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Performance-Enhancing Drugs

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Author Disclosure
Drs Dandoy and Gereige have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Educational Gap

Performance-enhancing drug (PED) use by children and teenagers rose sharply in the past decade. One study shows 3.3% of high school students admit anabolic steroid use; another finds 8% of girls and 12% of boys report using products to improve appearance, muscle mass, or strength. Pediatrics clinicians must monitor PED usage trends, screen perceptively, and offer anticipatory guidance.

Objectives

After completing this article, readers should be able to:

1. Recognize the signs and symptoms of the use of anabolic steroids and growth hormone.
2. Know how to diagnose the use of anabolic steroids and growth hormone by data collection (history, physical examination, and laboratory evaluation).
3. Know the side effects of anabolic steroids.

Introduction

The use of performance-enhancing drugs (PEDs) by preteenagers and teenagers has increased tremendously over the past decade. This trend is driven by multiple factors, including the decrease in the age of participation in competitive sports; the increase in popularity of team/competitive sports; the focus of the media on 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.

The pediatric clinician must be aware of the use of performance-enhancing substances by pediatric patients; be prepared to identify risk factors, signs, and symptoms; ask screening questions; and offer anticipatory guidance related to their use. Table 1 lists the common classes of PEDs. This review will focus on a select group of commonly used PEDs. The reader should know that anabolic steroids are synthetic substances derived from testosterone and are also called anabolic-androgenic steroids (AASs) or just “steroids.” Steroid precursors also are used as performance-enhancing agents.

Epidemiology

Over the past 25 years, there has been an explosion in youth sports participation, resulting in a dramatic increase in the total number of athletes under age 18 years. It is estimated that more than 30 million children and adolescents are participating in organized sports today. Title IX, which was passed in 1972, promoted equal numbers of male and female college athletes and increased the number of female athletes. In 1972, there were ~25,000 female high school athletes, in comparison to 3 million in 2000. (1) This number has been stable at 3 million in 2007, according to Title IX data.

With the increase in number of childhood athletes, the stress to perform at a high level has increased. Parents, coaches, and the players themselves are constantly pushing themselves to perform. This drive to be successful in athletic competition often is a positive one, resulting in increased self-

Abbreviations

AAS: anabolic-androgenic steroid
DHEA: dehydroepiandrosterone
EPO: erythropoietin
hGH: human growth hormone
PED: performance-enhancing drug

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Table 1. Classes of Commonly Used Performance-Enhancing Drugs

Anabolic Agents
Anabolic steroids
Testosterone
Steroid precursors
Dehydroepiandrosterone
Androstenedione
Nutritional Supplements
Creatine
Protein/amino acids
β-hydroxy β-methylbutyric acid
Stimulants
Ephedrine
Caffeine/Guarana
Other
Human growth hormone
Erythropoietin
Blood doping
Diuretics
Actovegin (calf blood extract)

confidence, a drive for hard work, and cooperation among peers. This drive, however, can turn negative when competition and winning is “at all costs.” When athletes lose sight of the meaning of fair competition by taking performance-enhancing substances, they put their future health at risk and compromise their ability to practice sportsmanship.

There are many historic examples of athletes over the last century who relied on PEDs to improve their performance. During the original Olympic Games, cash awards were given to the winners of the games. At that time, the use of performance-enhancers was widely accepted. Athletes would consume large amounts of meat and herbs with the belief that it would give them a competitive edge. They would also consume a type of opium juice called “doop”; this term was the origin of the word “doping.”(2)

Gladiators of Roman times used to ingest strychnine to avoid injury and to decrease fatigue. During the 1950s, the Soviet Union dominated power lifting by providing their wrestlers testosterone injections. In the 1960s, *Sports Illustrated* documented the use of amphetamines, tranquilizers, cocaine, and other drugs by professional athletes. (3) In 1988, Ben Johnson turned in a record-breaking performance in the 100-m dash but was stripped of his title after he tested positive for the anabolic steroid stanozol. (4)

Recently, over concerns about the medical complications of performance-enhancing substances and the

potential influence professional athletes have on children’s performance in sports and sports-related behavior, athletes are being monitored for use of substances that enhance performance. Despite this focus, athletes in baseball, cycling, football, and basketball continue to test positive for PEDs on a frequent basis.

Risk Factors

Specific factors place the adolescent at increased risk for use of performance-enhancing substances. Adolescents, by their nature, are particularly vulnerable to risk-taking behaviors and experimentation. Teenagers often feel invincible and lack insight into long-term complications. Among athletes who use PEDs, those who play football, baseball, and basketball, who wrestle, and who are involved in gymnastics and weight training are at increased risk. (5)

Some adolescents not involved in sports use performance-enhancing substances. At risk are the teenagers who are preoccupied with appearance or are focused on weight building or performance in the gym. Project EAT-II, a longitudinal study in which the authors reviewed eating, activity, and weight in 2,500 adolescents over a 5-year period of time, revealed that 1.4% of girls and 1.7% of boys reported having used anabolic steroids in the past year. The two variables that were predictors of steroid use in males were (a) having an ideal body size that is larger than one’s current body size and (b) self-report of healthy weight control behaviors. In girls, the two predictors of steroid use were (a) low satisfaction with weight and (b) high BMI. (6) Other factors that have been predictors of steroid use in adolescents include peer pressure, media influence, and parental pressures with regard to weight and muscles. Adolescents with a history of depression, those who have a negative body image, and teenagers who have a tendency to compare their own bodies to those who are known users of steroids are at increased risk of using as well. (7)(8)

The pediatrician who cares for adolescents also must consider the media and its effects on adolescents taking performance-enhancing substances. Field et al (9) found that 8% of girls and 12% of boys reported using some type of product to improve appearance, gain muscle mass, or improve strength. Adolescents who reported that they wanted an improved physical appearance were more likely to use performance-enhancing substances. Also, girls who wanted to lose weight were more likely to use some type of PED.

Studies have revealed that males who read men’s, teenager, fashion, or health and fitness magazines were

twice as likely to use a performance-enhancing substance to improve strength. Females wanting to look more like women in the media were more likely to use products that enhance their physiques. Adolescents who lift weights or play football were more likely to use creatine, amino acids, dehydroepiandrosterone (DHEA), growth hormone, or anabolic steroids.

Anabolic Agents

Anabolic-Androgenic Steroids

PHYSIOLOGIC EFFECTS. As mentioned, AASs are synthetic derivatives of testosterone that have been modified to maximize anabolic effects. These testosterone derivatives have several general effects: they promote an increased nitrogen concentration in muscle, which in turn promotes an anabolic state; the agents inhibit the binding of catabolic glucocorticoids to muscle, preserving muscle mass and prohibiting muscle breakdown; and AASs have an effect on aggression, promoting athletes to train and push themselves harder. When combined with strength training, AASs increase fat-free mass and muscle strength. Strength gains can be substantial, with increase of strength to 5% to 20%. Clinical trials testing aerobic activity have not demonstrated significant improvements. With use of anabolic steroids, muscle mass increases through muscle hypertrophy as well as an increased number of muscle fibers. (10)(11)(12)(13)(14)

PREVALENCE OF USE. The National Youth Risk Behavior Surveillance System, conducted every 2 years, surveys ~16,500 9th- through 12th-graders in private and public schools regarding priority health-risk behaviors. In relation to steroid use, the survey asks if the teenager “ever took steroid pills or shots without a doctor’s prescription one or more time during their life.” The incidence from 1991 to 2003 grew from 2.7% to 6.1%. That number has revealed a decrease from its peak in 2003 to 3.3% in 2009. Boy respondents (4.4%) were more likely than girls (2.2%) to have used steroids at least once. Race was not a contributing factor to steroid use. (15)

Monitoring the Future is a long-term study of adolescents and adults based at the University of Michigan Institute for Social Research. Each year, the survey investigates substance abuse and use in ~50,000 8th-, 10th-, and 12th-grade students. In 2010, the survey revealed the annual male adolescent prevalence rates for steroid use of 0.7% for 8th-graders, 1.3% for 10th-graders, and 2.5% for 12th-graders. The annual female adolescent prevalence is 0.3% in 8th-graders, 0.5% in 10th-graders, and 0.3% for 12th-graders.

Since 1993, perceived risk and disapproval were asked of the adolescents. Between 1998 and 2000, there was a sharp decline in perceived risk of steroid use. This decline could be related to the use of performance-enhancing substances by professional athletes. There has been a small rise in perceived risk of steroid use; however, the perceived risk still remains at 59%. Fewer adolescents perceive steroids as “fairly easy or very easy” to get since 2003. Finally, more adolescents disapprove of steroid use since 2003 as well. (16)

ADMINISTRATION. Steroids can be injected, taken orally, or absorbed transdermally. Injectable forms of steroids are more potent and last longer. Oral anabolic steroids are converted in the liver into active testosterone. Anabolic steroids often are “stacked,” which means taking multiple steroids at the same time, and taken in 4- to 12-week cycles. The doses often are in a “pyramid” sequence with the largest dose at the middle of the cycle. The doses often are 50 to 100 times what would be needed to maintain the normal physiologic level of testosterone. A large market has developed creating “designer steroids” that are modified to evade detection.

TESTING. Testing for exogenous testosterone can be accomplished by determining the urinary ratio of testosterone glucuronide to epitestosterone glucuronide. The ratio is normally 1–3:1. When someone is taking anabolic steroids, endogenous testosterone glucuronide and epitestosterone glucuronide are suppressed, leaving just the exogenous testosterone. A testosterone to epitestosterone ration of more than 4:1 is considered positive. Another way to monitor for exogenous testosterone is to obtain urine testosterone and luteinizing hormone. Because exogenous testosterone suppresses luteinizing hormone, this ratio is high (more than 30) in those taking anabolic steroids. (17)

ADVERSE EFFECTS. There are many adverse effects of anabolic steroids, and some can be serious and lifelong. These symptoms are prominent with the use of AASs as well as steroid precursors. Table 2 highlights the major adverse effects.

The Anabolic Steroid Control Act of 1990 made AAS a schedule III controlled substance. The Anti-Drug Abuse Act of 1988 made AAS illegal to use for anything other than disease treatment.

Steroid Precursors

Anabolic steroid precursors or prohormones have gained popularity as PEDs in the past 15 years. These substances

Table 2. Adverse Effects of Androgenic–Anabolic Steroids and Steroid Precursors

Musculoskeletal	Skin
Acne	Striae
Muscle hypertrophy	Hirsutism
Epiphyseal closure	Edema
Increased rate of tendon strains and rupture	Male pattern baldness
Reproductive	Cardiovascular
Boys/Girls	Elevated cholesterol
Altered libido	Decreased high-density lipoproteins
Girls	Increased blood pressure
Deepening of voice due to thickening of vocal cords	Thrombosis
Hypertrophy of the clitoris ^a	Urinary
Hirsutism	Wilms tumor
Amenorrhea	Immunologic
Uterine atrophy	Decreased immune globulin A
Breast atrophy	Psychologic
Boys	Aggression
Testicular atrophy	Psychosis
Oligospermia	Depression
Abnormal sperm morphology	Emotional instability
Prostate hypertrophy	Addiction
Prostate cancer	Withdrawal and dependency
Impotence	Gastrointestinal
Gynecomastia ^a	Liver tumor—benign hepatoadenoma
Endocrine	Hepatic carcinoma
Increased glucose tolerance	Peliosis hepatitis
	Cholestasis
	Gastrointestinal irritation
	Infectious
	Local wound infection at injection site
	Septic arthritis
	Hepatitis B or C
	HIV infection

^aIrreversible and permanent.

were first marketed and sold over the counter, promoting increased endogenous testosterone and thus promoting lean body mass. In the late 1990s and early part of this past decade, there was an explosion of the use of steroid precursors. These steroid precursors include, but are not limited to, the following: androstenedione (also known as “andro”), androstenediol, norandrostenedione, norandrostenediol, and DHEA. (18)

Most androgenic steroids in humans are derived from DHEA, which is secreted from the adrenal cortex. DHEA is converted to androstenedione and androstenediol, which is then converted to testosterone. Steroid precursors were produced and distributed in hopes that these substances would increase free testosterone. The effects that are hoped for are often not seen because these precursors bind poorly to androgen receptors. Multiple studies have been done with steroid precursors; most of them have revealed increases in androstenedione and estradiol but little

to no increase in serum testosterone. There have been no studies revealing increased muscle mass or improved athletic performance. (19)

Although these steroids have minimal desired effects, they still have many of the negative effects of anabolic steroids (Table 2). In female athletes, these substances have an androgenizing influence, including general virilization and male pattern baldness. Males can experience gynecomastia, acne, and testicular atrophy. In both genders, decreased high-density lipoproteins, increased lipids, and stunted growth can result. Finally, these substances can downregulate endogenous testosterone over time. (20)(21)

In 2005, androstenedione was classified as a schedule III controlled substance. DHEA continues to remain an over-the-counter nutritional supplement. Unfortunately, the Dietary Supplement Health and Education Act of 1994 allows many steroid precursors to be sold over the counter with minimal regulation.

Nutritional Supplements

Nutritional supplements have become increasingly popular among adolescents in the past 18 years. In 1993, the Proxmire Amendment limited jurisdiction of the Food and Drug Administration over nutritional supplements. This decision severely limited federal regulation. From that point forward, there was a market explosion. Dietary supplements can be found in health food stores, supermarkets, and even the corner gas station. The easy availability and advertising campaigns directed at young athletes have led to a high rate of use among adolescents.

There are hundreds of nutritional supplements and more are being produced each year. These products undergo little human testing and no testing in children and adolescents, which can be potentially dangerous. (22) Currently, most nutritional supplements are not recommended for consumption by those under age 18 years.

Creatine

Creatine is the most popular nutritional supplement, accounting for \$400 million in sales annually. Despite recommendations against creatine use in adolescents under age 18 years, its use is still common. In 2001, Metz et al (23) questioned 1,103 adolescents and found creatine use in 5.6% of them. Those that used creatine were in each grade level from 6th to 12th, and improved sports performance was cited as the goal in 75% of these cases.

Creatine is a nonessential amino acid that is made in the liver, pancreas, and kidneys and helps create adenosine triphosphate. Creatine can be found in meat, milk, and fish among other foods, and the total daily requirement is 2 g per day. Often, athletes use two to three times this amount when using creatine for improved sports performance.

Creatine has been shown to improve performance in short, high intensity exercises, including weight lifting. There are smaller benefits found in performances of longer duration. Creatine-related adverse effects include weight gain, water retention, gastrointestinal cramping, fatigue, and diarrhea. (12)

Human Growth Hormone

Human growth hormone (hGH) is an endogenous hormone produced in the pituitary gland. In children and adults, the main reason hGH is given is to treat growth hormone deficiency and short stature in order to increase linear growth. However, hGH has been used by sports competitors for performance-enhancement since the 1970s. Recently, the use of hGH by professional athletes has received attention in the media from players in the

National Football League to Major League Baseball. The reason this drug has been popular among athletes is because it is difficult to detect.

Studies evaluating growth hormone in healthy individuals reveal that endogenous growth hormone does increase lean body mass and decreases fat mass. However, growth hormone has little effect on strength and athletic performance and might worsen exercise capacity by increasing exercise-induced lactate levels. (24) Adverse effects such as diabetes, cardiomyopathy, hepatitis, and renal failure have occurred with the use of high-dose growth hormone. Also, participants in studies evaluating the effects of growth hormone often complained of soft tissue edema, joint pain, carpal tunnel syndrome, and increased fatigue. (25)

Currently, hGH is on the World Anti-Doping Agency banned substance list. Blood tests currently exist for its detection; however, there is only a small window of opportunity for its detection. Currently, there are two methods of detection in the blood. The "markers" method looks for alterations in the ratios of serum proteins that exogenous hGH would alter. The "isoform" method looks for alterations in the growth hormone structure. (26)

Erythropoietin

Erythropoietin (EPO) has gained notoriety recently as a PED used by cyclists and endurance athletes. EPO administration leads to increased production of red blood cells, which in turn leads to increased oxygen delivery to muscles. Unfortunately, this rise in hematocrit can create complications, including dehydration and increased viscosity and sluggishness of blood, which can lead to stroke and pulmonary emboli. Detection of EPO can be done through urine sample electrophoresis. (27)(28)

Stimulants

Stimulants such as ephedrine and caffeine are used by adolescent athletes for their ergogenic effects. (29) Stimulants are an attractive ergogenic option because they are widely available, easily accessible, and difficult to detect. Stimulants reduce the perception of fatigue and increase time to exhaustion. They improve alertness, as well as neurocognitive and aerobic performance.

Ephedrine is available in cough and cold remedies over the counter. Ephedra was banned by the Food and Drug Administration in 2004 due to its numerous adverse effects, such as hypertension, weight loss, insomnia, anxiety, tremors, headaches, arrhythmias, strokes, and psychosis. The drug has been implicated in several deaths in athletes. Since its ban, ephedra was replaced by other sympathomimetics that have similar effects.

Caffeine is used in beverages, soft drinks, and pill forms. Guarana is a plant extract sold in drinks and energy shots. Guarana seeds contain 9,100 to 76,000 ppm of caffeine. Caffeine use for performance-enhancement has been reported in 27% of adolescent athletes in the United States. Caffeine produces ergogenic effects at a dose as low as 250 mg (3.0–3.5 mg/kg). Caffeine does not seem to be useful for sprints or short bursts of activity but may be effective for prolonged sports containing short bursts, such as tennis and team sports.

General Approach

The general approach to dealing with PED use in the young athlete is similar to the approach to any other type of substance abuse. In fact, PEDs have been considered gateway drugs because teenagers and preteenagers who engage in the use of PEDs, marketed legally or illegally, are more likely to exhibit risk-taking behavior in other ways and to engage in the use of other substances of abuse (opioids, narcotics, and cocaine, etc). The clinician should maintain a high degree of suspicion and look for “red flags” in the history and physical examination.

History

The psychosocial history should include, in addition to inquiring about the use of alcohol, smoking, and drugs, asking about the use of PEDs in all shapes and forms, including nutritional supplements. The clinician should inquire about sources of PEDs, motives behind their use, the patient’s understanding of the effects and adverse effects of the PEDs being used, and the use of PEDs by peers, which is a strong predictor of use. It is important to remember that not all PED users are involved in athletic activities and the motive might be to enhance looks.

Physical Examination

The clinician must look for red flags on physical examination that might point to the effects and adverse effects of PEDs. Sudden increases in muscle mass and lean weight over a short period of time, facial and body acne at a time that is asynchronous with when acne is expected to develop in a teenager, stretch marks, even mood changes and anger outbursts in boys and signs of virilization in girls, all raise suspicion for AAS use. Coarse features and rapid growth suggest hGH use.

Anticipatory Guidance and the Role of the Clinician

The clinician must include questions about the use of PEDs in the psychosocial history on all youth, regardless of their involvement in sports. Education and discussion

should begin early (elementary school) before the youth becomes a user. The following are a few tips for the clinician to address PED use in teenagers and preteenagers:

- Maintain an opened dialogue
- Understand the motive behind the use of PEDs
- Educate the athlete against the use of banned/illegal ergogenics
- Tell the youth what is known and not known about these substances
- Discuss the adverse effects and dangers
- Be aware that drug testing has not proven to be a deterrent alone
- Promote balanced meals, good nutrition, and training
- Discuss safe alternatives
- Know that occasionally, tests that reveal a low sperm count in AAS users can motivate the user to stop using AASs

Summary

- Clinicians should screen for anabolic steroid use because there is evidence that, based on results of the National Youth Risk Behavior Surveillance System, 3.3% of 9th- to 12th-graders admit to using steroids in the past. (15)
- It is an established fact that adolescents are vulnerable to risk-taking behaviors and experimentation, feel invincible, and lack insight into long-term complications. (2)
- Based on epidemiologic data, among all athletes who use performance-enhancing drugs, athletes who play football, wrestle, are involved in gymnastics, play baseball and basketball, and participate in weight training are at increased risk of use. (15)(23)
- Based on strong evidence, the predictors of steroid use in boys are desire for an ideal body size that is larger than one’s current body size and self-report of healthy weight control behaviors, whereas in girls, predictors of steroid use are low satisfaction of weight and high BMI. (3)
- Strong evidence suggests that risk factors for steroid use include: peer pressure, media exposure, parental pressure, a history of depression, a negative body image, and a tendency to compare one’s own body with those who are known users of steroids. (3)(4)(5)(15)

Suggested Reading

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PIR Quiz

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New Minimum Performance Level Requirements

Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based continuing medical education activities that are certified for *AMA PRA Category 1 Credit™*. To successfully complete 2012 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

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1. You are seeing a 16-year-old girl for a sports physical examination. Her older brother used anabolic steroids to enhance his performance on his football team. The boy had significant adverse effects and no longer uses the drugs. The family would like to make sure the daughter does not use any drugs to enhance her sports performance. You discuss the risk factors for the use of performance-enhancing drugs (PEDs). You are most likely to tell the mother that the condition most predictive of her teenage daughter using PEDs is the girl having a:
 - A. Critical view of the portrayal of women in the media.
 - B. Desire to be team captain.
 - C. High BMI.
 - D. Longstanding eating disorder.
 - E. Self-report of healthy weight control behaviors.
2. A 16-year-old boy sees you for a sports physical. Since his last examination 1 year ago, he has gained 15 kg. On physical examination, he has gynecomastia and papular acne. Laboratory screening reveals elevated triglycerides and low high-density lipoprotein cholesterol levels. Of the following, the PED you suspect this young man is taking is:
 - A. Androstenedione.
 - B. Creatine supplement.
 - C. Erythropoietin.
 - D. Human growth hormone.
 - E. Stimulant medication.
3. A 15-year-old boy has fatigue and complains of abdominal cramping and intermittent diarrhea. He has mild edema on physical examination. His mother is concerned that he is working too hard to keep up on the school wrestling team. Of the following, the PED you suspect this young man is taking is:
 - A. Anabolic steroids.
 - B. Creatine supplement.
 - C. Erythropoietin.
 - D. Human growth hormone.
 - E. Stimulant medication.
4. The effect most likely to be seen with the use of anabolic-androgenic steroids is:
 - A. Decreased nitrogen concentration in muscle.
 - B. Decreased fat-free mass.
 - C. Muscle mass increases through muscle hypertrophy.
 - D. Promotion of muscle breakdown.
 - E. Promotion of the binding of catabolic glucocorticoids to muscle.
5. A 16-year-old girl and her mother come to you because the mother is concerned that her daughter is taking PEDs. The girl runs long distance track and the mother has heard from other parents that the girls on the team are using drugs. The mother notes that the girl is doing well on the team, but she seems more anxious, is sleeping less, has lost weight, and has had frequent headaches. Of the following, the PED you suspect this young woman is taking is:
 - A. Anabolic steroids.
 - B. Creatine supplement.
 - C. Erythropoietin.
 - D. Human growth hormone.
 - E. Stimulant medication.

Performance-Enhancing Drugs
Christopher Dandoy and Rani S. Gereige
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