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Performance-enhancing drugs snare nonathletes, too

High school athletes aren't the only ones seeking an edge. Here are the red flags and unexpected drugs to watch for

Practice recommendations

- Multiple adverse effects, including serious cardiovascular effects, have prompted bans on the sale of anabolic androgenic steroids (AAS) and their use in competition (A).
- Most users of AAS and other performance-enhancing drugs are nonathletes or recreational body builders who begin using these substances in their teen years. Ask about steroid or supplement use during yearly physicals (C).

Strength of recommendation (SOR)

- A Good-quality patient-oriented evidence
B Inconsistent or limited-quality patient-oriented evidence
C Consensus, usual practice, opinion, disease-oriented evidence, case series

JC, a 23-year-old man, is in your office for evaluation of high blood pressure, after failing a commercial driver's license exam the previous week. He has been your patient for the past 10 years, and his previous annual physicals have been unremarkable. He is 5'10" tall, weighs 209 pounds, and has a muscular build. His blood pressure today is 160/90 and his heart rate is 62 and regular. The rest of his physical exam is normal.

He is a nonsmoker, rarely uses alcohol, and denies illicit drug use. He ex-

ercises regularly, has been taking some protein shakes and what he refers to as a "natural" supplement. His lab work shows some elevation in his aspartate aminotransferase (AST) and alanine aminotransferase (ALT), with a negative hepatitis panel. The rest of his metabolic panel is within normal limits.

JC was on the track team in high school, and since graduation has continued to work out and stay fit. You ask him if he takes steroids, and he tells you he was warned about the risks of anabolic androgenic steroids (AAS) in high school. He sticks to a "natural" supplement, which he buys online or through friends at the gym. Still, you know that elevated liver enzymes and hypertension can be associated with AAS use and that dietary supplements don't have to meet the same standards the Food and Drug Administration (FDA) imposes on drugs. (See "What's in that supplement? Labels don't always help" on page 18.) You warn him that supplements aren't always safe, and ask him to bring in his supplement bottle so you can go over the label and, possibly, have the contents tested.

Pursuit of that "edge" extends beyond Olympians

Even before the start of the modern Olympic games, athletes have used

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ergogenic aids—substances used to enhance performance, energy, or work capacity—to give themselves a “competitive edge.”^{1,2} Athletes still use these substances today, and they have been joined by nonathletes—some of whom simply want to look good.

A 2004 Internet study of AAS users reported that the majority are recreational bodybuilders or nonathletes. Twenty-five percent of participants in this survey reported starting using steroids during their teenage years.³

An ongoing study of high school students and young adults indicates an AAS use prevalence rate of 1.1% to 2.3% in boys and 0.4% to 0.6% in girls. Approximately 40% of survey participants noted that obtaining steroids was relatively easy.⁴

The Centers for Disease Control and Prevention (CDC) reports that 4.4% to 5.7% of boys (grades 9 through 12) have used illegal steroids and that 1.9% to 3.8% of girls have.⁵

Few AAS users tell their physicians of their steroid use. Part of the reason, of course, is that illegal substance use is stigmatized and can lead to prosecution. Another reason, though, is that these patients think physicians don't know much about these substances.³ Still other patients, like JC, don't tell because they may not even be aware that some substances billed as “natural” conceal potential dangers.

For help in spotting patients who are using these agents, see “Red flags for performance-enhancing drug use” on page 20.

■ Performance-enhancing drugs go by many names

Refining your care of patients who are taking performance-enhancing drugs requires that you know the various names these drugs go by, the reason your patients may be taking them, and the adverse effects associated with them. This review, and the **TABLE**, will help.

Anabolic androgenic steroids: Often paired with energy drinks

Teenagers may refer to AAS as “pumpers,” “gym candy,” or “juice.” Trade names for AAS are Dianabol, Anadrol, Deca Durabolin, Parabolin, and Winstrol. AAS are often used with nutritional supplements like creatine, multivitamins, and energy drinks, in the belief that these regimens will make the user stronger, more muscular, and a better athlete.^{6,7}

AAS are synthetic analogues of testosterone and come in oral, injectable, and transdermal forms.^{8,9} At supraphysiologic doses, testosterone has been found to increase lean body (fat-free) mass and muscle strength in humans.¹⁰ The anabolic effects are more pronounced when AAS are used at higher doses over longer periods of time, especially when combined with a strength training program.^{9,10} AAS have also been found to stimulate the production of growth hormone and insulin-like growth factor and to counteract the catabolic effects of cortisol.¹¹

The use and possession of AAS without a doctor's prescription is illegal in the United States. A majority of AAS users buy their medications through Internet suppliers, with some of the drugs being manufactured overseas or in illicit labs.³ Substandard quality control in manufacture poses an increased health risk to consumers.

Adverse effects include injection site pain, acne, baldness, gynecomastia, testicular atrophy, sexual dysfunction, and psychological disturbances (also known as “roid rage”).^{8,9,11-13} Increases in liver enzymes with the oral forms of AAS have also been noted.⁸ In the prepubertal athlete, premature physeal closure may occur, resulting in permanent short stature.¹⁴ Women who take AAS may have virilization effects, menstrual irregularities, and early menopause.¹¹

The cardiovascular risks of AAS use are substantial. High-dose and long-term AAS use has been linked to cardiomyopathy and sudden death.¹⁵⁻²⁰ Some data suggest the development of accelerated

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The combination of high doses of caffeine and ephedrine has a potential for life-threatening arrhythmia, hypertension, and stroke

What's in that supplement? Labels don't always help

Under the provisions of the 1994 Dietary Supplement Health and Education Act (DSHEA), supplement manufacturers, not the Food and Drug Administration (FDA), are responsible for guaranteeing the safety of their products.⁵² Components of the various supplements available are not uniform, and do not need to be submitted to the FDA for analysis. A study analyzing several nutritional supplements revealed the presence of anabolic androgenic steroids (AAS) (14.8% of 634 products) not mentioned in the labeling.⁵³

Using supplements can result in positive drug tests for banned substances and unwanted side effects. It is important to ask about supplement use during annual checkups and sports physicals—especially if the patient has unexplained high blood pressure or other somatic complaints.

atherosclerosis with AAS use, leading to hypertension, coronary artery disease (CAD), and acute myocardial infarction.^{15,16,18-21} An unfavorable lipid panel has also been noted, with an increase in LDL and decreased HDL.¹⁸⁻²¹

Tetrahydrogestrinone: A “designer” steroid

Tetrahydrogestrinone (THG) was initially developed to avoid detection by testing protocols current at the time.²²⁻²⁴ This drug has garnered significant media attention in the past few years because of scandals involving professional and Olympic athletes. THG is chemically related to 2 other banned steroids, trenbolone and gestrinone.^{22,24} It is used similarly to AAS to increase muscle bulk and enhance performance. It is more hepatotoxic than AAS, with highly potent androgenic and progestin properties in *in vitro* bioassay studies.^{22,25}

Marketing of this agent is banned in the United States. There are no long-term studies of its effectiveness or side effect profile.

Androstenedione: Initially an anti-aging drug

Androstenedione, aka Andromax and

Androstat 100, is a precursor of testosterone. This substance is produced in the adrenal glands and gonads.² Initially marketed as a dietary supplement and anti-aging drug, it was banned by the FDA in 2004 because of its potent anabolic and androgenic effects.²⁶ Ergogenic use includes promoting muscle building and strength and fat reduction.² Studies on healthy young men found no improvement in skeletal muscle adaptation to resistance training with androstenedione supplementation for 8 to 12 weeks.^{27,28} Studies of its effect on increasing blood testosterone levels are conflicting.^{27,29} Several studies noted an increase in estradiol levels after oral androstenedione supplementation.^{9,11,27-29}

Endocrine pathways with this drug are similar to AAS, and the side effect profile is similar as well, although not as pronounced. Larger, long-term studies are needed to fill out this drug's profile and document its effects on the athletes who use it.

Dehydroepiandrosterone: Marketed as a “wonder drug”

Dehydroepiandrosterone (DHEA), marketed under the names Prastera, Fidelin, and Fluasterone, is another precursor of testosterone. It is produced in the adrenal cortex and has weak androgenic properties.² DHEA is a dietary supplement marketed as a “wonder drug” and, like androstenedione, is advertised to promote muscle-building and fat-burning. It is also said to have anti-aging properties.^{11,14} DHEA has been used by athletes in the belief that it will increase testosterone levels and muscle bulk.³⁰

In studies done in healthy men, however, even large doses of DHEA (1600 mg/d) did not result in an increase in testosterone levels. An increase in estradiol levels was noted in elderly men. Women who supplement with DHEA were found to have increased levels of testosterone and virilization effects, even at small doses (25-50 mg/d).³¹ Because of the risk of these side

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TABLE

Performance-enhancing agents: What to watch for

DRUG/SUPPLEMENT	ERGOGENIC USE	ADVERSE EFFECTS	COMMENTS
Anabolic androgenic steroids (AAS)	<ul style="list-style-type: none"> • Increase lean muscle mass at supraphysiologic doses • Increase protein synthesis • Stimulate production of growth hormone • Decrease perception of fatigue 	Acne, gynecomastia,* testicular atrophy,* virilization in females,* premature physeal closure, elevated liver enzymes, increased aggression, hypertension, CAD, sudden death	<ul style="list-style-type: none"> • Polypharmacy with other ergogenic agents and anti-estrogens is common • Possession and use are against the law, and athletes found to be using AAS are banned in competition by sports authorities
Tetrahydrogestrinone (THG)	Data on ergogenic use are insufficient	Hepatotoxicity; side effect profile probably similar to AAS	<ul style="list-style-type: none"> • Evidence on effectiveness and side effects is insufficient • Use is illegal
Androstenedione (Andro)	Increase testosterone levels in order to build muscle	Increased estradiol levels, feminization, priapism; side effect profile probably similar to AAS	<ul style="list-style-type: none"> • Conflicting evidence on how drug affects testosterone levels • Banned in competition by sports authorities
Dehydroepiandrosterone (DHEA)	Increase testosterone levels for anabolic effects	Increased estrogen and estradiol levels, virilization, increased risk of endometrial cancer in females	<ul style="list-style-type: none"> • Insufficient evidence to support claims as an anabolic or anti-aging agent • Sold as a supplement but banned for use in competition
Human growth hormone (HGH)	Increase protein synthesis and muscle mass without unwanted androgenic effects, decrease body fat	Insulin resistance, premature physeal closure, acromegaly, hypertension, cardiomegaly	<ul style="list-style-type: none"> • Insufficient evidence that use enhances athletic performance • Expensive • Usually used in addition to AAS • Banned for use in competition
Ephedrine	Weight loss, increase energy, increase concentration	Anxiety, panic attacks, hypertension, tachycardia, MI, stroke	Banned by the FDA because of cardiovascular and stroke risk
Caffeine	Increase alertness and energy, weight loss, improve endurance	Agitation; potential for withdrawal symptoms; hypertension, arrhythmia, and stroke when used with ephedrine or other stimulants	Urinary threshold in NCAA and Olympic competition
Erythropoietin (EPO)	Increase oxygen-carrying capacity of blood in endurance athletes	Pulmonary embolism, MI, stroke, development of anti-EPO antibodies	Banned in all sports competition
Creatine	Increase production of ATP in skeletal muscle during anaerobic exercise	Muscle cramps, weight gain, minor gastrointestinal upset	<ul style="list-style-type: none"> • No long-term studies available • Not recommended in minors • Legally sold as a dietary supplement
Sildenafil	Vasodilation, increase oxygenation and exercise capacity	Headache, flushing, dyspepsia, blurring of vision	No action yet to ban in athletic competition

ATP, adenosine triphosphate; CAD, coronary artery disease; FDA, Food and Drug Administration; MI, myocardial infarction; NCAA, National Collegiate Athletic Association.

* These adverse effects may be irreversible.

Red flags for performance-enhancing drug use

- Rapid increase in muscle bulk and loss of body fat
- Unexplained high blood pressure, cardiomyopathy, or arrhythmia in a previously healthy adolescent or young adult
- Signs and symptoms of feminization in males or virilization in females
- Increased aggression, violent behavior, or insomnia
- Abnormal lab work, including increases in liver enzymes or hematocrit
- Polypharmacy or increased use of medications and dietary supplements.

effects and the lack of long-term studies, DHEA supplementation is not recommended for use by adolescents or women.³⁰ There is no convincing evidence to support claims of the anabolic and anti-aging effects of DHEA.

Human growth hormone: Side effects include hypertension

Human growth hormone (HGH) is an endogenous pituitary hormone with anabolic functions that increases muscle mass without the androgenic side effects. It is used medically for patients with decreased endogenous levels of GH or dwarfism. As an ergogenic aid, it has been found to increase levels of insulin-like growth factors, and the combination leads to increased protein synthesis and muscle mass.³²

Side effects of HGH include insulin resistance, GH-induced myopathy, and acromegaly-like effects.¹¹ There have been reports of hypertension, cardiomegaly, ventricular hypertrophy, and abnormal lipids with excessive use.^{19,33} Premature physeal closure may occur in the adolescent HGH user.⁸ It's unclear whether HGH actually enhances sports performance, because the evidence is insufficient.³⁴

Ephedrine: Used by hockey players

Ephedrine is a stimulant derived from the

herb *ma huang*. It goes by many names, among them Ma Huang, Bolt-ephedrine, Asia Black 25, Hot Body Ephedra, and Thin Quick. Its chemical structure is related to amphetamine. Among college athletes, ephedrine and amphetamine use is more common in power sports, those requiring increased concentration (eg, rifle shooting, fencing), ice hockey, and field sports.³⁵ Users feel less fatigue, experience bursts of energy, and lose weight.^{8,36}

Users may experience irritability, anxiety, insomnia, and tremors, especially if stimulants are used in conjunction with high doses of caffeine.^{35,37} Ephedrine stimulates the release of norepinephrine, which produces increases in blood pressure, peripheral vascular resistance, and heart rate. These norepinephrine effects are the proposed mechanism for reported cases of myocardial infarction, cerebral artery vasoconstriction, and stroke associated with ephedrine use.¹³

Marketing of dietary supplements that contain ephedrine has been banned by the FDA because of the stimulant's potential for increasing cardiovascular and stroke risks.³⁸

Caffeine: May give sprinters a leg up

Caffeine—which is found in everything from coffee to energy tablets and energy drinks—increases a person's energy level. In endurance sports, it also increases time to exhaustion.³² Studies in endurance-trained cyclists have shown that caffeine intake reduced leg pain, increased maximal leg force, and lengthened time to fatigue.^{39,40} A recent study in Australia also showed that caffeine may improve intermittent-sprint performance in competitive male athletes.⁴¹

Serious cardiovascular risks and even death have been documented when caffeine has been used with other stimulants, such as ephedrine or amphetamines. The combination of high doses of caffeine and ephedrine has a potential for life-threatening arrhythmia, hypertension, and stroke.⁴² Other

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Viagra is the latest entry in the list of drugs competitive athletes may be using to try to improve sports performance

psychomotor side effects include anxiety, irritability, tremor, and the potential for withdrawal symptoms.^{42,43} Because of caffeine's stimulant nature, the International Olympic Committee and the National Collegiate Athletic Association have set urinary thresholds for its use in competition.

Erythropoietin: Promotes endurance

Erythropoietin (EPO) is a hormone produced in the kidneys that stimulates production of red blood cells (erythropoiesis). Marketed under the brand names Epogen and Procrit, EPO has legitimate medical uses. As an ergogenic substance, EPO is used to promote endurance by increasing the oxygen-carrying capacity of the blood with the increased red blood cell mass. In endurance athletes, the benefits of recombinant erythropoietin (rEpo) may last several weeks.²³ There is also a practice called "blood doping," which is a transfusion prior to competition, to produce the same effect.

Adverse effects of EPO use are attributed to increased blood viscosity and thrombotic potential. Pulmonary embolism, stroke, myocardial infarction, and sudden death can occur.¹⁹ Cases of death due to severe bradycardia, usually occurring during the night, have also been reported.²³ Development of anti-EPO antibodies may also occur, causing paradoxical anemia.²³ Athletes found to be using rEPO are banned from competition by sports-governing organizations.

Creatine: Popular among body builders

Creatine is a popular supplement used by athletes and recreational bodybuilders to provide energy to skeletal muscles in short-duration, maximal exercise.⁴⁴ It is an endogenous substance found mainly in skeletal muscle and is synthesized by the liver from the amino acids glycine, arginine, and methionine.^{11,44} It is also found in meat.

Creatine monohydrate supplements

have been found to increase creatine stores in muscles.⁴⁵ In the phosphorylated form, creatine serves as a substrate for adenosine triphosphate resynthesis during intense anaerobic exercise.^{11,44-46} Numerous studies support its ergogenic effect on short-term, intermittent maximal activities such as bodybuilding, swimming, and jumping. Similar benefits have not been proven for endurance aerobic activities, such as long-distance cycling or running.^{46,47}

This supplement is sold in many forms under such names as Rejuvinox, Cell Tech Hardcore, Muscle Marketing, Femme Advantage, and NOZ. Although not recommended for those under age 18, creatine is actually used by approximately 5.6% of high school athletes, with the highest levels of use (44%) occurring in the 11th and 12th grades.⁴⁸ Reported side effects of creatine include muscle cramps, weight gain, and some minor gastrointestinal upset. Long-term studies on creatine supplementation are still needed.

Viagra (that's right, Viagra)

Viagra (sildenafil) is the latest entry in the list of drugs competitive athletes may be using to try to improve sports performance. The World Anti-Doping Agency is financing a study investigating whether sildenafil can create an unfair competitive advantage by dilating blood vessels and increasing oxygen-carrying capacity.⁴⁹ Studies of the impact of sildenafil on exercise capacity of climbers at the Mt. Everest base camp and on exercise performance during acute hypoxia have been published.^{50,51} Sildenafil was found to improve athletic capacity in both. To date, no action has been taken to ban the substance in athletic competition.

■ Are your patients using these agents? Ask them

Family physicians need to be alert to the red flags that may indicate steroid use and gently explore the full list of medications, over-the-counter products, and

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Web resources

www.usantidoping.org
 www.drugfreesport.com
 www.ncaa.org/wps/portal
 www.wada-ama.org
 www.steroidabuse.org/
 www.usdoj.gov/dea/pubs/abuse/10-steroids.htm
 www.fda.gov/fdac/features/1998/598_guid.html
 www.whitehousedrugpolicy.gov/streetterms/default.asp

dietary supplements patients may be using. Take advantage of annual checkups and sports physicals to ask about use of performance-enhancing substances, educate patients on the risks involved, and emphasize good nutrition and sensible exercise routines as healthy ways to build a strong, attractive physique.

Education was certainly in order for your patient, JC, described at the beginning of this article. He thought the dietary supplement he used was natural and therefore harmless. Not so. It contained potentially dangerous substances, so you advised him to stop using it. Nutritional counseling and a vigorous exercise routine have allowed JC to maintain his fitness ideal. His blood pressure and liver enzymes returned to normal levels, and he passed his commercial driver's license exam. ■

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Disclosures

The authors reported no potential conflicts of interest relevant to this article.

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Take advantage of annual checkups and sports physicals to ask about use of performance-enhancing substances

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