anabolic-androgenic steroid–induced hypogonadism (ASIH). SERM = selective estrogen receptor modulator; TRT = testosterone replacement therapy.

Rahnema. Anabolic steroid–induced hypogonadism. Fertil Steril 2014.

ASIH may suffer from sexual dysfunction (9), administration of AIs in this population may still be considered, but proper monitoring is advised.

Management of sexual dysfunction. Erectile dysfunction and decreased libido are common complaints of AAS users, especially during the post-cycle period when endogenous T levels are lowest. Adding to the complexity of evaluating these patients, the types of AAS used may contribute uniquely to the pathophysiology of AAS-induced sexual dysfunction. Certain synthetic AASs, such as nandrolone, have a reputation for causing erectile dysfunction when used alone. This effect is likely due to an unopposed progestin-like action of the steroid along with the relatively lower androgenic activity of its 5-alpha metabolite dihydronandrolone (compared with dihydrotestosterone). By concurrently administering injectable T, AAS users attempt to mitigate the sexual side effect profile of synthetic AASs such as nandrolone (Table 2).

More than 25% of users report using PDE5i either prophylactically or as treatment for erectile dysfunction (9, 17). Several popular Internet AAS suppliers offer drugs such as dapoxetine, bromocriptine, and cabergoline as well as PDE5i. In addition, AAS users commonly purchase over the counter herbal "aphrodisiacs" that have been previously found to contain designer analogues of licensed PDE5i (42). Indeed, for AAS users, initial therapy for erectile dysfunction consists of PDE5i. Although controversial, the restoration of a normal hormonal milieu may be important for optimal response to oral PDE5i therapies.

Management of inferility and testicular atrophy. AAS use can be an important cause of male-factor infertility (12). Although several recent reviews have addressed the effects of androgen consumption on male fertility (6, 12, 29, 95, 96), some clinicians remain unaware of the fact that the use of exogenous androgens suppresses the HPG axis and, by decreasing intratesticular T (ITT), results in infertility (6, 97, 98). Because an adequate ITT concentration is necessary for spermatogenesis (52), it is not surprising that AAS users have presented to fertility clinics with azoospermia or oligospermia as well as sperm dysmorphia and dysmotility (12, 95, 99). A return of ITT is the most important factor for restoration of spermatogenesis, and therefore initial management of AAS-induced infertility should parallel strategies for the correction of the underlying hypogonadotropic hypogonadism (29, 52).

A review of the literature suggests that most cases of AAS-induced oligospermia or azoospermia are likely to resolve spontaneously within 4–12 months after AAS discontinuation (29). Although some authors have argued for reserving medical treatment for cases of azoospermia lasting >24 months (100), SERMs and/or gonadotropins have been successfully used after much shorter intervals of AAS cessation (67, 101, 102). Spermatogenesis recovery time, however, with or without medical treatment, appears to be highly variable and is difficult or impossible to predict for an individual patient.

In a case series of four azoospermic men, Gazvani et al. reported on the spontaneous return of sperm concentration to normal levels over a variable period of 5–18 months after AAS cessation (100). Turek et al. reported a single case of AAS-induced azoospermia successfully treated with hCG, and pregnancy was achieved after 3 months of therapy (102). Menon et al. reported a return to normal semen parameters after 3 months of treatment with hCG and hMG in a patient who had been untreated and azoospermic for 1 year after stopping AAS (67).

As far as we know, cases of persistent azoospermia despite exhaustive medical treatment have not been described in the literature. Clearly, the management of AAS-induced male infertility should begin with conservative or medical management. Histopathologic abnormalities, such as sperm maturation arrest, have been described in AAS users and animal models (102, 103), and although there are no published data confirming the success of sperm retrieval techniques with subsequent IVF-ICSI for cases of AAS-induced

TABLE 2

An example (considerable variations exist) of a bodybuilder's 12-week AAS cycle followed by 4 weeks of post-cycle therapy.

Week	Testosterone cypionate, mg/wk	Nandrolone (Deca-Durabolin), mg/wk	Metadienone (Dianabol), mg/d	hCG (IU/2–3 d)	Anastrazole (Arimidex), mg/d	Clomiphene citrate (Clomid)	Tamoxifen (Nolvadex), mg/d
1	500	500	25				
2	750	500	25				
3	750	500	25				
4	750	500	25				
5	1000	500	50				
6	1000	500	50				
7	1000	500	50				
8	1000	500	50				
9	1000	500	0	500	0.25		
10	1000	500	0	500	0.25		
11	750	500	0	500	0.25		
12	500	500	0	500	0.25		
13						200	40
14						100	40
15						50	20
16						50	20

Note: AAS = anabolic-androgenic steroid.

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azoospermia, invasive procedures such as microdissection testicular sperm extraction (micro-TESE) may be used for the exceedingly rare case of unrelenting azoospermia that does not resolve after a thorough attempt at medical treatment has been made.

Regarding testicular atrophy, hCG preserves testicular function and prevents testicular atrophy (104). Treatment with hCG is known to increase testicular volume, based on studies in patients with hypogonadotropic hypogonadism (105, 106). Furthermore, AAS users typically self-administer hCG at low doses, such as 250-500 IU subcutaneously or intramuscularly daily or every other day for several weeks toward the end of long cycles and through the first few weeks of their post-cycle regimen (Table 2). SERMs may be equally efficacious for the prevention of AAS-induced testicular atrophy, although quality comparative studies are not available. hCG may be added to the protocol if response to primary SERM treatment is inadequate.

Management of polycythemia. Supraphysiologic levels of plasma androgens stimulate erythropoietin production in a dose-dependent manner and may lead to clinically significant secondary polycythemia (107, 108). The increase in plasma viscosity may be a contributing factor to adverse cardiovascular events in AAS users, especially in those patients with preexisting coronary risk factors (109); however, this potential relationship has not been definitely demonstrated by meta-analysis (108). Nevertheless, correction of severe polycythemia in AAS users should be attempted by phlebotomy. However, ultimately the discontinuation of AAS and a restoration of normal endogenous hormone levels are paramount for reducing the patient's risk for potential polycythemia-associated complications.

DISCUSSION

Recently, a retrospective database review of 6,033 hypogonadal men found ASIH to be a common cause of profound hypogonadism ($T < 50$ ng/dL) (16). Even more surprising, it was found that as many as one out of five men who were being treated for symptomatic hypogonadism had previously used AAS (16). These important new data identify ASIH as a concerning and preventable cause of hypogonadism, especially in younger hypogonadal men. Despite being the only class of U.S. Drug Enforcement Administration scheduled drugs for which the Diagnostic and Statistical Manual of Mental Disorders does not recognize a dependence syndrome, expert psychiatrists now appreciate AAS dependence as a valid diagnostic entity (31). The primary goal of counseling patients with ASIH should be to deter future and potentially harmful use of nonprescribed AAS. Understanding the patient's motivations for use can help to deliver the most effective counseling and may identify treatable pathologies such as primary hypogonadism, delayed puberty, or psychopathology, all of which could be safely addressed through medically supervised treatment strategies.

Symptomatic hypogonadism is common after completion of an AAS cycle (16). After a complete endocrine and metabolic assessment, management strategies for hypogonadism include use of transient TRT, SERMs, and hCG. Responses may be quite variable, depending on specific characteristics of AAS use. Recognition of the specific details of the user's AAS cycle is important for their subsequent medical management. Use of AIs may be more problematic in light of recent evidence suggesting that their use may lead to potential sexual side effects (94).

For the treatment of acute gynecomastia, tamoxifen should be used as the SERM for the recovery protocol. hCG may exacerbate or cause gynecomastia in patients with ASIH. Erectile dysfunction may be effectively managed with a temporary course of short- or long-acting PDE5i while the HPG axis recovers function. Likewise, symptoms of decreased libido will likely improve gradually as endogenous T production returns to the patient's baseline levels. Management strategies for male infertility secondary to ASIH should parallel strategies for correction of the underlying hypogonadal state, and hCG should be included in the recovery protocol for these patients. Normal spermatogenesis is likely to be achieved as the ITT concentration improves. Treatment with hCG may be of benefit for patients with infertility secondary to ASIH.

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