Performance-Enhancing Drugs: A Review

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Abstract

Performance-enhancing drugs and substances have been an integral part of athletics and society. The immense popularity and financial compensation associated with success in sports often results in a desire to win at all costs, which stimulates a never-ending appetite for use of ergogenic aids. Athletes have experimented with these substances (ranging from over-the-counter supplements to anabolic-androgenic steroids and beyond) if a possibility of advantage exists, whether scientifically or theoretically supported. As the technology to create new designer drugs becomes more available, the ability to test for the presence of these substances lags slightly behind. The knowledge base of sports-medicine physicians must constantly grow as new drugs and testing protocols change yearly. To help identify and evaluate the effects of performance-enhancing drugs on patient-athletes, I reviewed the history and current studies on anabolic steroids and related substances such as androstenedione, human growth hormone, Beta-2 agonists, stimulants, creatine, erythropoietin, beta blockers, and beta-hydroxy-beta-methylbutyrate. It is critical to be aware of the substances and related side effects to properly educate athlete-patients in decision making and help keep them eligible for participation in sports.

Introduction

In athletic competition, participants have historically sought advantages to win. Ancient Greeks drank special concoctions such as a viscous opium juice called "doop" that became known more generally as "dope."[1] Specific meals such as sheep hearts and testicles were eaten to enhance male performance. Ancient Romans used hallucinogenic substances known to be mushrooms, plants, and sesame seeds to aid performance. In this period, the origins of strychnine, an amphetamine-like substance, had its beginning.[1] The Romans also fed horses with hydromel (ie, honey-flavored alcohol) to increase the animals' competitive edge.[2]

The use of performance-enhancing drugs has remained prevalent in sports. However, scientific data to determine evidence of benefit are relatively limited.[3,4] To help identify and evaluate the effects of performance-enhancing drugs in sports, I reviewed historical perspectives and current studies on commonly used anabolic steroids and related substances such as androstenedione, human growth hormone (HGH), Beta-2 agonists, stimulants, creatine, erythropoietin (EPO), beta blockers, and beta-hydroxy-beta-methylbutyrate (HMB).

Development of Performance-Enhancing Drugs: Modern Era

The modern era of performance-enhancing drugs began in 1865 when Dutch swimmers experimented with stimulants. Fifteen years later, two competitive cyclists died after eating ether-coated sugar cubes and drinking cocaine-laced wine.[1] At the 1904 Summer Olympics, the marathon runner Thomas Hicks collapsed at the finish line after receiving several injections of strychnine during the race.[5] (He was not disqualified and retained the Gold medal.) In 1889, Brown-Sequard self-injected extracts of Monkey testicle in attempt to reverse the aging process and increase sexual prowess. Furthermore, Adolf Butenandt isolated androsterone in 1931; he and Ruzicka synthesized testosterone in 1935.[6] Two years later, the first human trials with testosterone began.[6] A few years after that, the first clinical trials using anabolic steroids would begin.[7]

During World War II, German scientists began synthesizing anabolic steroids and testing the result on humans. This included studying chronic wasting to concentration-camp inmates; these testosterone derivatives may have also been given to German soldiers to increase levels of aggression and endurance.[6] Additionally, it was rumored that a physician gave Hitler anabolic steroids for treating certain ailments.[7]

Throughout the 1940s and 1950s, the governments of East Germany and the Soviet Union implemented steroid regimens and weight-training programs for amateur and professional athletes.[8] To counteract the resultant unrivaled success, an Olympic team physician of the United States (US), John Ziegler, helped create methandrostenolone or dianabol. The US Food and Drug Administration (FDA) approved the drug in 1958 originally to treat patients with malnourishment and burns, which quickly

became essential for weight lifters and athletes.[9] Such testosterone derivatives were later modified to enhance effectiveness and duration by alkylation, esterification, and aromatization.[9]

However, the investigation to determine benefits of anabolic steroids as performance enhancers was delayed owing to results of a study in 1972, which showed no difference between use of anabolic steroids and placebos concerning performance enhancement.[3] Researchers later noted that the study lacked consistent controls and statistical significance; however, the evidence remained unchallenged for 18 years. It was not until 2001 that studies showed clear differences between groups with and without high-doses of anabolic steroids in muscle mass, strength, and fat.[3]

Anabolic Steroids

AAS or anabolic-androgenic steroids are synthetic, testosterone derivatives that exert their effects by two different but overlapping pathways.[10] The first pathway, the anabolic pathway, is responsible for the more desirable effects including muscle hypertrophy, increased muscle mass, and decreased fat storage. This is facilitated by activating steroid receptors and increasing mRNA, thus creating more protein. Furthermore, anabolic steroids stimulate increased growth hormone release and blunt the negative effects of cortisol which facilitates quicker recovery time. In addition, they increase erythropoiesis, appetite, and bone remodeling. However, the second pathway (androgenic pathway) results in virilizing characteristics such as infertility, testicular atrophy, and gynecomastia in men and, alopecia, vocal-cord hypertrophy, and clitoralomegaly in women. Adolescent patients typically experience stunted growth from premature physeal closure and precocious puberty.[10]

Other notable side effects of AAS include increased aggression, mania, depression, severe acne, kidney damage commonly focal segmental glomerulosclerosis, liver damage (eg, hepatocellular carcinoma), peliosis hepatis, and increased metabolic burden from oral steroids. Hypertension and lipid abnormalities (ie, increased low-density lipoprotein [LDL] and decreased high-density lipoprotein [HDL]) are common and associated with a mortality risk at 4.6 times higher than non-AAS users. Because the tendons cannot compensate for extreme and accelerated muscle hypertrophy, there is also predilection for tendon rupture. Supplemental medications are used to counteract negative side effects of testosterone derivatives, including aromatase inhibitors, HCG (human chorionic gonadotropin) agonists, and selective estrogen antagonists.[9]

Although the FDA has approved some medical use of AAS (including bone marrow stimulation, growth stimulation, appetite stimulate, hormone replacement therapy, and gender dysmorphia), the typical use is non-medical. Several studies found that the average AAS user is an educated, non-athlete man seeking cosmetic benefit. (This patient population appears to be well read and successful, challenging the typical "meat-head" stereotype.) The substances are delivered orally, parenterally, and transdermally. Stacking and pyramiding are common tactics used, which involve multiple forms of steroids and cycle them for 4 to 18 weeks, respectively. This method facilitates competition-based training and may help avoid positive test results for drug use.[9]

Anabolic steroids are considered Schedule III controlled substances, meaning a prescription is required and possession is punishable by up to 7 years in prison. Yet legality differs among countries, and some such as Mexico and Thailand have no legal ramifications.[7] Legislation in the US changed considerably after Ben Johnson tested positive for a banned substance at the Summer Olympics in Seoul, which resulted in the Anabolic Control Act of 1990.[7] The law expanded in 2014 to include 24 new substances and crimes for mislabeling. In 1994, the Dietary Supplement Health and Education Act was passed, allowing supplements and prohormones to be available over-the-counter and not subjected to strict regulations by the FDA. Major sporting bodies (ie, International Olympic Committee, National Football League [NFL], Major League Basketball, National Hockey League, National Basketball Association, and National Collegiate Athletic Association [NCAA]) have banned use of anabolic steroids (Table 1).[7]

Although testing for use of anabolic steroids is commonplace in professional associations, high-school testing has been described as unsuccessful thus far.[4] Texas led the way in legislation and testing of young athletes, spending up to 10 million dollars; however, owing to minimal positive tests out of thousands and the high cost of testing equipment and processes, the funding for high-school testing was canceled in 2015.[4] A normal ratio of testosterone to epitestosterone in adult males is 1.3:1, respectively. Rarely can a ratio of 4:1 be observed, yet a ratio of 6:1 equates to a positive test result.[9]

The substances are usually obtained using illegal channels, often smuggled across borders with other illegal drugs. Today, anabolic steroids are rarely produced in the US and commonly reflect a veterinary grade. Domestically, purchasing occurs by mail-order advertisements in workout magazines, websites, and most frequently at local gymnasiums.[7] Recently, counterfeit drugs and supplements have been making headlines.[11] Because the substances are not regulated, producers are diluting products to maximize profit and sometimes add toxic additives.[11]

Table 1. Banned substances of major sports as noted by the World Anti-Doping Agency[a]

All times[b]	In competition[c]	In particular sports	NCAA, NFL, NBA, and MLB
Anabolic agents	Stimulants	Alcohol[d]	Stimulants
Peptide hormones, growth factors, related substances, and mimetics	Narcotics	Beta blockers[e]	Anabolic agents
Beta-2 agonists	Cannabinoids		Alcohol and beta blockers
Hormone and metabolic modulators	Glucocorticoids		Diuretics and masking agents
Diuretics and masking agents			Illicit drugs Peptide hormones, analogues Anti-estrogens Beta-2 Agonists

NCAA, National Collegiate Athletic Association; NFL, National Football League; NBA, National Basketball League; MLB, Major League Baseball.

[a] WADA. Prohibited List January 2017. Montreal, Canada: World Anti-Doping Agency; effective January 1, 2017.

[b] "All times" refers to substances banned at all times, eg, even during training.

[c] "In competition" refers to substances banned only during the actual game.

[d] Alcohol is banned in air sports, archery, and powerboating.

[e] Beta blockers are banned during archery, billiards, darts, golf, shooting, skiing, snowboarding, and underwater sports.

Androstenedione

As Mark McGwire and Sammy Sosa set the baseball world on fire during the historic homerun race of 1998, so came the interest in an over-the-counter supplement called "Andro". After being discovered in Mark McGwire's locker, the drug gained great popularity, associated with increased muscle mass and rapid recovery after injury. Androstenedione is a direct precursor to testosterone and theoretically converts to testosterone. In reality, most studies have shown no increase in testosterone levels after androstenedione use.[12]

Furthermore, studies have found no improvement in athletic performance, lean body mass, or strength.[12,13] Because most of the side effects are shared with anabolic steroids, some studies have described an increased predilection of androstenedione to cause considerable increases in estrogen levels and decreased HDL.[13,14] Although it was readily available during the late 1990s, androstenedione is now banned by all major sports associations and considered a Schedule III controlled substance. The Anabolic Steroid Act was amended in 2004 to include androstenedione.[13]

Human Growth Hormone

Originally discovered by Cushing in 1912, HGH is produced in the anterior lobe of the pituitary gland and responsible for accelerating linear growth and increasing body weight and muscle mass.[15] GnRH, sleep, exercise, L-Dopa, and arginine regulate growth-hormone release. HGH effects almost every tissue in the body.[15] In 1956, it was isolated from cadaver brains of monkeys and humans. The drug was then used to treat dwarfism and in children until the discovery of Creutzfeldt-Jakob disease transmission. Subsequently, HGH was discontinued until a recombinant form came in the 1980s.[16]

Numerous studies have shown significantly increased muscle hypertrophy but no increase in strength with use of HGH supplementation.[16] Overall, limited research has been conducted on HGH supplementation. Results of recent polls have revealed that since 2012, high-school teenager use of HGH has doubled.[17] Serious side effects from exogenous administration include insulin resistance, increased cholesterol and triglycerides, hypertrophic cardiomyopathy, hypogonadism, osteoporosis, acromegaly, and myopathic muscles.[15] HGH is available only by prescription.[16] It is banned by all major sporting associations but extremely difficult to detect. In 2010, only 15 positive test results were noted of 18,000, and the 2014-2015 NFL test revealed zero positive tests of 290.[18]

Beta-2 Agonists

Well known for the use in treating asthma and chronic obstructive pulmonary disease, beta-2 agonists have also been used as performance-enhancing drugs. Specifically, athletes have abused clenbuterol and salbutamol owing to the known bronchodilation and anabolic effects. Clenbuterol and salbutamol increase protein synthesis and lean body mass.[19]

Bodybuilders have used high doses of clenbuterol before competitions because of the "cutting" or rapid fat-loss effect. Furthermore, many well-known celebrities have used these substances for weight-loss aids.[20] Beta-2 agonists also act as tocolytics and increase basal metabolic rate.[19,20] For example, the Tour de France Cyclist Alberto Contador tested positive for clenbuterol and was stripped of his 2010 crown. Side effects of using beta-2 agonist include tremor, agitation, palpitations, tachycardia, hypertension, myocardial infarction, and thyrotoxicosis.[19]

Stimulants

Some of the oldest and most used performances-enhancing drugs include amphetamines and caffeine. Other, less-known stimulants include ephredrine, bromantane, and meldonium. In theory, these substances act by stimulating the sympathetic nervous system.[21]

Caffeine is the most widely available ergogenic aid and highly effective at delaying onset of fatigue. It is allowed in competitive athletics in small to moderate doses, and only levels greater than 800 mg are detectable by testing.[21] Doses of caffeine at 3 mg/kg to 9 mg/kg have been shown to increase performance in prolonged exercise and in intense short-duration exercises.[21,22] Side effects of caffeine include dehydration, tachycardia, and increased susceptibility to heat-related injury. Amphetamines have a potent ergogenic effect by increasing cardiac output and metabolism of free fatty acids.[22] Their mechanism involves central nervous system stimulation, which increases aggression, mental alertness, and decreases perception of fatigue.[23]

Ephedrine, ephedra or ma huang became popular in the 1990s as a weight-loss drug and energy enhancer.[24] It has been shown to promote short-term, modest weight-loss but with notable side effects.[24] These side effects include psychiatric symptoms, ventricular dysrhythmias, hypertension, and increased heat-related illness and stoke risk.[25] Numerous deaths have been associated with athletic activity and ephedrine usage.[25] Most notably, Korey Stringer, a football player (specifically, a lineman) of the Minnesota Vikings, died after sustaining a heat-related stroke during practice while using ephedrine.[25] The NFL has now banned ephedrine.[25]

Bromantane, originally used by Russian soldiers to decrease fatigue and shorten recovery time, gained prominence at the 1996 Summer Olympics when several Russian athletes tested positive for the substance.[26] Bromantane is a psychostimulant and anxiolytic with dopaminergic effects. It is thought to increase physical as well as mental performance.[26] It was later banned in 1997 as a stimulant and masking agen.[26] Use of bromantane is now researched as a treatment of numerous neurological disorders.[26]

Meldonium or mildronate made headlines when Maria Sharapova, professional tennis player, was suspended 2 years owing to testing positive for the substance. Meldonium had been described as a "metabolic modulator" owing to its ability to mo-effect enzymatic reactions in the body. Medically, its uses include treatment of coronary artery disease by vasodilation, anticonvulsant, and antihypnotic.[27] Although meldonium was placed on the banned list of substances in January 2016, there is limited evidence of benefit as a performance enhancer.[27] The potential benefits of meldonium include increased utilization of fatty acids, decreased production of lactic acid, improved utilization of glycogen, decreased oxidative stress, and enhanced aerobic endurance.[28]

Creatine

First discovered by Chevreul in 1832, creatine was not seen in athletic performance until 1992 during the Barcelona Summer Olympics.[29] Creatine has since become the most popular nutritional supplement in history.[29] Several studies have shown a 50% use-rate among collegiate athletes and 33% in NFL players.[29]

Creatine is a naturally occurring compound primarily synthesized in the liver, pancreas, and kidney. Almost 95% of creatine is stored in skeletal muscle. It is made from the amino acids glycine, arginine, and methionine. Creatine provides energy during short-duration maximal bouts of anaerobic exercise. The phosphorylated form donates a phosphorus atom to resynthesize adenosine triphosphate.[30]

Multiple performance studies have described the effectiveness of Creatine supplementation for simple, short-duration maximal anaerobic events.[30,31] Weight lifters typically have increased single repetition (maximum, 20%-30%); cyclists, increased muscular force and power; sprinters, about 1% to 2% decrease in sprint times; and all athletes have been noted with increased weight and lean body mass.[30] However, studies have noted up to a 30% non-responder rate in the population and suggested increased mass owing to water retention.[31] Dehydration and muscle cramping have been the most common side effects.[31]

Creatine appears to be safe for short-term use, although

the effects of long-term use are unknown.[32] Intake of creatine supplements appears to be enhanced with carbohydrate ingestion, though multiple forms of creatine exist, creatine monohydrate appears to be most effective.[32] Creatine is an abundantly available over-the-counter substance and not tested or banned by any major sporting associations. The NCAA does not allow teams to provide creatine to players but it is not prohibited. [32]

Erythropoietin

EPO and transfusion of red blood cells increases the oxygen carrying capacity of red blood cells and thus improves aerobic capacity and performance of working muscles.[33] The ergogenic benefit may be primarily in the endurance athlete who relies on aerobic metabolism. Subsequently, use of EPO has become extremely popular with cyclists, runners, and triathletes. The presence of EPO is difficult to detect, making it more enticing to endurance athletes.

EPO is a naturally occurring hormone produced in the kidney, which stimulates erythropoiesis in the body.[33] Additionally, a synthetic form can be produced with use of recombinant deoxyribonucleic acid (known more commonly as DNA) technology. Many highly publicized scandals, most notably Lance Armstrong, involved cyclists using and abusing EPO. Five Dutch cyclists died in 1987 after synthetic EPO release; between 1997 and 2000, eighteen cyclists died of stroke, myocardial infarction, or pulmonary embolism. EPO and blood doping is prohibited in all major sporting associations but continues to be difficult to detect. However, training at high altitudes and hyperbaric oxygen chambers are acceptable. Severe side effects exist with EPO use: transfusion risks, hyperviscosity syndrome, stroke, MI, heart failure, pulmonary embolism, dehydration, and death.

Beta Blockers

Although drugs with antihypertensive and antianxiety effects would seem contradictory to performance enhancing, successful shooting and archery rely on fine motor control. In those certain sports, beta-blockers have been considered performance-enhancing drugs. A study from 1986 showed increased shooting performance of a beta-blocker group compared to the placebo group.[34]

Beta-hydroxy-beta-methylbutyrate

HMB is a leucine metabolite, marketed as an anticatabolic supplement and aid in recovery time.[35,36] Use of HMB has been thought to result in increased testosterone levels, delayed anaerobic metabolism, and avoidance of exercise-induced muscle damage.[35,36] HMB has a minimal side-effect profile, and some studies show it may be cardioprotective owing to its ability to lower LDL, total cholesterol, and systolic blood pressure. HMB is available over-the-counter as a nutritional supplement and is not banned by any sporting leagues or governing bodies.[35,36] Although several studies have shown promise in suppressing protein breakdown and muscle damage, studies have also noted minimal ergogenic advantage.[37,38]

Conclusion

Performance-enhancing drugs have historically been an integral part of athletic competition. In the modern era, the use of performance-enhancing substances remains common (ie, anabolic steroids and related drugs such as androstenedione, HGH, beta-2 agonists, stimulants, creatine, EPO, beta blockers, and HMB). Although research on the potential effects of performance-enhancing drugs remains extensive, the results of some studies have questioned any significantly measurable evidence of benefit.[12,13,27, 31,37,38] Furthermore, the difficulty in testing the presence of performance-enhancing substances (ie, testing protocols associated with high costs and minimal detections) may complicate study results.

Further studies are needed to evaluate the true prevalence of performance-enhancing drugs among athletes and differentiate sport-specific rates. Such studies may stem from randomized testing of athletes. Randomized, controlled studies are also needed to resolve conflicting data on specific substances and their effects on performance in sports.[39] Owing to constant discoveries and changes in the realm of performing-enhancing substances, sports-medicine physicians should be aware of available and current drugs to better educate and guide decisions of patient-athletes.

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Conflict of Interest

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