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“May the Best Athlete Win—The Use of Anabolic-Androgenic Steroids in Athletic Sports”

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Abstract

Anabolic-androgenic steroids (AAS) are derivatives of testosterone, which has physiological effects on sex drive and boosts muscle mass, enhancing athletic performance in men and women. Illegally, these drugs are regularly self-administered by athletes, bodybuilders, and powerlifters to improve their sportive performance. As a result, most competitive sports have banned AAS. Although, the use of synthetic derivatives has been challenging to establish allowable limits for testosterone in competition as the use of AAS has dynamically increased in both exercise and winning in competition. Testosterone may promote athletic performance, not only through its long-term anabolic actions but also through rapid behavioral effects. Studies have shown that testosterone has potent anabolic effects on the musculoskeletal system, including increased lean body mass, dose-related hypertrophy of muscle fibers, and increased muscle strength for athletes requiring speed and strength. Thus, making illegal steroids a powerful lure, despite the risk of negative side effects. However, severe side effects appear following prolonged use of AAS at a high dose, but their occurrence is limited. In the world of sports and competition, the use of anabolic androgenic steroids is frowned upon in the anti-doping community.

Introduction

The history of sports dates back to the ancient world. Athletics, derived from the ancient Greek term “athlos”, in which humans pursue competitive sports requiring physical skill (Figure 1). An athlete, meaning “one who competes for a prize”, must showcase their stamina, fitness and skill in athletic sports as human physical competition (Lunt 2009). Whether an athlete was to compete as an individual or as a team was contingent on the sporting event. Victor(s) of an event were given honor, wealth

Figure 1 **Pankration,** mixture of boxing and wrestling**,** in the Olympic games. Theagenes, son of a god became to be one of the most competitive and dominant fighters that ever lived. Often described as an extremely strong, muscular, and tall man, Theagenes went on to win two Olympic titles, in boxing in 480 BC and pankration in 476 BC (Karasavvas 2017).

and recognition all the while having the title of high-caliber athlete(s). The downside was that these perceived "superior human(s)" developed addictive personalities with the athletes win at "all cost" mentality leading to cheating in athletic sports. Thus, began sabotage, or manipulation involving bribery or foul play to develop bias towards the athlete's achievement. Gladiators of Roman times used to ingest strychnine to decrease fatigue and thus avoid injury (Dandoy 2012). During the Olympic Games in the First Century AD, it was also reported that the Greek runners were drinking an herbal beverage to increase their strength and to be capable of competing in long duration events (Chrysopoulos 2016). Athletes were also known to drink "magic" potions

Figure 2 Paul Masson, 21-year-old Frenchman cyclist (left). Paul Masson with no international pedigree went on to win three out of six titles at Neo Phaliron Velodrome, a sports arena in the used for the cycling events at the Athens 1896 Summer Olympics.

Image courtesy of 1896 / COMITÃ© INTERNATIONAL OLYMPIQUE (CIO) / MEYER, ALBERT

that consisted of dried figs, wine potions, herbal medications, and eating exotic meats, in the hopes of gaining an athletic edge on their competition. Fast forwarding to the late 19th century, cyclist from Europe became (Figure 2) acquainted with a multitude of performance-enhancing drugs from caffeine to ether-coated sugar cubes to Vin Mariani, a cocaine-laced wine – in order to alleviate the pain and exhaustion resulting from their sport (Lee 2016). Nonetheless, the use of performance-enhancing drugs has progressed from herbal potions, to the use of cocaine and caffeine to anabolic-androgen steroids. This article highlights how cheating has evolved today as athletes have succumbed to anabolic-androgenic steroids (AAS) in order to gain physical sport-specific superiority. Athletes in the 21st century have been prone to accepting larger contracts

with financial incentives, because sports have also turned into a large business industry (Berman 2015). Competition among athletes has been and will always continue to be a contest to demonstrate who is the "superior athlete".

S0: Non-approved Substances

Any pharmacological substance which is not addressed by any of the subsequent sections of the List and with no current approval by any governmental regulatory health authority for human therapeutic use (e.g. drugs under pre-clinical or clinical development or discontinued, designer drugs, substances approved only for veterinary use) is prohibited at all times.
(WADA 2020)

As modelled by other governing bodies including the Food and Drug Administration (FDA), the United States Anti-Doping Agency (USADA), and National Anti-Doping Organization (NADO). To maintain order in the athletic community, the World Anti-Doping Agency (WADA) annually updates its Prohibited List that which a substance is to be considered forbidden if it checks off two of the three criteria. **One**; the substance has shown the potential to enhance an athlete's sport performance. **Two**; shown as a health risk for an athlete or has the potential too. **Lastly**; violates the spirit of the sport as some substances may be banned from use at all times and others only during competitions (USADA 2015). Thus, promoting health, fairness and equality for all athletes competing worldwide. The WADA program provides the opportunity to participate in doping-free sports as they are dedicated to the perseverance of the athletes' natural talent. In doing so, they implement various anti-doping programs from the national to international level to ensure the prevention of doping, including:

Education *— to raise awareness, inform, communicate, to instill values, develop life skills and decision-making capability to prevent intentional and unintentional anti-doping rule violations.*
Deterrence *— to divert potential dopers, through ensuring that robust rules and sanctions are in place and salient for all stakeholders.*
Detection *— an effective Testing and investigations system not only enhances a deterrent effect, but also is effective in protecting clean Athletes and the spirit of sport by catching those committing anti-doping rule violations, while also helping to disrupt anyone engaged in doping behavior.*
Enforcement *— to adjudicate and sanction those found to have committed an anti-doping rule violation.*
(WADA 2021)

The WADA code does not only protect the athlete, it protects the validity of the sport as athletes under the WADA umbrella know that they are all playing on the same level. Whether athletes

are in or out-of-competition the WADA Code is to advance the effort of eliminating doping in competition. The Prohibited List identifies substances and methods that must not be used to enforce anti-doping rules from anabolic agents, stimulants to federally illegal drugs such as cannabinoids and narcotics.

Anabolic-androgenic steroids

Anabolic-androgenic steroids (AAS) in sports have been labeled as the benchmark in improving the physical performance of athletes since it became public in the 1970's (Brooks 1975). Testosterone particularly is a principal androgenic steroid as it is present in males and is produced mainly in the testis (Alen 1988). In females, smaller amounts are present where it is produced in the ovary and the adrenal gland (Neischlag 2015). The interest in testosterone by athletes is based on its' androgenic properties that stimulate anabolic activities. With the rapid increase of competitive sports, the need for testosterone to increase physical fitness is becoming more prevalent in childhood athletes. The use of testosterone trend has caught on over the years as it has been driven by the increase in competitive sports; increase in popularity of team/competitive sports; the focus of the media on the thinness in females and muscular bodies in males; pressure from parents and coaches; the age-related characteristics of taking risks and feeling invincible; and the availability of various PEDs in many forms and shapes (Dandoy 2012). Performance-enhancing agents such as testosterone, or its' derivatives has had a positive influence on athletes' performance as it has been shown to preserve muscle mass, prohibit muscle breakdown and increase recovery. In addition, when combined with strength training athletes were able to see a substantial strength gain of 15% (Dandoy 2012). However, the administration of AAS comes with risks. Side effects may include increased aggressiveness, insomnia, pathological anxiety, and paranoia. The severity of which depends on the drug, dosage and duration of use and can cause adverse effects in the following categories: cardiovascular, hepatic, endocrine/reproductive, and psychological. As popular as it is, the use of anabolic androgenic steroids as performance-enhancing drugs is frowned upon in the anti-doping community.

Testosterone & Synthetic Anabolic-Androgenic Steroids

Shortly after the isolation of testosterone (Figure 3) in the 1930s, it was discovered that there was no active form of the compound when taken orally (Saudan 2006). Upon ingestion, the oral testosterone is absorbed from the small intestines and passes via the portal vein to the liver, where it is rapidly metabolized, mostly to inactive compounds (Coert 1975). Since then, testosterone discovery has led researchers to open up the world to synthetic forms of anabolic steroids. Chemical modifications of testosterone have been useful pharmacologically to alter the relative anabolic-androgenic potency, slow the rate of inactivation, and change the pattern of metabolism (Handelsman 2000).

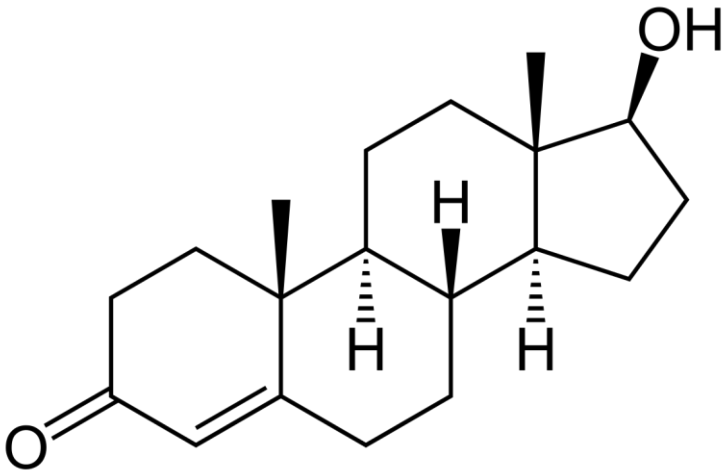

Figure 3 Molecular structure of testosterone. Image courtesy of www.chemspider.com

Most oral synthetics regarding anabolic-androgen steroids (AAS) are 17α-alkyl esters derived from testosterone to be relatively resistant to hepatic degradation.

Injectable forms of AAS involve the esterification of 17β-hydroxyl ester groups that increase the compound's solubility in lipid vesicles. In doing so, the lipid vesicles slow the release of the injected steroid in blood circulation. The most widely used compounds are 17α-alkyl and 17β-ester derivatives for their oral and injectable administration, as shown in figure 2. Androgenic and anabolic effects of AAS vary with their affinity to androgenic receptors. The distinction between these biological effects depends on the organs and target tissues (Janne 1993). Dihydrotestosterone (DHT) is an androgenic metabolite of testostorone that is more readily bound to androgen receptors giving it an androgenic effect. It is formed from the conversion of testosterone by the 5α-reductase enzyme (Handelsman 2000). Thus, DHT is more potent than testosterone in affecting sex glands and invoking gender-specific changes. This enzyme activity is essential in the brain, bones, skin, testis, prostate and adipose tissues as the androgenic effects of AAS predominate in these organs. The anabolic effects would involve the muscles, bones, the heart, and kidneys as these organs possess little 5α-reductase activity. Thus, anabolic-androgenic steroids, particularly testosterone, induce protein synthesis, muscle fiber development, erythropoiesis, stimulation, and bone growth (Mottram 2000). Furthermore, anabolic steroids displace glucocorticoids from glucocorticoid receptors and inhibit muscle protein catabolism, leading to an anabolic or muscle building effect (Kuhn 2002).

Mechanism of Action

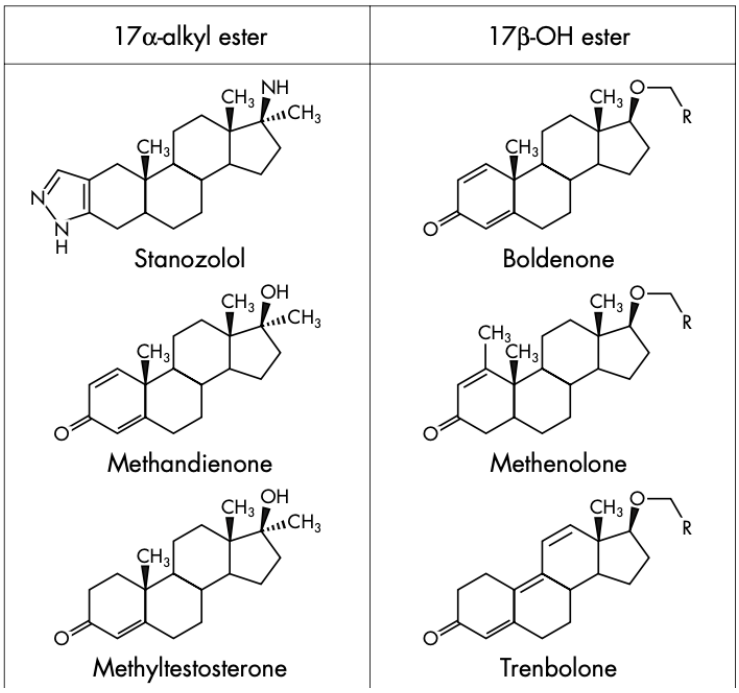

Figure 4 Anabolic-Androgen Steroids: molecular structure of most commonly used 17α-alkyl and 17β-ester derivatives of testosterone. Imaged modified from (Saudan 2006.)

AAS's anabolic effect is mediated primarily by androgen receptors (AR) in skeletal muscle (Bamman 2001). ARs regulate target gene transcription that controls the accumulation of DNA required for muscle growth. Studies showed that ARs would be upregulated by exposure to AAS (Kadi 2000) in addition to strength training. It suggests that a possible mechanism by which supraphysiologic doses of AAS combined with exercise might complement each other (Evans 2004). There also have been thoughts that AAS exert several complementary anabolic actions, including a psychoactive effect on the brain, glucocorticoid antagonism, and stimulation of the growth hormone (GH), insulin-like factor-1 (IGF-1) axis (Kuhn 2002). Similar to skeletal muscle, ARs are widely distributed throughout the brain as testosterone exhibits diverse effects on several central nervous system neurotransmitters (Rubinow 1996). High doses of AAS in normal users increase euphoria, energy, and sexual arousal (Su TP 1993). The cerebrospinal fluid of testosterone-treated men contains higher 5-hydroxyindoleacetic acid levels that correlate with AAS-related effects (Daly RC 2001).

Therapeutic Effects

In a number of clinical studies has shown that potent anabolic effects of AAS have positive benefits among users (Mauras 1998). The following illustrates the psychological replacement doses of therapeutic testosterone (Table 1).

Restore hormone levels in hypogonadal men, thereby increasing fat-free mass, muscle size and strength, and bone density
Improve mood and alleviate depression

Increase body weight, muscle mass, and strength in healthy gonad patients with secondary wasting syndromes, such as infection with HIV when maintaining lean body mass may be beneficial for long-term survival
Augment muscle mass in older men and prevent age-related sarcopenia (degenerative skeletal muscle mass and strength) that contributes to frailty falls

Table 1 Positive benefits among the use of testosterone therapeutically. Image modified from (Evans 2004).

Pre-competition

Wingfield (1990) proposed the "challenge hypothesis," which hypothesizes that during mating seasons and times of resource scarcity, testosterone concentrations rise to facilitate competition, particularly amongst males. The challenge hypothesis applies to human competition in the world of sports (Archer, 2006). An athletic match is a competition between individuals over scarce and valuable resources such as victory itself, prize money, fame, and prestige (Evans 2004). The challenge hypothesis postulated pre-competition concentrations of testosterone rise in male and female athletes in anticipation of the impending competition (Bateup 2002). The speculation is that the pre-competition increase in testosterone may facilitate competition by increasing motivation to compete (Booth 1989) in addition to physical ability. However, further studies of the mediating effects of pre-competition testosterone increase on motivation and physical ability changes are needed.

Post-competition

Testosterone in men commonly increases following victory and decreases following a loss (Booth 1989), including vicarious victory and defeat (Bernhardt 1998). However, this main effect of winning or losing on men's testosterone is not always observed (Gonzalez-Bono 1999). Dominance-motivated individuals, who positively value interpersonal dominance and dislike submission, are those most likely to experience outcome-dependent changes in testosterone (Schultheiss, 2005). The level of engagement of competitors is also relevant to testosterone changes (Van der Meij 2010), such that men's testosterone increases are most significant when one's opponents feel more confident. An elite athlete in an international competition is likely to be more engaged and value victory and defeat much more significantly than a participant in laboratory manipulations with cognitive games (Wood 2012).

Adverse Effects

The overuse of anabolic-androgen steroids (AAS) disrupts the normal production of hormones in the human body that can cause both reversible and irreversible changes. However, the side effects associated with AAS develop virtually only during long-term use (Thiblin 2005). The most common side effects are merely superficial. They include headaches, fluid retention (mostly in extremities), gastrointestinal irritation, diarrhea, stomach pains, and oily skin (Jan van Amsterdam 2010), which are reversible with cessation. Side effects with clinical signs include menstrual abnormalities, hypertension, and jaundice, in addition to infections that can develop at the injection site. Furthermore, in both sexes, acne can develop at puberty (i.e., not in adults) during treatment with androgens due to the growth of sebaceous glands and the secretion of the natural oil sebum (Király 1987). The severity of the conditions is contingent on the drug, the dosage, and duration of use.

Chronic adverse effects

The chronic effects of anabolic-androgen steroid overuse can include urogenital problems, acne, cardiovascular and hepatic disease (Melchert 1995). Males can see changes in reduced sperm

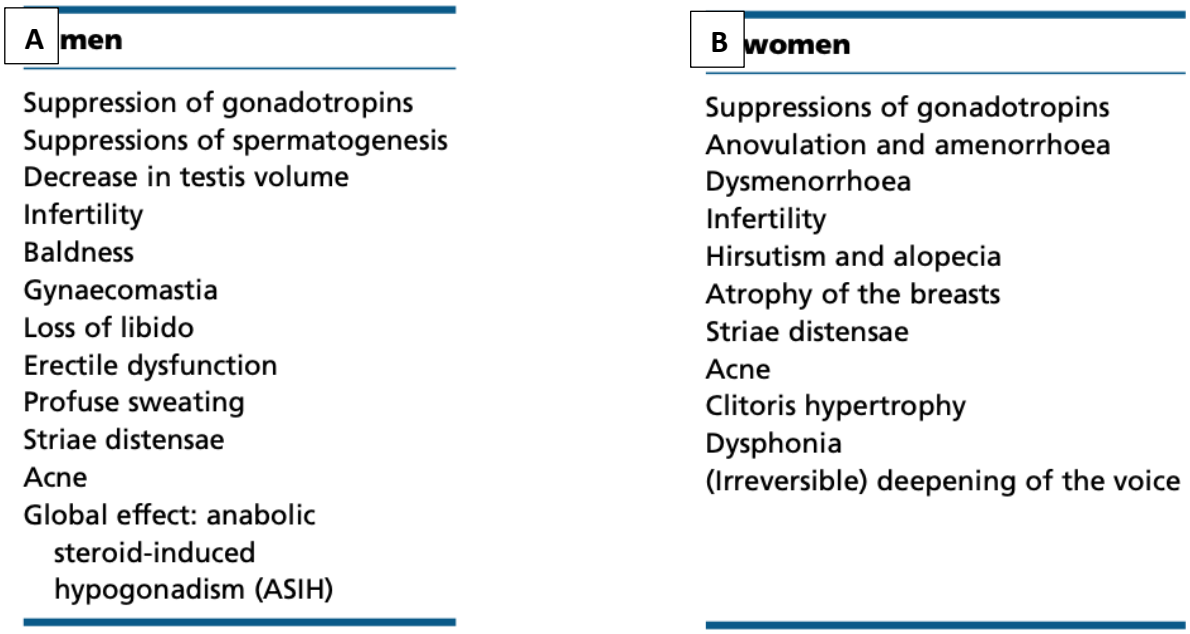

Figure 5A Side effects associated with the overuse of anabolic-androgen steroids on sexual organs in men. Figure 5B Side effects associated with the overuse of anabolic-androgen steroids on sexual organs in women. Image adapted from (Nieschlag 2015).

production, infertility, difficulty or pain in urinating, and hypogonadism, as shown in figure 5A. It has been shown that that of (N = 4339) AAS abusers 35% had testicular atrophy, acne and either reversible or irreversible breast development (Jan van Amsterdam 2010), commonly characterized as gynecomastia. In females, the overuse of anabolic-androgen steroids results in menstrual irregularities and the development of more masculine attributes such as decreased breast size, deepening of the voice, hirsutism, alopecia as well as clitoris hypertrophy (figure 5B). The longer the steroid administration, the more likely the side effects are to become irreversible (Shifren, 2004). Prolonged steroid use can cause the development of more severe side effects such as cardiovascular disease, leading to hypertension, heart attack, and stroke. Oral steroids, in particular, decrease the level of high-density lipoprotein cholesterol (HDL-cholesterol) and increase the level of low-density lipoprotein cholesterol (LDL-cholesterol) (Jan van Amsterdam 2010). Notably, the alkylated and orally used AAS such as stanozolol (6 mg/day p.o. for six weeks) lower HDL-cholesterol by 33%, particularly HDL2-cholesterol, which is reduced 23–80% (Bagatell 1996).

AAS use and Psychopathology

Neuropsychiatric effects

John Ziegler, the physician for the 1950's US men's weightlifting team, was among the first to observe AAS use to enhance athletic performance and its link with psychology. It was stated, "What I failed to realize until it was too late was that most of the weightlifters had such obsessive personalities. To them, if two tablets were good, four would be better" (Bowers 2009). The behavioral and psychiatric effects of AAS abuse surpass the socially acceptable mild irritation and physical training drive to heightened aggression, hostility, depression, and mania. Furthermore, it is often difficult to judge whether the behavioral and psychiatric effects are attributable to AAS use instead of the underlying personality traits of the AAS abuser, or psychosocial factors surrounding AAS use (Jan van Amsterdam 2010).

DSM-5 Criteria
The substances are often taken in larger quantities or over a longer duration than was intended
There is a constant desire or unsuccessful effort to end use or control the use of the substance
A majority of time is spent in activities necessary to obtain the substance, use the substance, or to recover from the effects
A persistent craving, or a strong desire or urge to use the substance

Recurrent use of the substance resulting in failure to fulfill major role in obligations regarding work, school or home
Continued use of the substance despite having persistent or recurrent social or interpersonal implications caused or exacerbated by the effects of its use
Important social, occupational, or recreational activities are reduced or forfeited due to use of the substance
Recurrent use of the substance in situations in which is it physically hazardous
Use of the substance is continued despite knowledge of having continuous or recurrent or psychological problem that is likely to have been caused by the substance
Tolerance, as defined by either of the following: a) a need for markedly increased amounts of the substance to achieve intoxication or the desired effect b) a markedly diminished effect with continued use of the same amount of the substance
Withdrawal, as manifested by either of the following: a) the characteristic withdrawal syndrome for other (or unknown) substance b) the substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms

Table 2 DSM-5 diagnostic criteria for anabolic androgen steroid dependence. At least two of the following criteria must be met over a 12-month period. A mental disorder can occur in a broad range of severity, basing on the number of symptom criteria endorsed: mild, if 2 to 3 symptoms are present, moderate if 4 to 5 symptoms are present, and severe if 6 or more symptoms are present (American Psychiatric Association 2013). Image adapted from (Piacentino 2015).

In doing so, the American Psychiatric Association integrated a diagnostic criterion for AAS dependence in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (Table 2). The use of the code, "other substance use disorder," indicates a mental disorder in which the repeated use of a "supplemental substance" typically continues despite the individual's knowledge that the substance causes severe implication (American Psychiatric Association 2013). The substance cannot be classified with alcohol, caffeine, cannabis, hallucinogen, opioid, sedative, hypnotic, stimulant, or tobacco categories (Piacentino 2015). The most prominent psychiatric features were manic-like presentations defined by hostility, aggression, euphoria, grandiose beliefs, hyperactivity, and reckless or dangerous behavior (Clark 2003). As many users reported while using androgen anabolic steroids, they felt good about themselves but would experience extreme mood swings, including symptoms that could heighten aggression and violence (Pope 1988).

Mood Disorders

Bidirectional relationships between AAS use and mood disorders have been described, with physiological AAS doses affecting mood minimally and even showing beneficial effects in dysthymia and refractory depression (Amiaz 2008). Bodybuilders and football players used

AASs and found 22% qualified for mood disorders (Pope 1988). In a subsequent study, 23% of athletes who abused AASs met DSM-III criteria for mood disorders, from major depressive disorder to type I and II bipolar disorders (Pope 1994). Athletes met these criteria during AAS consumption significantly more than in its absence and substantially more than AAS non-users. The higher the AAS dose, the more severe the psychopathological symptoms.

Behavioral effects

AAS use has led to behavior changes, such as increased aggression, hostility, and unprovoked rage attacks. The typical sudden and exaggerated aggressive AAS-induced response to minimal provocations is commonly termed “roid rage” (Conacher 1989), defined by the challenge hypothesis. The challenge hypothesis is the temporal patterns of testosterone in blood determined by a trade-off between the degree of male-male competition that increased testosterone, and the expression of paternal care that required a decrease in testosterone, grew out of a combination of field endocrine investigations that then informed laboratory experimentation (Wingfield 2017). The challenge hypothesis suggests testosterone levels increase and reach moderate puberty levels, hence supporting reproductive physiology and behavior. Testosterone levels in men are associated with different behavioral profiles concerning life-history strategies involving either mating or parenting (Archer 2004).

Eating Disorders

It is common for athletes to be affected by somatic symptom disorders and/or eating disorders. Physical appearance and eating patterns are interrelated; there is evidence that young boys and men are becoming as concerned about these aspects as young girls and women (Piacentino 2015). However, women seek thinness, while men strive to increase muscle mass and body size, in line with media-endorsed stereotypes and their relevant role in the "pressure to look good," inducing body dissatisfaction, weight control, and muscle development. The media's goal is to promote a body stereotype that emphasizes strength and muscularity for men and thinness for women, leading to lower satisfaction with physical attractiveness and body dimensions and, ultimately, related disorders (Labre 2002). However, studies have shown that media use and eating disorders in young adults found that media exposure significantly influenced men's, but not women's endorsement of personal thinness and dieting (Harrison 1997). In addition to exploring media's role in triggering weight concerns among preadolescent/early adolescent children, boys and girls who strived to resemble same-sex media icons were more likely than their peers to develop a preoccupation with weight and become constant dieters (Field 2001).

Dependence

In contrast to common drugs of abuse, AAS are not firmly euphorigenic in that they do not trigger a rapid influx of dopamine, which are responsible for the "high" that often drives substance abuse behaviors. Still, the effect of the well-being of AAS use and the dysphoric effects of withdrawal may contribute to a syndrome of AAS dependence in some individuals (Kanayama 2009). Long-term use of AAS can eventually impact some of the same brain pathways – such as serotonin, dopamine, and opioid systems – that are affected by drugs of abuse (Wood 2012). AAS abusers may become addicted to the drugs, as evidenced by their continued abuse despite physical problems and adverse effects on social relations (Brower 2002). Testosterone's positive effects on mood are well established, and several studies have found testosterone replacement to substantially reduce negative mood states relating to fatigue, depression, and self-esteem (Anderson 1999). A two-stage model has been proposed for AAS dependence (Brower 2002). Users initiate steroid use for their anabolic effects, but with continued exposure, dependence on AAS's psychoactive effects develops. However, the abuse liability of AAS in the classical pharmacological sense is deficient, although some recent studies suggested AAS dependence to be reasonably common (Brower 2009). Individuals using high doses of AAS are at risk of developing a dependency on AAS because they may develop depressive symptoms, anhedonia, fatigue when they stop taking AAS. Finally, a point of concern is the AAS-induced hypogonadism (Tan 2009), which may contribute to dependence liability because users go back on AAS to self-treat their AAS-induced hypogonadism (Scally 2009). In a study of 49 male weightlifters, 84% reported withdrawal effects, which varied from steroid craving, fatigue, depressed mood, restlessness, loss of appetite, insomnia, reduced sex drive, headache, to muscle and joint pain (Brower 1991).

Conclusion

There has been increasing knowledge of androgen steroid metabolism in the past decades. Since then, sports authorities have provided analytical guidance in the use of anabolic-androgen steroids, although the detection of doping with testosterone remains a challenge in competitive sports due to the rapid clearance of orally administered testosterone esters. In doing so, anti-doping organizations perform drug testing analysis of athletes' urinary concentration in the first hours after administration (Baume 2006). As testing is determined by random selection and is conducted in accordance with the selection options in the guidelines for implementing an effective testing program (WADA 2020). AAS can be administered orally or by injection and is used by athletes to enhance performance and appearance; users often see an increase in body weight and muscular strength. However, the long-term effects of AASs are still unknown;

documented physiological effects are those on the liver, serum lipids, and reproductive system. Research findings have shown effects of increased irritability, aggression, personality disturbance, and psychiatric diagnoses are among the adverse psychological effects of AAS (Jan van Amsterdam 2010). In addition, AAS abuse may be associated with adverse somatic, behavioral, and psychiatric effects, but their incidence and prevalence seem limited. If present, the side effects have resulted from the prolonged use of AAS at high concentrations. The more frequent side effects have been acne and testicular atrophy but can disappear upon discontinuation of use. In some cases, it has been reported that some AAS users show aberrant social and psychological traits, like low self-esteem, low self-confidence, suffered hostility, previous abuse, childhood conduct disorder, and tendency to high-risk behavior, which may explain the presumed association between AAS use and aggressive behavior (Jan van Amsterdam 2010). The use of performance-enhancing substances has been reported in numerous countries (McKillop 1987). The abuse of anabolic agents is no longer confined to Olympic (Segura 1993) and professional sport; it is now an international problem that affects a broader population, including adolescents and young adults (Newman 1994). Unfortunately, societal values related to the importance of sports, winning, and physical appearance frequently influences the demand for anabolic agents (Bahrke 1994). In order to stem the growing demand for anabolic agents among young people, prevention efforts should be strengthened through expanded information and education programmers. Since current knowledge regarding the abuse of anabolic agents is primarily limited to doping in sports, there is an urgent need for increased research and dissemination of present knowledge to concerned experts and authorities (Pope 1994).

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