Medical and Illicit Use of Anabolic Steroids

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician, behavioral health professional, or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, nurses, physician assistants, and mental health professionals in the primary care setting who are involved in the care of individuals who may use anabolic steroids.

Accreditations & Approvals

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This course is considered self-study by the New York State Board of Mental Health Counseling.

A complete Works Cited list begins on page 31.

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This course is considered self-study by the New York State Board of Marriage and Family Therapy.

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Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 5 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

This activity has been designated for 5 Lifelong Learning (Part II) credits for the American Board of Pathology Continuing Certification Program.

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NetCE designates this continuing education activity for 5 ANCC contact hours.

This activity was planned by and for the healthcare team, and learners will receive 5 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 6 hours for Alabama nurses.

NetCE designates this continuing education activity for 5 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

NetCE designates this activity for 5 hours ACPE credit(s). ACPE Universal Activity Numbers: JA4008164-0000-22-025-H04-P and JA4008164-0000-22-025-H04-P.

Social workers completing this intermediate-to-advanced course receive 5 Clinical continuing education credits.

NetCE designates this continuing education activity for 2 NBCC clock hours.

NetCE designates this continuing education activity for 5 continuing education hours for addiction professionals.

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Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective

The purpose of this course is to provide healthcare professionals with the knowledge necessary to recognize and intervene early in order to prevent adverse and potentially irreversible consequences of anabolic-androgenic steroid misuse.

Learning Objectives

Upon completion of this course, you should be able to:

1. Describe the pharmacology and mechanism of action of anabolic steroids, specifically testosterone.
2. Outline the range of therapeutic indications of anabolic steroids.
3. Identify the epidemiology, risk factors, and characteristics of anabolic steroid abusers.
4. List the potential adverse effects of anabolic steroid use.
5. Discuss the signs and symptoms of anabolic steroid use and abuse.
6. Recall appropriate interventions to manage the physical and neuropsychiatric effects of acute and chronic anabolic steroid use in current and past users.

Pharmacy Technician Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the epidemiology and pathophysiology of hypertension.
2. Describe pharmacologic and nonpharmacologic options for the management of hypertension.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Anabolic steroids, also referred to as anabolic-androgenic steroids (AAS), include the male hormone testosterone and related compounds that have muscle-building (anabolic) and masculinizing (androgenic) effects. Anabolic steroids have gained the attention of the lay public and the medical community due to the proliferation of media attention on their use in professional sports and the growing prevalence among amateur athletes. While most often discussed in terms of illicit use, anabolic steroids are also used to treat a variety of medical conditions. This course will explore the history, pharmacology, and mechanism of action of anabolic steroids and the use of anabolic steroids in three different contexts. These will include the legitimate medical use of testosterone replacement in hypogonadal male patients, the legitimate medical use of anabolic steroids in patients with conditions that benefit from either the anabolic or androgenic properties of these agents, and the illicit use of anabolic-androgenic steroids with the goal of increased muscle mass or cosmetic improvement. For the sake of clarity, the abbreviation AAS will be used when illicit, non-medically supervised use of these drugs is discussed.

HISTORY AND BACKGROUND

The testes have been linked with sexual vigor and longevity since antiquity, when the Greeks and Romans used "satyricon" preparations made from goat and wolf testicles as stimulants and aphrodisiacs [107]. Human testes were discovered as providing hormones affecting the body in 1849, and in 1889, physiologist Charles E. Brown-Sequard made the first public claims regarding the effects of anabolic steroids [110]. He announced that he had extracted and used on himself a compound from dog and guinea pig testicles that, when injected, increased his strength, improved his intellect, relieved constipation, and increased the arc of his urine [132].

Testosterone was first isolated in the 1930s, and synthetic derivatives of testosterone quickly followed. Both testosterone and its derivatives were widely used in medicine by the end of the following decade, primarily to treat male hypogonadism [75]. Also in the 1930s, anabolic steroids were discovered to facilitate the growth of skeletal muscle in laboratory animals [75]. Introduction of the muscle-promoting effects of anabolic steroids to Western medicine and culture began in the 1950s. An American physician attending the 1954 World Weightlifting Championship in Vienna was apparently told by a Russian official that the Soviet athletes were ingesting testosterone. Upon return to the United States, this physician began administering the drug to weightlifters at his gym, and the publication of his experiments in the lay press began the era of AAS use in sports and bodybuilding [33]. However, throughout the 1960s and into the 1970s, AAS use was largely limited to the elite levels of athletics. The efficacy of these agents remained a well-kept secret among athletes, aided in part by sports physicians and medical texts that continued to proclaim the ineffectiveness of AAS in gaining muscle mass [47].

The popularity of competitive bodybuilding soared by the late 1970s. Fitness and bodybuilding magazines proliferated, typically with AAS-using male models on the front cover, and increasing numbers of young men became aware of the dramatic muscle gains achievable with AAS use [93]. Western culture during the 1980s became increasingly focused on male muscularity [93]. Highly muscled male bodies began to proliferate in women's magazine advertisements, and the male centerfolds in *Playgirl* magazine became increasingly more muscular during this period [59; 94]. Even action toys such as GI Joe began to acquire the hypermuscled bodies of AAS users [92]. This climate promoted the more widespread use of AAS beyond the domain of elite athletics into the general population [47].

The use of AAS among elite athletes has never been as widespread and systematic as occurred in East Germany between 1965 and 1989, during which time the government masterminded and implemented a national system of athlete doping perpetrated by physicians, sports scientists, and coaches. Driven by the desire for international recognition and respect through success in sports, the East German government began a sophisticated talent identification program. Sports schools and clubs were established and staffed by sports medicine specialists, scientists, and coaches who, in addition to the athletes, were provided with substantial financial reward for athletic success [33]. In the three Olympic Games between 1956 and 1964, before the implementation of the program, East Germany won 45 Olympic medals compared with 81 by West Germany. In 1968, soon after the program began, East Germany won 25 medals to West Germany's 26. During the next three Olympic Games in which both countries competed (boycotts eliminated West Germany from 1980 Moscow and East Germany from 1984 Los Angeles Olympics), in 1972, 1976, and 1988 East Germany won 258 medals compared with 119 by West Germany [33].

During this time, western scientific literature significantly lagged behind the underground press in documenting the increase in lean body mass (LBM), stamina, and strength from AAS use. The underground press combined knowledge acquired from scientific journals with personal knowledge and experience of AAS-using athletes and the work of East German scientists (obtained clandestinely several years after the German reunification in 1989) to prove the efficacy of AAS in improving athletic prowess. One explanation is that before 1996, uncontrolled studies of AAS used physiologic doses in sedentary volunteers and found no anabolic effect. This changed in 1996 with the first randomized controlled trial documenting the anabolic effects of supraphysiologic doses of testosterone enanthate [10; 33; 123].

By the late 1980s, epidemiologic studies began to document substantial rates of AAS use among American teenagers and young adult males. In 1991, AAS were included for the first time in the National Household Survey (NHS) of drug use; the conservative results of this survey indicated that nearly one million American men had used AAS by 1991 [97]. These demographics convey very important implications. Results from multiple data sources indicate that by 2010, 500,000 to one million men in the United States who have engaged in the non-medical use of steroids will have turned 45 years of age or older. This cohort of aging AAS users is the first of its kind—the leading wave of a new epidemiologic phenomenon. Although most have likely discontinued AAS use, these former users remain vulnerable to a wide range of psychiatric and medical effects long after their last AAS exposure [47].

At the end of 2015, media reports began surfacing regarding a massive athletic doping scheme in the Russian Federation. The World Anti-Doping Agency published a report in November 2015 and commissioned an independent report, published in July 2016, that revealed the Russian program had run from at least 2011 to 2015, involved members of the government and state intelligence services, and incorporated falsifying lab results and tampering with drug-test samples [141]. The inquiry eventually led to a ban of approximately 120 Russian competitors from the 2016 Olympic Games. Months before the opening of the 2016 Olympics, a Russian runner came forward with additional information pertaining to the widespread state-sponsored doping program in what some experts have estimated to be similar in extent to the East German doping program [140]. Former East German athletes have warned Russian Federation athletes about the consequences of doping that they are now facing several decades later, including multiple organ failure (e.g., calcified heart, coronary artery disease, kidney failure), liver tumors, skeletal damage, and psychologic disorders [142].

ENDOGENOUS ANDROGENS

FUNCTION

Androgens are the major circulating sex hormone in men and regulate a wide range of physiologic processes through an intracellular androgen receptor (AR) [12; 58; 133]. In men, normal total plasma testosterone levels range from 300 ng/dL to 800 ng/dL, with most of the testosterone bound to sex hormone-binding protein and inactive. Free testosterone is the active form and comprises only 2% to 3% of circulating testosterone [110].

Androgens play a vital role in sustaining reproductive function in men and also enhance female sexual desire and arousal [53]. Testosterone significantly contributes to cognitive functioning such as attention, alertness, memory, and spatial skills. Endogenous androgen concentrations are positively correlated with well-being and joyfulness and negatively correlated with depression and anxiety [53].

Androgens exert their effects in reproductive tissues, muscle, bone, the liver, the kidneys, hair follicles in the skin, and the hematopoietic, immune, and central nervous systems [68; 134]. The androgenic effects of androgens are associated with masculinization, while the anabolic effects are associated with protein building in skeletal muscle and bone and linear growth [53; 134]. Alterations in circulating androgens, AR function, or changes in the dynamic intracellular AR complex leads to multiple disorders such as hypogonadism, muscle wasting, cachexia, osteoporosis, loss of reproductive function, and prostate cancer [73].

SYNTHESIS

Testosterone is the most important androgen, and testicular Leydig cells produce roughly 95% of endogenous testosterone. Leydig cell testosterone synthesis is stimulated by luteinizing hormone, which target these cells to increase cyclic adenosine monophosphate (cAMP) production. This, in turn, enhances the activity of the enzymes needed for testosterone synthesis and increases the availability of their primary substrate, cholesterol. A cascade

of enzymatic reactions yielding testosterone as the final product ensues [7]. Steroid-converting enzymes at the cellular level modulate the effects of androgens within the particular target tissue. Androgen modulation may also occur at the molecular level due to the variable distribution of AR co-regulators in various tissues [53].

AGE-RELATED CHANGES

Unlike female menopause, the decline in serum testosterone concentration in men is gradual, with considerable interindividual variability; thus, terms such as "male climacteric," "male menopause," "andropause," and "viropause" are misnomers as testosterone production and reproductive capacity does not cease in most men [107]. Serum testosterone concentration declines steadily following young adulthood, and by 80 years of age, the testosterone secretion rate is approximately half that of a younger man [13]. A longitudinal study found that testosterone levels declined by approximately 100 ng/dL per decade (***Table 1***) [70].

Abnormally low serum testosterone is referred to as hypogonadism, and age-related changes contributing to hypogonadism in older men occur in both the hypothalamus and testes. The rise in luteinizing hormone following a decrease in testosterone is considerably blunted with age and likely stems from the failure of the hypothalamus to generate an appropriate burst of gonadotropin-releasing hormone (GnRH) secretion that may be attributable to age-related hypothalamic-pituitary hypersensitivity to the negative feedback effect of testosterone [54; 72; 116; 117; 122]. In older men, declining circulating testosterone also correlates with declining Leydig cell numbers, structural changes within the Leydig cells, and decreased Leydig cell testosterone output in response to human chorionic gonadotropin [74]. This decline in bioavailable testosterone may partially explain the osteoporosis, mood disturbances, decreased muscle mass, and frailty observed in older men [13]. Although changes in libido, mood, energy, and cognition are associated with declining testosterone levels in older men, many other hormonal changes occur during the same period that may play a contributory role [107].

HORMONAL CHANGES IN HEALTHY AGING MEN

Hormone	Direction of Change
Testosterone	Decrease
Luteinizing hormone	Increase
Follicle-stimulating hormone	Increase
Dihydrotestosterone	None
Estradiol	None
Dehydroepiandrosterone and its sulfate	Decrease
Growth hormone/insulin-like growth factor I	Decrease
Thyroid-stimulating hormone	Decrease
T3	Decrease
Insulin	Decrease

Source: [107] *Table 1*

PHARMACOLOGY

The anabolic steroids are a family of hormones that includes the natural male hormone testosterone and its many synthetic derivatives, all of which exhibit both anabolic and androgenic properties. Anabolic steroids should not be confused with other types of steroids such as corticosteroids (e.g., hydrocortisone, prednisone), which have no anabolic effects and little abuse potential [47].

Mechanisms believed to account for the actions of anabolic steroids include the modulation of AR expression as a consequence of intracellular metabolism, transformation of AR topology and subsequent interaction with coactivators and transcriptional activity, interference with glucocorticoid receptor expression, and alteration of non-genomic central nervous system pathways [53].

TESTOSTERONE AND ITS ANALOGS

Testosterone is the primary anabolic steroid. Testosterone analogs are synthesized by modifying the testosterone molecule with the goal of enhancing bioavailability and activity, minimizing side effects, or avoiding detection in antidoping tests. Anabolic steroids in current use are active when taken orally,

as an intramuscular (IM) depot injection, or via the transdermal route, depending on the position and type of the molecular alteration [71; 110].

Delayed-release formulations and structural modifications to the primary testosterone molecule are designed to increase effectiveness through eliminating the extensive first-pass metabolism that oral testosterone undergoes. These alterations include esterification of the 17ß-hydroxyl group to allow for IM use (Class A analogs); alkylation at the 17αposition to allow for oral administration, inhibition of hepatic metabolism, and increased bioavailability (Class B analogs); and numerous other modifications of the A, B, or C rings intended to increase potency (Class C analogs) [30; 53]. Alkylated analogs and analogs with a modified ring structure are metabolized at a slower rate in the liver than testosterone and its 17ß-esterified derivatives, making class B and C analogs available for oral use [7]. Commonly used anabolic androgenic steroids include [55]:

- 17ß-esters of testosterone
  - Cypionate
  - Enanthate
  - Heptylate
  - Propionate
  - Undecanoate
  - Bucrylate
- 17α-alkyl derivatives of testosterone
  - Ethyltestosterone
  - Fluoxymesterone
  - Oxandrolone
  - Stanozolol
- 19-Nortestosterone (nandrolone)
- 17ß-esters of 19-nortestosterone
  - Decanoate
  - Phenpropionate
- 19-Norandrostenedione
- 19-Norandrostenediol
- Tetrahydrogestrinone

Metabolism

Testosterone is metabolized into dihydrotestosterone (DHT), which has 10 times the potency of testosterone, and estradiol, which has feminizing effects [55]. The primary metabolic substrate of testosterone is the hepatic isoenzyme family of cytochrome P450. Class A derivatives have long alkyl side-chains, slowing their hepatic metabolism and increasing their half-life in peripheral tissue. Modification in the class B and C derivatives alters their metabolic pathway to produce a longer half-life. They are excreted either unaltered or as metabolites and conjugates in the urine or feces [7; 99].

Anabolic Effects

Administration of supraphysiologic doses of testosterone increases fat-free mass, muscle size, and maximal voluntary strength in eugonadal men, which correlates with increasing testosterone dose and circulating testosterone concentrations [8; 9; 10; 124]. The effects of testosterone on muscle performance are selective in that maximal voluntary strength and leg power are increased but fatigability and endurance measures, such as maximum rate of oxygen consumption and lactate threshold, are unaffected [108].

Maximal muscle strength during supraphysiologic testosterone administration is strongly affected by resistive types of exercise, which induce adaptive changes in neuromuscular function and muscle morphology. Timed protein intake intensifies this effect. Anabolic steroids boost muscle hypertrophy beyond inherent genetic limits by hypertrophy of type I and type II fibers and by increasing the nucleus-to-cytoplasm ratio due to accelerated activation of myogenic satellite cells [2; 11; 135]. Testosterone also inhibits preadipocyte differentiation into adipocytes, increases fractional muscle protein synthesis, and improves the reutilization of amino acids by muscle [11]. Indirect anabolic mechanisms on skeletal muscle include antiglucocorticoid action and interaction with the insulin-like growth factor-1 system. Additionally, oxandrolone increases AR expression in skeletal muscle [7].

SELECTIVE ANDROGEN RECEPTOR MODULATORS (SARMS)

Concerns over the long-term risks of prostate and cardiovascular disorders in older men treated with testosterone prompted the development of selective androgen receptor modulators (SARMs). SARMs have anabolic effects on muscle but lack the adverse effects on prostate and cardiovascular systems [73]. Unlike testosterone, which is converted to the active metabolites estradiol and DHT, nonsteroidal SARMs do not undergo aromatization or 5-α-reduction and act as agonists in muscle and bone and as partial agonists in prostate and seminal vesicles. Some nonsteroidal SARMs have more favorable pharmacokinetics, greater AR specificity, and are more amenable to structural modifications than their steroidal counterparts [11]. The discovery and development of SARMs may ultimately result in the use of steroidal androgens only as a therapy of final resort for many indications for which androgen efficacy has been established [18].

STEROID DIETARY SUPPLEMENTS

Analogues of established anabolic steroids have been introduced and marketed as nutritional and dietary supplements to bypass the statutory controls related to the manufacture and supply of anabolic steroids. Examples of these agents include dehydroepiandrosterone (DHEA), androstenedione, androstenediol, and their 19-nor equivalents (prohormones), and analogues of testosterone and stanozolol called 1-testosterone and prostanozol, respectively [21; 53].

DESIGNER STEROIDS

Designer anabolic steroids are defined as anabolic steroids that are manufactured specifically to circumvent doping tests in sports, although their use is no longer limited to athletes. This type of AAS can be found in over-the-counter products, often being promoted as "natural steroids," "testosterone boosters," "pro-hormones," and other descriptors that may under-emphasize the dangers of using such products [145]. A Northern California company called the Bay Area Laboratory Co-operative (BALCO) attracted media attention when investigators discovered that high-profile athletes, such as Barry Bonds of the San Francisco Giants baseball team, had been obtaining a transdermal preparation code-named "The Cream" and a sublingual preparation of a new anabolic steroid code-named "The Clear" from the company. The preparations contained testosterone and epitestosterone [53].

The development of most designer androgens encountered today originated during the 1960s and 1970s, when the pharmaceutical industry implemented androgen discovery and synthesis programs geared towards identifying a purely anabolic steroid [41; 145]. Information on these molecules, which were synthesized but never marketed, has been uncovered by underground chemists who produce the drugs clandestinely [53]. Most of these designer compounds have never undergone animal or human toxicologic or safety testing, and their growing use by athletes poses significant potential health concerns [21].

A 2015 review illustrated the limited information available on the effects of several popular designer steroids, including dimethazine, methylepitiostanol, methoxygonadiene, methylclostebol, methylstenbolone, and mentabolan/trestione [145]. Many of these steroids are found in products labeled as dietary supplements. The review found that chemists employed methods to deliver potent androgens without technically selling controlled substances by using pro-drugs that are unclassified compounds but that metabolize in vivo to Schedule III controlled AAS [145]. Alternatively, some compounds were not explicitly named in the Anabolic Steroid Control Act of 1990 and therefore have not been regulated in the same way. These factors make it challenging to classify new generation designer steroids as controlled AAS [145].

MEDICAL AND THERAPEUTIC USES

There are two broad therapeutic indications for anabolic steroid use: androgen-replacement therapy (ART) in men who are androgen deficient (hypogonadal) and pharmacologic androgen therapy (PAT), whereby testosterone use is analogous to use of any other xenobiotic agent [40]. A third area of therapeutic use involves the treatment of low testosterone levels in aging men who, although not strictly hypogonadal, exhibit age-related decline in areas of physical or psychologic function associated with testosterone deficiency. This last area of medical use is somewhat controversial and unproven.

ANDROGEN-REPLACEMENT THERAPY IN MALE HYPOGONADISM

Hypogonadism is the primary clinical indication for medical testosterone use [136]. The goal of ART is to provide physiologic-range serum testosterone levels (typically 280 – 800 ng/dL) and physiologic-range dihydrotestosterone and estradiol levels in order to facilitate optimal virilization and normal sexual function [1].

Definition

Hypogonadism is a condition defined by insufficient testosterone production necessary for normal growth, development, and sexual function [136]. Androgen deficiency occurs in about 1 in 200 men and is widely underdiagnosed due to cultural taboos regarding "maleness" and sexuality, the absence of patient experience of a normal eugonadal state, and lack of awareness among primary physicians [24; 76]. Klinefelter syndrome, an archetype of hypogonadism and its most frequent cause, is also seriously underdiagnosed, with only 25% of men with this condition receiving proper diagnosis [130]. The missed diagnoses of Klinefelter syndrome deprive many men of effective treatment that could enhance quality of life and prevent a lifelong descent into poorer health [40].

Due to the absence of an accepted threshold value of plasma testosterone for defining androgen deficiency and the lack of convincing evidence for an altered androgen requirement in older men, the normal range of serum testosterone in younger adult males is considered to be valid for older men as well [120]. However, based on data obtained from large samples of healthy, nonobese men, the lower limit of the normal range in elderly males is roughly 315 ng/dL (11 nmol/L) for total testosterone and roughly 6.5 ng/dL (0.225 nmol/L) for free testosterone, which corresponds to a bioavailable testosterone of around 140 ng/dL (5 nmol/L) [52; 118].

Etiology

Male hypogonadism stems from testicular disorders that directly reduce testosterone output or from hypothalamic-pituitary disorders that reduce pituitary luteinizing hormone secretion [24; 136]. Male hypogonadism is categorized according to etiology; if the origin of pathology occurs at the testicular level, it is considered primary hypogonadism, but if it occurs at the pituitary-hypothalamic level, it is considered secondary hypogonadism. Primary hypogonadism is characterized by elevated levels of luteinizing hormone and follicle-stimulating hormone in response to diminished testosterone (and estradiol and inhibin B) feedback. Secondary hypogonadism is marked by low levels of testosterone associated with low or normal levels of follicle-stimulating hormone and/or luteinizing hormone [76; 136].

The most frequent causes of male primary hypogonadism include [5; 76]:

- Castration
- Testicular trauma/tumor
- Klinefelter syndrome
- Orchitis
- Chemotherapy
- Radiation therapy to the testes
- Hormone insensitivity
- Drugs (cytotoxins and spironolactone)

SIGNS AND SYMPTOMS OF TESTOSTERONE DEFICIENCY		
Organ or Function	**Clinical Features of Testosterone Deficiency**	
	Before Completion of Puberty	**Following Puberty**
Bones	Eunuchoidal proportions, osteoporosis	Decrease in bone mass, osteoporosis
Larynx	Lack of voice maturation	No change
Hair	Horizontal pubic hair line, straight frontal hairline, sparse beard	No change in pattern, although density is reduced
Skin	Lack of sebum and acne, fine wrinkles	Atrophy, paleness, fine wrinkles
Bone marrow	Anemia	Anemia
Muscles	Underdeveloped	Atrophy
Fatty mass	Increased	Increased
Penis	Infantile	No change
Prostate	Underdeveloped	Atrophy
Spermatogenesis	Not initiated	Regression
Ejaculate	Anejaculation or small volume	Decreasing volume
Libido	Not developed	Absence
Sexual potency	Not developed	Erectile dysfunction

Source: [5; 76] *Table 2*

Secondary hypogonadism may be caused by [5; 76; 146]:

- GnRH insufficiency (idiopathic or Kallmann syndrome)
- Pituitary or hypothalamic tumor
- Hyperprolactinemia
- Pituitary surgery
- Systemic disorder
- Morbid obesity
- Illicit drugs
- Glucocorticoids
- Opiates
- Anabolic steroids
- Chronic disease

Late-onset hypogonadism is considered a mixed primary/secondary type.

Signs and Symptoms

Men with hypogonadism experience a myriad of symptoms that reflect the numerous physiologic functions of testosterone. Due to the central role played by testosterone in sexual maturation at puberty, an important determinant to make is whether the onset of hypogonadism occurred before or after puberty [136]. Other symptoms can include weakness, fatigue, lethargy, decreased motivation, loss of self-confidence, decreased energy, insomnia, flushing, and mood changes such as depression or irritability (***Table 2***) [5].

Diagnosis

Diagnosis of hypogonadism involves a combination of medical history, physical examination, and laboratory testing. Diagnosis in elderly men is complicated by the multiple nonspecific symptoms of testosterone deficiency that are features of many other medical conditions. Suspicion based on signs and symptoms must be confirmed with laboratory tests. Serum total testosterone concentration is the most commonly used first-line measure of biochemical male hypogonadism, and when measuring testosterone, bioavailable or free testosterone should be used, not just total testosterone [45]. Other measures, such as testicular size, follicle stimulating hormone, luteinizing hormone, and semen analysis, are used to assist in the differential diagnosis [1].

EFFICACY OF ANABOLIC STEROIDS IN CONDITIONS ASSOCIATED WITH CATABOLIC STATES		
Condition	**Weight Gain Efficacy**	**Disease-Specific Efficacy**
HIV	Yes	No
COPD	Yes	Conflicting
Liver failure	Yes	Yes
Post-operative recovery	Yes	Yes
Burns	Yes	Yes
Cancer	Yes	Yes
Renal failure	Yes	Yes
COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus.		
Source: [7]		*Table 3*

Treatment

Injectable testosterone esters have been the foundation of hypogonadism treatment since the 1950s, and the restoration of serum testosterone levels to the normal range using testosterone replacement therapy alleviates or resolves many of the symptoms of hypogonadism [76]. Absolute contraindications to androgen therapy are prostate or breast cancer in men, and ART should be started in men older than 40 years of age only after the exclusion of undiagnosed prostate disease [24]. The Fourth International Consultation for Sexual Medicine found no convincing evidence that ART treatment increases the development or progression of prostate cancer [147]. Meta-analyses have found that ART in men with hypogonadism is associated with an average 1.7 kg gain in fat-free mass and a 1.1 kg gain in body mass, with some studies reporting improvements in maximal voluntary strength and a decrease in fat mass [11]. Treatment of severe hypogonadism increases bone density and strength, but whether treatment of partial hypogonadism with testosterone has the same effect is unknown. Also, whether supraphysiologic doses of androgens have the same effect on bone density remains unresolved [22].

PHARMACOLOGIC ANDROGEN THERAPY

PAT involves the use of androgens to achieve an androgenic or anabolic effect in patients, usually males, with a variety of disease conditions. The ultimate goals of PAT include improving the quality of life and reducing morbidity, both of which have been demonstrated in many disease conditions [40]. Although anabolic steroids appear safe and effective in the treatment of several clinical conditions, androgens are now inexpensive, which provides a disincentive for companies to undertake the expensive clinical trial process required for regulatory approval of new indications. As a result, many useful clinical applications of testosterone and other androgens seem condemned to exist in the region of off-label use [40].

Treatment of Catabolic States/Cachexia

The medical use of anabolic steroids is estimated to have increased 400% between 1995 and 2001, mostly due to the treatment of wasting associated with acquired immune deficiency syndrome (AIDS) [7]. In addition to AIDS, cachexia is prevalent in many other chronic diseases, such as chronic renal failure, hepatic cirrhosis, cancer, and pulmonary disease (***Table 3***) [7]. The disease course of these conditions is characterized by loss of fat-free mass and increased risk of disability, dependency, and erosion in quality of life. Anabolic steroids are an attractive treatment option because they can restore fat-free mass, muscle strength, and physical function, and they lack the undesirable effects of other cachexia treatments such as the gain in fat mass with megestrol acetate and the high cost and side effects of growth hormone [7; 11].

HIV/AIDS

During the early years of the AIDS epidemic, wasting resulting from infection with human immunodeficiency virus (HIV) (weight loss greater than 10% of baseline) was a highly visible sign of the devastating effects of the virus. The gaunt appearance of some of these patients considerably added to the stigma of the diagnosis and created an extra hardship for patients. Despite ongoing improvements in AIDS therapy, HIV-associated wasting remains an issue and may actually be masked by highly active antiretroviral therapy-induced morphologic changes [83]. Wasting is associated with significant morbidity and mortality. A decline to 66% of ideal body weight or 54% of lean body mass is typically fatal, and as little as a 5% weight loss is associated with morbidity and the development of opportunistic infections, even when controlling for CD4+ cell count and other prognostic parameters [83].

Anabolic steroids should be given to patients with hypogonadism and AIDS-associated wasting. A meta-analysis found that androgen supplementation for three to six months in persons with HIV-associated wasting produced significantly greater gains relative to placebo in fat-free mass, lean body mass, and overall body weight. Testosterone administration was associated with significantly greater improvements in muscle strength than placebo. Testosterone esters were found to produce greater increments in fat-free mass than transdermal preparations [11]. Nandrolone decanoate has been shown to increase overall weight and lean body mass and improve quality of life among patients with AIDS who had lost 5% to 15% of ideal body weight [83]. Oxandrolone increased average weight, appetite, and lean body mass when used alone in patients with HIV wasting, with gains in weight highest among patients combining oxandrolone with progressive resistance training [7; 83]. Oral formulations are seldom used because of rapid metabolism and inactivation among class A analogs and liver toxicity among class B and C analogs. However, the orally active testosterone derivative oxandrolone may be suitable for treatment of HIV-associated wasting [83].

Testosterone supplementation in women with HIV infection at doses that elevated plasma testosterone into the high-normal range for women was found to be safe, but weight gain occurred from increases in fat rather than lean body mass [11; 83; 148]. Further study of the potential role of anabolic steroid therapy in women with wasting syndromes is very much needed [53].

A Cochrane review of 13 trials concluded that although anabolic steroids may be useful in the treatment of weight loss in individuals with HIV infection, due to limitations, treatment recommendations cannot be made.

(https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005483/full. Last accessed October 28, 2022.)

Level of Evidence: Meta-analysis

Chronic Obstructive Pulmonary Disease

Similar to patients with HIV, weight loss and muscle wasting in patients with chronic obstructive pulmonary disease (COPD) is associated with increased mortality [119]. Regimens consisting of 250 mg testosterone IM at baseline followed by 12 mg oral stanozolol daily for 27 weeks, nandrolone decanoate, or oxandrolone therapy (20 mg per day) have produced significant improvements in lean body mass and weight, with inconsistent improvement in respiratory parameters [32; 101; 105]. A possible explanation of the inconsistent improvement in COPD-related parameters is the additive effect of intensive pulmonary rehabilitation, which was only used in some of the trials [103]. Caution is recommended when treating COPD patients with androgens due to the risk of developing polycythemia (overproduction of red blood cells) [7].

Cystic Fibrosis

In a double-blind, placebo-controlled study, patients with cystic fibrosis received 2 mg/kg prednisone every other day for four years [149]. Prednisone helped improve growth and pulmonary function, as well as decrease morbidity. This study was repeated

to assess different dosages, and while the use of prednisone was found to be connected to significant improvements in pulmonary health, the dose of 2 mg/kg was found to increase the risk of cataracts, growth retardation, and glucose abnormalities. A 1-mg/kg dosage was associated with fewer complications [149].

Corticosteroid Therapy

Glucocorticoid administration, especially on a chronic basis, is associated with muscle atrophy and a high frequency of low testosterone levels due to generalized suppression of the hypothalamic-pituitary-testicular axis [96]. Controlled trials of testosterone supplementation in men receiving glucocorticoids for bronchial asthma or COPD found that men receiving active drug achieved significant increases in lean body mass and bone mineral density in the lumbar spine and significant decreases in fat mass [11; 28; 95].

Osteoporosis

Androgen-deficient men are at increased risk of osteoporosis. Although the extent to which testosterone can prevent or treat osteoporosis in men is unclear, a meta-analysis of eight studies found that IM testosterone moderately increased lumbar bone mineral density, with inconclusive effects on femoral neck bone mineral density and a lack of evidence on the impact on bone fracture [3; 112]. Although the efficacy from randomized trials appears modest, if testosterone seems warranted, treatment should begin when severe osteoporosis is present or when osteopenia is coupled with severe testosterone deficiency and/or hypogonadism [62]. A 2016 study elucidated the role of concomitant estrogen deficiency in bone loss in men with hypogonadism [143]. Circulating testosterone levels greater than 200 ng/dL and estradiol levels greater than 10 pg/mL are typically sufficient to prevent decreases in bone mineral density and increases in bone resorption in these patients.

Growth Stimulation in Male Puberty

Increases in skeletal mass and bone mineral density during puberty are primarily determined by an increase in bone size and not true volumetric bone mineral density. Androgens stimulate skeletal growth by activation of the AR. Adolescent hypogonadism impairs bone size and maintenance of volumetric bone mineral density, and ART in boys with hypogonadism using a biphasic pattern (i.e., starting at low doses and ending at high-normal doses) is safe and effective in facilitating the achievement of normal height and optimal bone development [26; 115].

Prophylaxis for Hereditary Angioedema

The anabolic steroids oxymetholone, stanozolol, and danazol, which induce the production of a C1 esterase inhibitor, have been used in the prevention and control of attacks of hereditary angioedema [53; 150]. Patients for whom anabolic steroid treatment of angioedema is contraindicated include pregnant women and prepubertal patients due to the risk of virilization [53].

Hepatic Disease

Patients with alcoholic hepatitis with malnutrition were randomized to either oxandrolone plus a high-calorie supplement or placebo and a low-calorie supplement. Significant improvement in liver function and overall survival was observed among the active drug group, and another study found decreased six-month mortality among alcoholic hepatitis patients receiving oxandrolone [66; 67]. The use of prednisone in patients with alcoholic hepatitis has been shown to reduce associated mortality [151]. Further studies are needed to fully characterize the effects of anabolic steroids, especially 17α-alkylated agents such as oxandrolone, in this patient population [7].

Female-to-Male Transgenderism

Transgenderism is an umbrella term for those whose gender identity or expression is different from that typically associated with their assigned sex at birth. This conviction is often coupled with a desire to live in the gender experienced as self, which necessitates hormonal, anatomic, legal, and psychosocial adaptations. Psychologic evaluation of these persons may

conclude that sex reassignment (or gender confirmation) surgery will provide relief to the individual. Such persons suffer from gender dysphoria, defined as the extreme and long-standing feeling of being "trapped in the wrong body" [35].

Testosterone is the key hormone in the process of transitioning from female to male for the development of secondary sexual characteristics, and the most commonly used formulations are testosterone esters 100–200 mg IM every two weeks (or 50–100 mg IM weekly) [69]. Following an ovariectomy, testosterone treatment in female-to-male transgender subjects is continued at a dosage level comparable to that given to hypogonadal men [35].

Hypoplastic Anemia

Anabolic steroids stimulate erythrocyte synthesis, which can be helpful in the treatment of hypoplastic anemia. However, use of anabolic steroids in developed countries is likely to be limited by the availability of recombinant human erythropoietin and its analogues [53].

Multiple Sclerosis

Researchers have known for decades that females are more susceptible to inflammatory autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, and psoriasis, and that these female patients experience clinical improvement during pregnancy and a temporary "rebound" exacerbation postpartum [34; 152]. These observations suggest an effect of sex hormones on disease, possibly indicating a role for the use of testosterone and the pregnancy hormone estriol in the treatment of multiple sclerosis [34; 152]. Preliminary results have shown a favorable safety profile of testosterone and estriol when used in men and women, respectively [34].

Sexual Dysfunction

Approximately 80% of erectile dysfunction is organic in origin [131]. Research indicates that testosterone therapy improves both erectile function and response to phosphodiesterase type 5 (PDE-5) inhibitors in patients with erectile dysfunction and hypogonadism, and interventional studies have shown that testosterone replacement therapy improves erectile function in men with hypogonadism who have not responded to PDE-5 inhibitor monotherapy. The full therapeutic potential of PDE-5 inhibitors only manifests in eugonadal men [126].

A meta-analysis of the effects of testosterone in men with sexual dysfunction and varying testosterone levels found that testosterone had a modest effect on erectile dysfunction and a moderate-to-large favorable effect on libido. The authors state that the desired benefits of testosterone are often misdirected in that although older men often seek treatment for what is primarily an age-related decline in sexual (mainly erectile) function, erectile dysfunction is mostly neurovascular rather than hormonal in origin and testosterone is unlikely to be helpful in these cases [40]. Also, because hypogonadism is a condition that is common to visceral obesity, metabolic syndrome, diabetes, cardiovascular disease, and erectile dysfunction, these factors should be considered in middle-aged and elderly patients complaining of erectile dysfunction [102].

Short-term studies of postmenopausal women experiencing sexual dysfunction despite sufficient hormone replacement have shown a modest but significant positive effect of transdermal testosterone therapy on libido. However, until longer-term safety studies are available, generalized or long-term use of testosterone therapy in women with sexual dysfunction is contradicted [6; 137; 153].

Depression

A trial evaluating the antidepressant efficacy of 1% testosterone gel 10 g per day among men with refractory depression and low-to-borderline testosterone levels found that testosterone significantly improved both vegetative and affective symptoms of depression, suggesting the possible utility of testosterone as a treatment option for the large underdiagnosed population of depressed men with low testosterone levels [89]. Controlled trials of testosterone in depressed patients with HIV infection failed to replicate the positive effects seen in earlier uncontrolled studies [5]. A meta-analysis of trials regarding the use of testosterone to treat depression in men found that treatment was associated with small improvements

in depressive symptoms, but these improvements were not proven to be clinically meaningful. The use of testosterone to treat depression is therefore not recommended [154].

Burn Injuries

A 2019 systematic review and meta-analysis found oxandrolone to be beneficial in the treatment of burn injuries. Specifically, studies showed that the use of oxandrolone helped to decrease the length of hospital stay and improving growth and wound healing [155].

USE IN NONHYPOGONADAL AGING MEN

The clinical consequences of androgen deficiency in older men have been grouped into three categories: somatic (body composition, glucidic and lipid metabolism, erythropoiesis), sexual, and psychologic (cognition and affectivity) [114]. However, the ultimate diagnosis of androgen deficiency in the elderly should be determined by the convergence of clinical symptoms and subnormal testosterone levels [52].

A meta-analysis of anabolic steroid use in men older than 45 years of age with low to low-normal testosterone levels found that anabolic steroids significantly increased lean body mass and grip strength and significantly reduced fat mass compared with placebo. Overall body weight did not change significantly, and changes in lower-extremity muscle strength and physical function were inconsistent [11].

Although demonstrations of increased muscle strength have been inconsistent, testosterone may be a valuable option in special populations at risk for developing a catabolic state, such as patients recovering from extended bed rest or joint replacement, and in older men with conditions associated with heightened risk of muscle wasting syndromes, such as COPD, coronary artery disease, corticosteroid therapy, and acute ischemic stroke [13]. Unfortunately, AAS abuse by male athletes has had the effect of deterring rigorous investigation into treatment with testosterone of clinical states that may be caused by or related to hypogonadism [5].

The importance of maintaining or restoring lower-body muscle strength in the elderly and the recognition of the risk of dose-dependent side effects with anabolic steroids has led to a novel protocol aimed at stimulating ARs by alternating testosterone with a SARM, or administering a higher dose of testosterone with the addition of a 5-α reductase inhibitor to prevent prostate symptoms [13]. The potential risk to the prostate and cardiovascular system of long-term testosterone use in non-hypogonadism elderly men must be evaluated in large prospective clinical trials [18].

MISUSE AND ABUSE OF ANABOLIC STEROIDS

Misuse and abuse of anabolic/adrenergic steroids (AAS) involves the use of supraphysiologic doses in eugonadal men with the goal of increasing lean body mass, muscle size, strength, power, motivation, and/or aggression [21]. This illicit use of AAS is largely dependent on obtaining androgens without a prescription for use in the absence of a recognized medical indication or supervision. The context of AAS abuse includes competitive power sports (e.g., baseball, weightlifting, football, swimming, rowing, boxing), recreational bodybuilding, cosmetic (body and appearance enhancement), and occupational (e.g., security, police, military) [24].

DEMOGRAPHICS AND EPIDEMIOLOGY

Although the use of performance-enhancing drugs such as AAS by professional athletes has been the focal point of media attention, athletes across a wide range of ability, age groups, and sports report using AAS. The majority of data available regarding the prevalence of illicit AAS use comes from surveys of high school students and young men. A 2013 poll found that 8% of men 18 to 25 years of age admitted to taking appearance- and performance-enhancing drugs (defined as anabolic steroids and/or human growth hormone); 28% reported knowing someone who had taken these drugs [128]. In a 2021 survey, 1.5% of male 12th graders reported using steroids at least once, with 0.8% reporting use in the past

month [129]. AAS use is greater among adolescent boys (1.5% of male 12th graders in 2021) than girls (0.2% of female 12th graders) [129]. In addition to athletes, AAS are now used by young men interested in enhancing their appearance by "bulking up" (i.e., increasing their lean muscle mass without increasing fat) [25; 156]. One survey of adult AAS users found that almost 80% were nonathletes attempting to achieve cosmetic benefits [78; 156]. According to surveys funded by the National Institute on Drug Abuse (NIDA), use of steroids has decreased by more than half among high schoolers since the early 2000s [129; 156].

The results of an Internet-based survey of 1,955 AAS users revealed several demographic trends [23]. The mean age was 31.1 years, 88.5% were white, roughly half had never been married, and most (64.21%) did not have children. Compared with the U.S. population, more respondents had completed college and graduate school and fewer had failed to graduate high school. The majority were employed as professionals, with a median household income between $60,000 and $79,999 per year. The average age of first use of AAS was 25.81 years; 94% commenced AAS use at 18 years of age or older. The average duration of AAS use was 5.53 years, and 61% began AAS within the first five years of weight training.

However, the results of a review of the psychiatric literature by Hall and Hall markedly differ from the data reported by this study [39]. The typical AAS abuser in Hall and Hall's study was found to be a male polysubstance abuser with poor self-esteem, poor school performance, and a cluster B personality disorders or traits (e.g., antisocial, borderline, histrionic, and narcissistic personality) who may or may not be involved in competitive athletics. Men were two to three times more likely to abuse AAS than women. Factors associated with AAS abuse included higher socioeconomic status, family history of drug abuse, higher rates of self-reported violence and aggression, lower self-esteem, and poor body image before AAS use. The stable-to-increasing prevalence rates of AAS abuse, despite efforts to curtail use through prevention programs, law enforcement attention, increased legal penalties, steroid testing programs, and stricter sanctions by professional and amateur sports organizations, likely reflects the virtually invisible nature of the largest segment of the AAS-using population: adult non-athletes [23].

A 2011 survey of 506 AAS users found that the average user was 29.3 years of age and that most (70%) were in-fact "recreational exercisers" who used an average of 11 performance-enhancing substances in their routine [144]. The survey also revealed a higher prevalence of substance dependence disorders among AAS users (23.4%) than non-AAS users (11.2%). An estimated 30% of illicit AAS users go on to develop a dependence syndrome, characterized by chronic AAS use despite adverse effects on physical, psychosocial, or occupational functioning. The average age of onset for AAS dependence appears to be the late 20s, considerably older than the apparent typical age of onset of 19 years for initial AAS use [48].

A 2018 analysis of the motivations to use AAS found four different "clusters" of users [159]:

- "You only live once" type: Younger and motivated by fat loss
- "Well-being" type: Motivated by becoming fit
- "Athlete" type: Motivated by gaining muscle and strength
- "Expert" type: Focused on specific fitness goals

Considering the motivations behind AAS initiation and continued use can help healthcare providers target associated risk behaviors and provide better risk aversion counseling [159].

RISK FACTORS OF MISUSE/ABUSE

Risk factors for AAS use are incompletely understood but include poor paternal relationships, history of conduct disorder, history of substance abuse, history of sexual abuse, and poor body image. Race, education level, and income do not appear to be significant factors. Among adolescents, boys are more likely to abuse steroids than girls, and participation in organized sports and knowing someone who uses anabolic steroids are predictors of future use [110; 144].

Muscle Dysmorphia

Abuse and dependence of AAS may be precipitated by muscle dysmorphia [48]. Muscle dysmorphia, also referred to as "reverse anorexia," is a mental condition characterized by pathologic preoccupation with muscularity and represents a variant of body dysmorphic disorder (BDD). Men with muscle dysmorphia believe that they look "puny" or "small," when they actually look normal or even muscle-bound. As a result, they may neglect important social or occupational activities because of shame over their perceived appearance flaws or their need to attend to a meticulous diet and time-consuming workout schedule. Some damage their health by excessively working out, and others report use of AAS in an attempt to get bigger [91]. Many of these men do not experience a resolution of their insecurity and preoccupation over their size through the use of AAS and the resultant increase in muscle mass [46].

Bodybuilders with muscle dysmorphia appear to be distinct from those without muscle dysmorphia, most of whom do not exhibit psychopathology [77]. One study found that compared with occasional and non-AAS using bodybuilders, heavy long-term AAS users were significantly more likely to report preoccupation with being too small and needing to become bigger, as well as a stronger endorsement of conventional and rigid masculine gender roles [46].

Muscle dysmorphia may be both a cause and a consequence of AAS use. Men with body-image pathology may be motivated to use AAS initially and then paradoxically become increasingly concerned about their muscularity even as they are growing bigger on AAS. Muscularity becomes central to their self-esteem, and the thought of loss of muscularity triggers intense anxiety. This phenomenon frequently contributes to the AAS dependency syndrome [14; 16; 47].

Psychosocial and Cultural Factors

Cultural factors may increase the likelihood of AAS abuse. These include increased competitiveness, body image concerns, and advances in biochemical technology. Younger people can be affected by these influences because of the highly competitive nature of high school and collegiate sports, especially considering that the performance enhancement provided by AAS may be the deciding factor in securing an athletic scholarship or acceptance into professional sports [110].

Evidence exists that body image disorders and associated non-medical AAS use are much more prevalent in Western societies than among other cultures. Several factors are believed to account for these cultural differences, including the emphasis on muscularity and fitness as a measure of masculinity in Western cultures, increasing exposure of men in Western cultures to muscular male bodies in media images, and greater decline in traditional male roles in the West resulting in greater emphasis on the body as a measure of masculinity [125].

Other Personality Factors

As noted, studies comparing personality disorders in AAS-using versus non-AAS using bodybuilders have found a higher prevalence of cluster B personality disorders of the histrionic and antisocial type among AAS users, higher scores among AAS users on measures of pathologic narcissistic traits (e.g., exhibitionism, entitlement, exploitativeness) and lower ratings for empathy. A significantly higher proportion of self-reported memories of childhood sexual or physical abuse have been found among AAS abusers [39; 144].

Compared with occasional AAS users and non-AAS users, men with AAS dependence have been found to be older and more muscular, more likely to have had a single parent by 13 years of age, more likely to report substance abuse in a first-degree relative, less educated, and more likely to have a history of conduct disorder. A history of non-alcohol substance dependence, particularly with opioid abuse and dependence, largely contributes to differences in lifetime substance abuse and dependence in AAS dependent individuals [46; 51].

Sensitivity to AAS Withdrawal-Induced Dysphoria

Regular AAS use produces a withdrawal syndrome characterized by both affective and hypogonadal symptoms. AAS abusers with more severe withdrawal symptoms following initial cycles of AAS use may become increasingly prone to resume AAS to prevent these symptoms. This heightened sensitivity may be mediated by a particular vulnerability residing in the hypothalamic-pituitary-thyroid (HPT) axis, opioidergic pathways, or other neurotransmitter mechanisms [48].

History of Victimization

Some persons who abuse AAS to increase their muscle mass have experienced physical or sexual abuse. One study of AAS-abusing male weightlifters found that 25% reported memories of childhood physical or sexual abuse [75]. Female weightlifters who had been raped were twice as likely to use AAS as those who have not been raped. Almost all of these women who reported being raped also reported markedly increasing their bodybuilding activities after the attack, believing that increased size and strength would discourage further attacks [75; 158]. Thus, compulsive weight lifting and AAS abuse may represent a form of response to the trauma of sexual assault [36].

MOTIVATION FOR NONMEDICAL USE

The Internet-based study previously discussed found the primary motivation for AAS use was the desire for increased muscle mass, strength, and physical attractiveness [23]. Other relevant but less frequently-endorsed reasons included a desire for increased confidence, decreased fat, improved mood, and attraction of sexual partners. Sporadically-reported factors in AAS use were injury prevention, recreational weightlifting, increased endurance, amateur bodybuilding, amateur or recreational sports, and power lifting. Loss of muscle and strength were important concerns should AAS become unavailable to the user, but low self-esteem was not found to be a frequent motivator of use. The finding that AAS use was significantly associated with the goal of achieving the desired image of the ideal body structure as large, muscular, and powerful is consistent with the Western ideal of masculinity. Unfortunately, current satisfaction with one's physique was not measured by the study. Almost all respondents (99%) denied a motivation to use AAS for the immediate psychogenic effects such as intoxication, arousal, or euphoria, suggesting that AAS is not experienced as euphorigenic [23]. Although not yet empirically validated, AAS users have repeatedly stated that AAS use facilitates the ability to train and compete more aggressively and intensely and to recover more rapidly from training competition [33].

SOURCES OF STEROIDS FOR NONMEDICAL USE

Anabolic steroids are correctly regarded by regulatory bodies in professional sports as performance enhancers and as harmful to the health. The International Olympic Committee Medical Commission identified anabolic steroids as a banned class of drugs in 1974 [53]. The Drug Enforcement Administration categorizes AAS as a schedule III controlled substance, defined as substances with accepted medical uses that may cause moderate or low physical dependence or high psychologic dependence. The Anabolic Steroid Control Act of 2004 lists 59 different AAS formulations as controlled substances [75]. The Designer Anabolic Steroid Control Act of 2014 expanded this list by adding 25 new compounds [160; 161].

Although AAS are controlled substances in Australia, Argentina, Brazil, Canada, the United Kingdom, and the United States, they are readily available in most other countries, where they can be sold legally without a prescription [27; 42]. Foreign distributors do not violate the laws of their own country when they sell AAS overseas via the Internet or by e-mail order. Much of the AAS used in the United States originates from Mexico and other countries, such as Russia, Romania, and Greece [27; 53]. Illicit AAS is also synthesized in clandestine laboratories or illegally diverted from pharmacies [75]. A large study of AAS users found that 52.7% of respondents

purchased their AAS via the Internet; other sources included local dealers (16.7%), friends or training partners (15%), a physician's prescription (6.6%), and trafficking AAS from foreign countries (5.8%) [23]. Some participants obtained AAS through multiple methods.

PATTERNS OF ILLICIT USE/ABUSE

Steroid regimens used by athletes and bodybuilders differ markedly from those used clinically to provide replacement therapy [56]. Several aspects unique to the illicit use and abuse patterns of AAS have been identified.

"Cycling"

"Cycling" entails taking multiple doses of steroids over a specific period of time, stopping for a period, and starting again [75; 162]. The periods of AAS use interspersed with periods of recovery/abstinence are intended to allow the endocrine system to return to homeostasis [23]. Before a cycle is initiated, the length, dosages, and compounds to be used are anticipated and obtained. The anticipated plan is usually adhered to, although cycles can be altered to change the dosage or avoid side effects [23].

"Stacking"

"Stacking" involves combining two or more types of steroids based on the theory that different steroids interact to produce a greater effect on muscle size than the effect of each drug alone. Stacks usually combine compounds with contrasting properties, such as long- and short-acting agents, aromatizable and reducible agents, or oral and injectable drugs. They also usually include ancillary compounds intended to intensify the AAS effect or minimize the side effects of AAS and may even include compounds designed for veterinary use [75; 123]. Stacking usually involves using oral and IM preparations at progressively higher doses until 40 to 100 times the typical physiologic levels is achieved; the use of five different drugs is typical [39]. The goal of stacking is to "activate more receptor sites" than is possible with single agents [123]. Because of the complex nature of stacking regimens, AAS abusers may have a "coach" to help them devise the schedule and the regimen [39].

"Pyramiding"

"Pyramiding" is a practice whereby users slowly escalate the intensity of the steroid regimen to reach a peak amount at mid-cycle, and then gradually taper the dose toward the end of the cycle [75; 162]. Users often pyramid their doses in cycles of 6 to 12 weeks, in some cases followed by a second cycle of training without drugs [75]. Pyramiding is performed with the goals of avoiding plateauing (i.e., developing tolerance to a specific steroid), allowing the body to adjust to high-dose AAS, and minimizing withdrawal symptoms when steroid use is suspended [75; 123).

"Plateauing"

"Plateauing" is a technique by which steroids are staggered, overlapped, or substituted with another type of steroid to avoid developing tolerance [156; 162].

With the planned cycling, healthy diet, ancillary drugs, blood work, and mitigation of harm via route of administration, AAS abuse involves more planning and organization than other illicit drug use. AAS users are likely to have substantial amounts of AAS on hand for long-term personal use in order to achieve the sustained supraphysiologic levels of steroid hormones. In one study, many respondents used up to 12 methandrostenolone tablets (5 mg each) per day, with some using more than 20 tablets, necessitating an initial possession of 1,000 tablets or more for personal use [23].

Nandrolone, oxandrolone, testosterone, stanozolol, methandienone, and methenolol are the most frequently abused AAS agents. IM formulations of these drugs are preferred over oral formulations, and combinations of androgens are used more frequently than single agents [21]. In one survey, the average total AAS dose of testosterone was 500–1,000 mg per week. The highest dosage of testosterone used for four or more weeks was 797.5 mg per week, and 95% of users injected their steroids [23].

COMMONLY USED ANCILLARY DRUGS AMONG AAS-USING BODYBUILDERS			
Ancillary Drug	**Prevalence**	**Reason for Use**	**Average Rating[a]**
Anastrozole	41.1%	Prevent estrogen side effects by halting the conversion of excess androgens into estrogen	2.6
Antianxiety medications	11.2%	Anxiety reduction	2.3
Antidepressants	9.3%	Mood elevation	2.1
Blood pressure medications	9.7%	Lower blood pressure	2.4
Clomiphene citrate	61.9%	Prevent estrogen-related side effects and stimulate follicle-stimulating hormone (FSH) to elevate reduced testosterone levels during a cycle	2.4
Exemestane	8.1%	Prevent estrogen side effects by halting the conversion of excess androgens into estrogen	2.7
Finasteride	10.8%	5α-reductase inhibitor that blocks the conversion of testosterone into dihydrotestosterone; used to prevent balding	2.1
Human chorionic gonadotropin (hCG)	43.0%	Reverse or prevent testicular atrophy by acting like luteinizing hormone and stimulating Leydig cells	2.6
Isotretinoin	7.7%	Prevent or treat acne	2.7
Letrozole	14.4%	Prevent estrogen side effects by halting the conversion of excess androgens into estrogen, and to stimulate FSH to elevate reduced testosterone levels during a cycle	2.7
Sildenafil and/or tadalafil	27.5%	Treatment of erectile dysfunction	2.6
Sleeping medications	22.7%	Sleep aid	2.6
Tamoxifen	65.3%	Estrogen antagonist used to prevent estrogen-related side effects (e.g., gynecomastia) and stimulate FSH to elevate reduced testosterone levels during a cycle	2.6
[a]User rating of ancillary drug effectiveness: 1 = not effective; 2 = moderately effective; 3 = highly effective.			
Source: [23]			*Table 4*

COMMONLY USED ANCILLARY DRUGS

AAS users frequently ingest a wide range of additional substances to gain muscle mass, lose fat, or counteract the side effects of AAS (***Table 4***). These include other hormones (e.g., human growth hormone, somatomedin-C, thyroid hormones, insulin, and human chorionic gonadotropin), beta agonists (e.g., clenbuterol), stimulants (e.g., amphetamine, ephedrine, pseudoephedrine, caffeine), drugs for weight or fluid loss (e.g., diuretics, laxatives), drugs believed to stimulate testosterone or growth hormone secretion (e.g., clomiphene, cyclofenil, gamma hydroxybutyrate, levodopa, clonidine), and numerous other agents, such as erythropoietin, tamoxifen, danazol, and yohimbine. Even industrial chemicals, such as 2,4-dinitrophenol, may be consumed. Although many of these substances are approved for use in patients with legitimate medical conditions, little is known of their safety or efficacy when used illicitly in combination with AAS [2; 30; 44; 45; 47].

Ancillary substances marketed as nutritional supplements are protected from the U.S. Food and Drug Administration regulation by the 1994 U.S. Dietary Supplement Health and Education Act. Manufacturers of these substances are not required to demonstrate proof of efficacy or safety, and there is no regulatory oversight for evaluating their purity. As a result, contamination and mislabeling have been frequently detected [30].

ATTITUDES TOWARD MEDICAL PROFESSIONALS

Research comparing trust in physician knowledge and advice between non-AAS-using versus AAS-using bodybuilders found that both groups gave physicians high ratings on knowledge about general health, cigarette smoking, alcohol, and conventional illicit drugs and low ratings on knowledge about AAS [84]. When rating the accuracy of different sources of information regarding AAS, users of AAS rated physicians as no more reliable than their friends, Internet sites, or the person(s) from whom they purchase steroids. Forty percent of AAS users trusted information from their drug dealers at least as much as information from any physician that they had interacted with, and 56% had never revealed their AAS use to a physician. The researchers concluded that AAS users show little trust in physicians' knowledge about AAS, and their lack of AAS use disclosure compromises physicians' ability to educate or treat the users.

Another study found that 66% of male bodybuilding participants were willing to seek medical supervision, and that 61% obtained a blood work-up at least annually to assess the effects of AAS use on their health [23]. However, 58% lacked sufficient trust in their physician to report their AAS use, 92% felt the medical community's knowledge of AAS use was lacking, and 99% believed the public had an ill-informed view of AAS side effects [23].

ADVERSE EFFECTS AND COMPLICATIONS

Testosterone is a potent ligand of the human AR, and nearly every cell in the human body possesses ARs [110]. Thus, testosterone can modulate cellular functions such as transcription, translation, and enzymatic function in diverse skeletal and myocardial tissue. However, these functions can affect numerous other tissues, leading to the potential for serious side effects [106]. Side effects from supraphysiologic doses of AAS range in severity from mild (e.g., acne, fluid retention) to distressing (e.g., gynecomastia, sleep apnea) or potentially life-threatening (e.g., hepatic failure, myocardial infarction, arrhythmias) and can occur with all anabolic steroids [39].

Several factors make the physical and psychiatric complications of AAS use difficult to study under controlled research conditions, including the illicit nature of their use, the possibly confounding effects of ancillary drugs and premorbid personality trails, and ethical concerns in providing AAS doses consistent with illicit promotion to human subjects [110; 123]. Thus, evidence of adverse effects of supraphysiologic doses of AAS come from case reports and uncontrolled series. Also, little is known of the lifetime prevalence of significant medical and psychiatric consequences of AAS use, primarily because these effects may not become clinically apparent for years after initiation of use [47].

PSYCHOLOGICAL/ PSYCHIATRIC EFFECTS

AAS misuse has been linked to severe mental disorders, including mania, depression, suicidality, and psychoses [29]. AAS impact the central nervous system via multiple mechanisms and pathways, including the release of endogenous opiate peptides and the conversion of AAS into estrogen derivatives that activate secondary messenger systems. Electroencephalogram changes induced by AAS are similar to those observed with amphetamines and tricyclic antidepressants [110].

Low or near-physiologic doses of AAS have minimal effects on mood and do not increase aggressive behavior in men [110]. The initial effects of supraphysiologic doses of AAS can include changes in mood and euphoria experienced as heightened confidence, energy, self-esteem, motivation, and enthusiasm. There is a corresponding reduction in fatigue and sleeplessness and an increased ability to train through pain [25]. Libido is usually increased, sometimes markedly, and irritability, anger, agitation, and a "strange edgy feeling" are often reported. Higher dose or prolonged use can lead to a loss of inhibition, poor judgment, mood swings, and grandiose beliefs, with users becoming

suspicious, quarrelsome, impulsive, and more aggressive. Severe effects manifest when these aggressive feelings increase to the extent that violent, hostile, antisocial behavior develops, aptly referred to as "roid rage" [25].

Studies using AAS abusers as their own controls to eliminate the confounding effect of personality disorders have shown differences in hostility, aggression, and severity of manic-like symptoms during periods of use versus nonuse [15; 60; 80; 86; 113]. Studies that have quantified AAS use have found that psychiatric symptoms became more common and severe with increasing dose levels; 23% of AAS abusers with a medium level of steroid use (300–1,000 mg per week of any AAS) or a high level of steroid use (more than 1,000 mg per week of any AAS) met the criteria for a major mood syndrome (mania, hypomania, and major depression), and 3.4% to 12% developed psychotic symptoms [39; 86; 87].

Aggression and Violence

Excessive and inappropriate aggression is the behavioral response most often associated with AAS abuse [98]. It appears that chronic AAS use modifies homeostatic processes, affects neurotransmitters, and can cause changes in brain structures, leading to increased anxiety and tendency for aggressive behavior or poor impulse control [163]. The "roid rage" from high AAS doses may be the manifestation of an AAS-induced hypomanic syndrome that begins with feelings of invincibility and worsens as dosages increase [29]. These rages can result in property damage, self-injury (including reckless driving or crashing cars), assaults, marriage breakups, domestic violence, child abuse, suicide, and attempted murder or murder [17; 19; 20; 61; 85; 100; 127]. The impulsive perpetration of homicide and attempted homicide has been documented as occurring in male AAS users with benign premorbid psychiatric histories, no evidence of antisocial personality disorder, and no history of violence, with steroid use playing a necessary, if not primary, role in the violent acts [85]. One group of men who may take high-dose AAS are those working as security officers or nightclub bouncers; under the influence of the drug, they may be provoked into a rage and engage in violent behavior resulting in injury or death [25; 31].

Intimate relationships may represent the most likely setting where AAS-induced aggression and violence manifest. Choi and Pope found that AAS abusers reported significantly more verbal and physical aggression and violence toward their partners when using AAS than when not using AAS. When not on an AAS cycle, the AAS users off-drug did not significantly differ from nonusers [19]. These findings support anecdotal evidence that partners of AAS users may be at risk of serious injury from users while they are on-drug.

The prevalence of AAS-induced rages is unknown. Although prolonged high-dose use of AAS is the most common antecedent, not all people taking high doses develop steroid rages, and reports exist of rages occurring with low-dose AAS use [25]. Although serum testosterone level is correlated with aggressiveness, the relationship between supraphysiologic doses of AAS and aggressive and/or violent behavior is complex. Pope, Kouri, and Hudson observed that most normal males given 600 mg testosterone did not experience psychiatric symptoms [88]. The overall effect was of increased manic symptoms, which was also variable, with few participants reporting increased aggression levels.

It is also likely that some violent rages occurring in AAS abusers might be better understood as part of a paranoid psychotic state. Psychotic symptoms associated with AAS generally unfold in persons consuming more than 1,000 mg testosterone per week [86]. Classic presentations include grandiose and paranoid delusional states occurring in the context of an overtly psychotic or manic episode. The symptoms usually resolve within a few weeks after AAS discontinuation but may persist for as long as one month, even when antipsychotic medication is administered [39].

Depression and Suicide

Many studies have associated depressive symptoms and reports of suicide with AAS abuse, especially during withdrawal from AAS at the end of a "cycle" that is likely attributable to HPT suppression [25].

AAS WITHDRAWAL SYNDROME CHANGES IN CENTRAL AMINERGIC SYSTEMS	
Symptom/Sign	**Neural Mechanism**
Myalgia, arthralgia, headache	Decrease in central dopaminergic transmission
Fatigue, insomnia	Increase in central noradrenergic transmission
Emotional lability, irritability, depression	Decrease in gamma-aminobutyric acid (GABA)-stimulated chloride influx
Autonomic hyperactivity, anorexia	Increased V1a vasopressin receptor activity Change in proopiomelanocortin (POMC)-related peptides Metabolism of AAS into estrogen, dihydrotestosterone, and 3α-androstanediol
Source: [43]	*Table 5*

Similar to highly aggressive behavior, depressive symptoms appear to be idiosyncratic, with occasional individuals showing marked symptoms and others showing none [47]. The risk of depression and suicide remain heightened even in former AAS users, suggesting that psychiatric disorder may either predispose a person to or result from AAS use [25]. Suicide has been found to be significantly more common among former AAS users than among other types of substance users, and a study of former elite Swedish male athletes found that former AAS users were significantly more likely to report having sought treatment for psychiatric symptoms compared to nonusers [47; 81].

Withdrawal

Recovery from long-term hypothalamic-pituitary-adrenal-axis suppression with continued AAS use may take weeks to months depending on the dose and duration of AAS use and in some ways resembles the glucocorticoid withdrawal syndrome [43]. The user experiences symptoms of androgen deficiency during the period immediately after AAS discontinuation, which can include loss of sexual desire and function, lack of energy, depressed mood, and hot flashes (***Table 5***). Major mood disorders such as mania, hypomania, and depression are experienced by as many as 23% of users, many of whom resume AAS use due to an inability to tolerate the psychologic symptoms of withdrawal [21; 43]. Other symptoms are related to the loss of the AAS-induced positive psychologic effect and include listlessness, apathy, loss of appetite, decreased libido, low self-esteem, anxiety, difficulty concentrating, and mood swings [25]. Withdrawal can also be associated with violent behavior and rage, and although severe steroid withdrawal is likely to be less of a problem in athletes due to more circumscribed phases and gradual dose reduction, body builders or weight trainers are likely to have greater problems during the course of withdrawal as a result of a loss of body image and enhanced musculature [25].

Effects in Women

The effects of AAS use are infrequently documented in women relative to male AAS abusers. However, female AAS users have been found to experience hypomanic symptoms during use, depression upon discontinuation, and a body image distortion similar to the "reverse anorexia" seen in some male AAS abusers [110].

MEDICAL COMPLICATIONS

Cardiovascular

Supraphysiologic doses of AAS can produce a range of adverse cardiovascular effects, including hypertension, cardiomyopathy, left ventricular hypertrophy, dyslipidemia, myocardial ischemia, adverse effects on coagulation and platelet aggregation, and arrhythmias. Some of these effects, such as hypertension, dyslipidemia, and coagulation abnormalities, remit after AAS use is discontinued, but effects such as atherosclerosis and cardiomyopathy are likely irreversible. These effects have been blamed for numerous premature deaths among athletes between 20 and 40 years of age known or believed to have used AAS, either from cardiac disease or cerebrovascular accidents. Older former AAS users now entering the age bracket of increased cardiovascular risk may display an increased rate of serious cardiovascular events [30; 47].

Potential mechanisms of cardiovascular toxicity from AAS use include atherogenic, thrombotic, vasospastic, and direct myocardial injury [30; 106]. Steroids contribute to the development of cardiovascular morbidity by causing substantial alterations in lipid metabolism, partly by changing the levels of lipoproteins that carry cholesterol in the blood [30]. Oral AAS increase the level of low-density lipoprotein and decrease the level of high-density lipoprotein [75].

The risk of cardiotoxicity among men with hypogonadism receiving testosterone is clinically negligible, and although the risk of long-term testosterone in aging men is largely unknown, exogenous testosterone treatment appears largely beneficial, partially explained by the aromatization of testosterone to estradiol [38; 65].

Reproductive

The reduced fertility associated with AAS use stems from gonadotropin suppression, which results in azoospermia, abnormalities in sperm motility and morphology, and testicular atrophy. Some studies have documented the irreversibility of these effects after AAS use has ceased, while other studies have noted a return to normal testicular function after AAS discontinuation [7].

Neuroendocrine

Long-term AAS use suppresses the HPT axis, and AAS users often experience hypogonadism at the conclusion of an AAS cycle. Normal HPT function usually recovers spontaneously within several weeks to several months, but some AAS users experience hypogonadism for more than a year [47]. AAS abuse disrupts the normal production of endocrine hormones, resulting in both reversible and irreversible changes. Potentially reversible changes include reduced sperm production and testicular atrophy, while irreversible changes include male-pattern baldness and gynecomastia in men [75]. AAS use can cause acne, cysts, and oily hair and skin [75].

Infectious

AAS users who inject anabolic steroids may use nonsterile injection techniques or share contaminated needles with other abusers. Some steroid preparations are manufactured illicitly under nonsterile conditions, and these factors increase the risk for acquiring serious and potentially life-threatening viral infections such as HIV and hepatitis B and C [21]. AAS abusers can also develop endocarditis, a bacterial infection that causes a potentially fatal inflammation of the inner lining of the heart, or bacterial infections at the injection site, causing pain and abscess formation [75].

Hepatic

Use of the orally active 17α alkylated AAS is associated with serious hepatic complications that include peliosis hepatis, intrahepatic cholestasis, hepatocellular adenomas or carcinomas, hepatic angiosarcomas, and spontaneous hepatic rupture [47]. Although these risks are greater with longer-duration AAS use, the overall prevalence of adverse hepatic complications from illicit AAS use is likely low [47]. Nonetheless, reports of hepatocellular adenoma following AAS abuse among bodybuilders suggest this group is at heightened risk of developing sex hormone-related tumors and should be monitored annually with ultrasound examination [104].

Orthopedic

Orthopedic complications, mostly tendon ruptures, have been reported with AAS use [110]. Excessive muscle hypertrophy without concurrent adaptation in the associated tendons and connective tissues may place users at heightened risk for tendon injury and rupture from the abnormal stress placed on joints and tendons [21].

Physical Complications in Female Users

The use of AAS by women who desire their anabolic effects has been found to produce consistent masculinizing side effects that are predictable, severe, and often irreversible long after AAS cessation. Physiologic changes include deepening of the voice, clitoral hypertrophy, menstrual irregularities,

decreased body fat, and increased facial hair. Behavioral changes include increased libido, aggressiveness, and appetite. Women may also experience acne and changes in breast size and body hair distribution [56; 75; 138].

COMPLICATIONS FROM LEGITIMATE MEDICAL USE

Although a tradeoff between anabolic effect and side effects occurs in the therapeutic use of anabolic steroids in conditions not associated with male hypogonadism, adverse events from use in medical disorders for which such treatment is an established indication are uncommon [11]. Virilization may occur with androgen therapy in women and children, and in these patients androgen therapy requires expert management. Truncal acne, hair growth, weight gain, gynecomastia, and male-pattern hair loss may be observed [24; 133].

The risk of side effects is greater in elderly men with hypogonadism than in young men with hypogonadism. In the elderly, the risks associated with testosterone replacement include fluid retention, gynecomastia, aggravation of sleep apnea, polycythemia, and accelerated development of benign or malignant prostatic disease [13; 52].

Serious adverse risks in testosterone therapy in female-to-male transgender individuals may be underestimated, and there are few data on the long-term effects that medications, like testosterone, may have on transgender men [69; 164]. The potentially interactive combination of increased weight, decreased insulin sensitivity, poor lipid profile, and an increase in hematocrit have raised concerns over the risk for cardiac and thromboembolic events [69]. A 2017 literature review found that testosterone treatment in transgender men increased body mass index, hemoglobin and hematocrit levels, and LDL cholesterol, while decreasing HDL cholesterol. Additional long-term studies are required in order to assess possible cardiometabolic risks in this patient population [165].

COMPLICATIONS FROM USE IN ADOLESCENCE

AAS use in younger adolescents carries the risk of stunting final adult height due to premature closure of the epiphyseal plates [123; 133]. Neural development is characterized during adolescence by a burst of rapid change involving both progressive and regressive events. Perturbations in the timing of pubertal hormone influences on the developing adolescent brain may have long-lasting consequences for adult behavior. Although experimental studies of the effects of AAS on the developmental neurobiology of puberty have been very limited, teenage AAS use would appear to disrupt the normal steroid milieu of the developing human adolescent nervous system [98].

AAS DRUG DEPENDENCE

Although AAS use produces minimal acute reinforcing effects, susceptible individuals exhibit many of the behavior changes seen in persons with drug dependence to classically addictive drugs such as cocaine or heroin [34]. The fundamental difference between AAS and classical drug dependence is that AAS abusers do not use AAS for the immediate effect of acute intoxication but instead for the delayed effect of increased muscle mass. Thus, standard diagnostic criteria for substance dependence devised for acutely intoxicating drugs must be adapted for cumulatively acting drugs such as AAS [48]. AAS are the only controlled substances for which the most current diagnostic and statistical manual of the American Psychiatric Association (DSM-5) does not explicitly recognize a use disorder [139]. Although experts had proposed that AAS dependence merited inclusion into the 2013 revision of the DSM, it remains listed under the other substance use disorder category [139].

Persons with AAS dependence engage in the compulsive use of AAS despite medical, psychologic, social, or occupational consequences. AAS dependence is also characterized by large financial expenditure and time involvement in obtaining AAS and withdrawal symptoms upon cessation of AAS consisting of mood swings, fatigue, restlessness, loss of appetite, insomnia, reduced sex drive, and steroid cravings [75]. Pharmacologic, psychologic, and genetic factors may all play a role in AAS dependence, and although an estimated 14% to 57% of AAS users develop a dependency syndrome, different substance abuse patterns occur among subgroups of AAS users [37; 75].

POLYSUBSTANCE ABUSE AND DEPENDENCE

Some AAS users begin using other illicit drugs with abuse potential to self-medicate the negative effects of AAS such as irritability, insomnia, withdrawal symptoms, or conditioning pain. AAS users often learn about illicit drugs from other AAS users and purchase these drugs from the people selling them the illicit AAS. Psychologic barriers to injection have been breached by AAS use, so injecting other drugs may seem like a small step [75]. Progression from AAS abuse to opioid abuse may represent a particular problem, and several reports have identified the opioid mixed agonist/antagonist nalbuphine hydrochloride as an emerging drug of choice among AAS users [47; 121]. Nalbuphine users may progress to classic opioid agonists such as heroin or morphine, and one study of 227 men admitted to opioid addiction treatment found that 9% reported beginning their substance use with AAS [4]. Although AAS users are often polysubstance abusers of traditional recreational drugs, even those who avoid traditional recreational drugs remain immersed in the drug culture of procuring steroids from suppliers or dealers, obtaining large-gauge needles to administer the drugs, concealing their use of AAS, and developing the means to continue paying for AAS [39].

SCREENING AND ASSESSMENT OF SUSPECTED AAS ABUSE

Although early recognition and intervention in patients who use AAS is vitally important to prevent or minimize the adverse and potentially irreversible consequences from their use, identifying past or current AAS abusers and the medical and psychiatric effects of AAS use poses a challenge for clinicians for a variety of reasons [110].

Most individuals with a history of AAS use have not yet reached an age at which the long-term effects become apparent. Clinicians are often much less familiar with AAS use than other forms of substance abuse and may fail to seek a history of AAS exposure in an individual exhibiting medical or psychiatric problems. This is especially likely with patients who are older and not visibly athletic [48; 50]. Also, because AAS misuse rarely compromises performance or causes acute adverse effects in a manner similar to cocaine or alcohol, AAS abusers may be less likely to seek help or treatment as the result of impaired occupational or social function or subjective distress [48; 49]. The slow course of AAS effects and the lack of acute impairment contribute to dependence that is undetected by clinicians trained to recognize the abuse and dependency of acutely intoxicating drugs [48]. AAS users are reluctant to disclose their AAS use to physicians in part because to admit to AAS use is to admit that one's muscularity and physical prowess is the result of taking a drug. Finally, AAS users are much less likely than other substance abusers to view their behavior as pathologic [23; 90].

A 2017 study found that 35.23% of AAS users visited a physician about concerns about undesired health effects [166]. Users with sexual side effects were most likely to seek treatment. Users who did seek health services reported satisfaction with mental health assessments and diabetes screening, providing some evidence that they do have an interest in monitoring the impact of drug use on their health [166]. AAS users would benefit from health services that are nonjudgmental and that focuses on harm reduction and monitoring negative effects of use [166].

PHYSICAL EXAM

Healthcare providers should screen for AAS use in muscular patients. The first step in this process involves looking for visual or behavioral "red flags" of AAS use. These include [29; 90]:

- Very low body fat
- Extreme muscularity
- Disproportionately large upper torso
- Recent rapid muscle gain
- New-onset acne on face, shoulders, or back
- Pigmented striae on skin of pectoralis muscle
- Excessive facial or body hair
- Superficial confidence
- Feelings of invincibility or grandiosity
- Restlessness, anxiety, guardedness
- Frustration or excessive argumentativeness to the point of rage
- Obsession with weight training, conditioning, body image, and appearance
- Dissatisfaction with appearance despite the perception of others
- Extremely baggy or loose clothing

During a review of systems, additional signs of past or recent AAS abuse may emerge. These include [110]:

- Cardiovascular: Cardiac disease or thrombotic events in the absence of risk factors
- Dermatologic: Alopecia, acne, male pattern baldness in women, needle marks on buttocks and thighs
- Endocrine: Glucose intolerance, lipid abnormalities
- Hepatic: Abnormal liver function tests, hepatic masses, jaundice
- Infectious: Deep abscesses in the thighs or buttocks, HIV infection, hepatitis
- Musculoskeletal: Tendon injury
- Neurologic: Stroke in absence of risk factors, unexplained syncope
- Psychiatric: Mood changes (mania or depression), personality changes, psychosis
- Reproductive: Breast atrophy in women, clitoromegaly, gynecomastia in men, testicular volume decrease, virilization in women with voice changes

In general, the suspected AAS user should be approached as with any other suspected substance abuser—as a person at risk for potentially serious medical and psychiatric consequences. Maintain a high index of suspicion when evaluating muscular young male patients, even when use of AAS is denied [90].

PATIENT HISTORY

If any of the described "red flags" are present during the physical examination, providers should attempt to substantiate their initial suspicion by follow-up inquiry for further elucidation. Areas to further pursue with questions include [29]:

- Athletic or fitness activities: Young males who lift weights are at greatest risk of AAS use.
- Use of mail-order or over-the-counter supplements such as protein shakes, creatine, or DHEA: Use of supplements is commonly associated with AAS use.
- Relationship to anyone who has tried AAS
- History of trying or thinking about trying AAS

If the patient admits AAS use, the provider should pose the following questions [29]:

- What are the patient's perceptions of AAS benefits and risks?
- What are the dates of first and last use, types of AAS, sources (e.g., prescription diversion, veterinary, Internet), routes of administration, and use patterns?
- What measures are taken to avoid detection?

- Is there depression during withdrawal periods? How severe? How does the patient cope with withdrawal?
- Has the patient used other drugs to augment AAS effects, reduce side effects, or mask use?

Considerations for Non-English-Proficient Patients

For those who are not proficient in English, it is important that the patient history and information regarding the risks associated with the use of AAS be obtained in the patient's native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter. In any case in which information regarding diagnostic procedures, treatment options, and medication/treatment measures are being provided, the use of an interpreter should be considered. Print materials are also available in many languages, and these should be offered whenever necessary.

LABORATORY TESTS

Urinalysis should be performed at a laboratory with the capability of testing for AAS. Standard urine tests do not screen AAS, especially variants produced to elude drug tests. However, standard drug screens should be ordered as well, given the association of AAS with polysubstance use. Blood testosterone levels may be grossly depressed because AAS inhibits endogenous testosterone production [29].

INTERVENTION AND TREATMENT OF PATIENTS WITH AAS ABUSE/DEPENDENCE

Although few AAS abusers seek substance abuse treatment, this may soon change because of the advancing age of a large cohort of AAS abusers who began using AAS during the 1980s and the likely emergence of medical and psychiatric complications among these individuals [49]. An AAS user seeking help to stop the drug use would be analogous to a woman with anorexia nervosa voluntarily asking for help in gaining weight. There is an absence of rehabilitation centers, clinics, 12-step programs, or the like for AAS users because the demand simply does not exist. AAS users are more likely to come to clinician attention through legal channels, such as being required to undergo random urine testing as a condition of probation for an assault committed while experiencing an AAS-induced hypomanic episode. In this context, the monitoring clinician essentially acts as an arm of law enforcement, although it may still be possible to forge an alliance with the patient in this context [90].

The few studies of treatment for AAS abusers have been based largely on the experiences of a small number of physicians who have treated patients undergoing AAS withdrawal. Supportive and educational therapy is sufficient for some patients, while others may require medications or hospitalization if withdrawal symptoms and suicidal thoughts are severe or prolonged [75]. Some medications have been used to restore the hormonal system, while others target specific withdrawal symptoms such as depression, headaches, and muscle and joint pains [75]. Some patients require assistance beyond pharmacologic treatment of withdrawal symptoms and are treated with behavioral therapies [75].

In a Norwegian study, AAS users were provided with a one-hour education session addressing characteristics of AAS, physical and mental health problems related to its use, and motivations for treatment [157]. After the session, 77.2% of participants reported a desire for substance use disorder treatment to quit using the drug [157].

ESTABLISHING CREDIBILITY

Many non-medical AAS users consider themselves intelligent and informed users of AAS and possess an attitude of personal invulnerability [79]. Their information on AAS typically comes from popular literature written by steroid "gurus," word-of-mouth from other AAS users, and their own personal experiences from experimentation. They may perceive athletes who fail an AAS screening test as showing no obvious signs of ill health and conclude that information related to the health consequences of anabolic steroids is exaggerated [53]. Many athletes who use AAS possess a rudimentary understanding of pharmacology from personal experience and anecdotal information and will dismiss the warnings of the lack of efficacy and potential dangers of AAS misuse that are traditionally used with potential or current substance abusers to deter future use [57]. Attempts to devalue the achievements of sports figures accused of using AAS often backfire. Attempting to communicate a social and moral admonishment of "cheating" to curtail AAS use also serves to highlight what may be seen as otherwise unattainable achievements. AAS users likely view AAS as a form of enhancement with an acceptable cost/benefit ratio [23].

To achieve credibility with AAS-abusing patients, providers should instead acknowledge the muscle development ability of AAS while emphasizing the risks and must also convey an understanding of the body-building lifestyle, how AAS are used, and AAS slang [29]. Providing the patient with this balanced perspective is mirrored by prevention research showing that such an approach is more effective in convincing adolescents about steroids' negative effects because of the greater perceived credibility of the information and provider [29].

TREATMENT OF PSYCHIATRIC COMPLICATIONS FROM AAS ABUSE

The first step in treating the psychiatric consequences of AAS use is to convince the patient to stop using [109; 110]. Stopping AAS use reverses most, but not all, physical and psychologic consequences [29]. Depression is common during AAS withdrawal, typically easing without medication after several weeks. However, severe depression may lead to suicidal ideation, and patients with severe or persistent depression should be treated by a mental health professional. Severe or persistent depressive symptoms respond to selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, which is also effective for body dysmorphic disorder [29; 63; 85; 110].

Manic symptoms usually remit when AAS use is stopped. Short-term treatment of these effects can include neuroleptics or other antimanic drugs. If a patient has a history of mood disorders or if manic/psychotic symptoms persist for longer than two weeks, an underlying disorder should be investigated [29]. A short course of an antipsychotic medication can help treat mania and psychosis. In severe cases, hospitalization may be required [64].

In patients with panic or anxiety symptoms, short-term use of a benzodiazepine is usually sufficient to control symptoms. If long-term treatment is needed, SSRIs or tricyclic antidepressants should be used [64]. Psychotherapeutic interventions to encourage and maintain abstinence are essential in helping the patient maintain remission of psychiatric symptomatology [110].

TREATMENT OF AAS DEPENDENCY

Emerging evidence indicates that treatment of AAS dependence should address at least three mechanisms believed to underlie the development and maintenance of the disorder. First, psychologic and/or pharmacologic treatment should address body image disorders such as "muscle dysmorphia" in appropriate patients, as a desire for the anabolic effects of AAS may have contributed to the dependency. Treatment with SSRIs and cognitive-behavioral therapy have shown efficacy in the treatment

of body dysmorphic disorder and should be given to suitable AAS abusers as a component of treatment and prevention [46; 82]. Second, prolonged suppression of the male hypothalamic-pituitary-gonadal axis from AAS use may result in a prolonged dysphoric withdrawal syndrome, potentially leading to resumption of AAS use for symptom alleviation [49]. AAS-induced hypogonadism during withdrawal may require treatment with human chorionic gonadotropin or clomiphene to reactivate neuroendocrine function, and the psychologic distress associated with the AAS withdrawal syndrome can be ameliorated by administration of clonidine, tranquilizers, analgesics, or fluoxetine [43; 63; 111]. Third, AAS does possess some hedonic effects that probably promote dependence in susceptible persons via mechanisms shared with classically addictive drugs, especially opioids. By inference, pharmacologic and psychosocial treatments for opioid dependence may possibly benefit AAS-dependent persons [49].

Aftercare and Relapse Prevention

In order for patients to maintain abstinence from AAS and to prevent relapse, they may require support and encouragement in changing their lifestyle. This can entail switching gyms and changing workout friends, competitive events, and/or sports. Discussions of body image issues may be necessary. Some patients will benefit from referral to specialists who can help them develop healthy fitness regimens. Providers working with AAS-dependent patients are advised to form strong relationships with experts in sports medicine for advice and referral [29].

CONCLUSION

The medical uses of anabolic steroids include the treatment of male hypogonadism, chronic wasting conditions such as cancer and AIDS, certain anemias, the stimulation of bone growth and appetite, and the induction of male puberty. However, people also use AAS to enhance performance or appearance, and AAS can be used and abused for a variety of reasons, including athletic performance, appearance and physical attractiveness, lean body mass, and psychologic effects.

It is imperative for healthcare providers to recognize the risk factors and acute and chronic signs and symptoms of current and past AAS abuse in order to identify and treat these patients. The course provided information regarding the motivation to use AAS and warning signs and symptoms that may indicate abuse. Many of the gaps in identification, assessment, and appropriate treatment of patients with current and past AAS use and abuse can be addressed through provider education.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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