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INTRODUCTION — Some athletes take medications to attempt to improve their performance. They are motivated by a desire to win and the perception that certain medications improve performance. The focus of the general news media is on the athletes who are caught using these medications in popular sporting events, such as the Olympics, baseball, and the Tour de France bicycle race [1]. In comparison, the emphasis of the sports medicine literature is on methods of detection of the newest medications that athletes are using. The focus of this review is on the effects of these compounds that might be encountered by a physician who sees an athlete as a patient.

The United States Preventive Services Task Force found insufficient evidence to recommend for or against routine screening for drug abuse in adolescents, including abuse of anabolic steroids [2]. The American Academy of Family Physicians, American Medical Association Guidelines for Adolescent Preventive Services, and the American Academy of Pediatrics all suggest that clinicians discuss the dangers of drug abuse with children and adolescents and include questions about substance abuse as a part of routine adolescent visits.

Use of androgens and other drugs by athletes

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UpToDate performs a continuous review of over 350 journals and other resources. Updates are added as important new information is published. The literature review for version 14.1 is current through December 2005; this topic was last changed on October 26, 2005. The next version of UpToDate (14.2) will be released in June 2006.
HOW THIS AREA OF MEDICINE IS DIFFERENT—This area of medicine differs from most others because athletes who take medications to improve their performance do so surreptitiously. There are several consequences of the clandestine nature of this use:

- Athletes often obtain the medications from sources other than physicians.
- Athletes obtain their information about the medications from other athletes, trainers, magazines, underground publications, and the Internet.
- Athletes often take several medications simultaneously in an attempt to increase the overall effect on performance, or to counter a side effect of one medication with another medication. As an example, an athlete might take human chorionic gonadotropin (hCG) to counteract the decrease in testicular size resulting from high-dose androgen use, and take an antiestrogen to counteract the gynecomastia from administration of high doses of hCG.
- Athletes discontinue the medications periodically, often to avoid detection when they know they will be tested just before a competition.
- Physicians who see these athletes are often unaware that they are taking these medications.
- Physicians' knowledge of the possible effects of these medications is poor because the doses and even the medications used have rarely been studied in a controlled fashion.

EPIDEMIOLOGY—It is difficult to know how commonly athletes take these medications since they are so often taken surreptitiously. In fact, athletes use elaborate schemes to avoid detection.

Available information about prevalence comes from unannounced testing during training, testing at the time of competitions, and surveys of athletes.

- In a mail survey of 26 members of the United States Power Lifting Team, 10 replied that they had taken androgens, and 5 stated that they had been able to circumvent the International Olympic Committee's detection procedures [3].
- In a survey at 21 gymnasia in England, Scotland, and Wales, 9 percent of
1310 men and 2 percent of 349 women reported taking androgens [4].

- In a survey of 2547 16- to 18-year-old schoolchildren in South Africa, the reported prevalence of androgen use was only 1 percent overall; 3 percent in boys and 0.1 percent in girls [5].

- In a survey of 1881 schoolchildren ages 13 to 17 years in Richmond County, Georgia, 6 percent of boys and 2 percent of girls reported taking androgens without a physician's prescription [6].

ANDROGENS

Kinds of androgens— Virtually all androgens produced for human or veterinary purposes have been taken by athletes (show figure 1). These include testosterone esters, which are usually taken by injection, the 17-alpha-alkylated androgens, which are usually taken orally, and androgen precursors. Some athletes also take hCG, which acts like luteinizing hormone (LH) by stimulating the Leydig cells of the testes to secrete testosterone.

- The testosterone esters include the enanthate and cypionate, which are also used for hormone replacement. (See "Testosterone treatment of male hypogonadism").

- The 17-alpha-alkylated androgens were originally developed to have a greater anabolic to androgenic effect than testosterone, specifically a greater trophic effect on the levator ani muscle than on the ventral prostate in rats [7]. They were therefore given the name "anabolic steroids," which persists today. However, whether these compounds have a higher ratio of anabolic to androgenic activity than testosterone in humans is uncertain. Although there is only one androgen receptor [8], which is present in genital tissue, muscle, and many other tissues, there are many cofactors that influence the transcriptional activity of the androgen receptor, and these, called coactivators or corepressors, differ from tissue to tissue [9]. These coactivators and corepressors provide a theoretical basis for a compound to affect the androgen receptor in one tissue differently from the receptor in other tissues. Nevertheless, no compound has yet been found to have a greater anabolic effect than androgenic effect in humans, and therefore they will all be referred to here simply as androgens.
**Androgen precursors**— The androgen precursors include androstenedione and dehydroepiandrosterone.

- Androstenedione is available as an over-the-counter nutritional supplement, it is not regulated as are many other androgens, and it is widely promoted in body-building magazines. Administration of 300 mg of androstenedione once daily for one week to normal young men increased their mean serum testosterone concentration [10], but administration of 100 mg three times a day for eight weeks did not [11]. In a third study, in which 100 mg of androstenedione or placebo was given to normal men three times a day in a double-blind fashion for four weeks, the total testosterone concentration did not increase in the androstenedione-treated men, but free testosterone (measured by an analog assay, which may not be accurate), dihydrotestosterone, and estradiol did [12].

- DHEA is also available as a "nutritional supplement" and is widely touted in body building magazines as an agent that will increase muscle strength. It is not androgenic itself, but is converted to testosterone. When healthy young men were given either a placebo (n=5) or 50 mg (n=4) or 100 mg (n=5) daily for six months, serum concentrations of testosterone did not change, but serum concentrations of DHEA, DHEA-sulfate, and androstanediol glucuronide, a metabolite of dihydrotestosterone, did increase [13]. The clinical implications of these changes are as yet unknown.

- In a randomized, double-blind trial, 40 trained men (>1 year of weight training) were given DHEA (100 mg/day), androstenedione (100 mg/day), or placebo [14]. There were no changes in lean body mass or muscle strength in either treatment group when compared to placebo.

Other uses of DHEA are discussed elsewhere. (See "Dehydroepiandrosterone and its sulfate" and see "Treatment of depression in adults" section on Dehydroepiandrosterone).

**Efficacy** — It seems intuitive that androgens increase muscle mass and muscle strength, given the obvious differences between men and women. While exogenous testosterone administration results in increases in serum testosterone
concentrations and muscle strength, there is no evidence that androstenedione increases muscle strength.

- In one placebo-controlled, double-blind study of exogenous testosterone, 43 normal men were randomly assigned to one of four groups: strength training exercise with either 600 mg of testosterone enanthate once per week (about six times a replacement dose) or with placebo; or no exercise with either testosterone or placebo [15]. Testosterone treatment increased fat-free mass and muscle strength, more so in those who exercised simultaneously.

- In contrast, in a double-blind, placebo-controlled study in normal men, administration of 100 mg androstenedione three times daily for eight weeks did not increase muscle strength; however, serum testosterone concentrations were not increased by this regimen [11]. Similarly, in a placebo-controlled study of 50 healthy men ages 35 to 65 years receiving androstenedione or androstanediol (200 mg/day), neither hormone altered body composition or muscle strength compared with placebo [16].

**Side effects** — All androgens have some side effects when taken in high doses; other side effects depend upon the structure of the androgen or the steroids it is converted to. Some side effects occur only in women.

**Suppression of endogenous testicular function**— All androgens suppress gonadotropin secretion and therefore suppress endogenous testicular function. Spermatogenesis and fertility are greatly diminished by high doses of androgens, although the sperm count usually returns to normal within four months after discontinuation [17]. Testicular size may decrease if androgen administration continues for many years. Gonadotropin and testosterone secretion remain suppressed for a few months after androgens are discontinued.

**Gynecomastia** — Gynecomastia occurs because testosterone is converted to estradiol via the action of the aromatase enzyme complex, so that high doses of testosterone result in high serum estradiol concentrations. Androgens that have been 5 alpha-reduced, such as dihydrotestosterone and synthetic androgens in which the A ring has been modified, cannot be aromatized and therefore cannot be converted to estrogens and do not cause gynecomastia.

**Erythrocytosis** — Erythrocytosis is a common side effect of pharmacologic doses
of all androgens, probably due largely to direct androgen stimulation of erythropoiesis.

**Hepatotoxicity** — Hepatic side effects occur only with 17-alpha-alkylated androgens and include high serum concentrations of liver enzymes [18], cholestatic jaundice, and peliosis, characterized by blood-filled hepatic cysts [19]. Hepatomas have also been reported, but the number of cases is few and causality is uncertain.

**Psychological disorders** — Many psychological abnormalities have been described, both in the medical literature and anecdotally, in men taking high doses of androgens. Most descriptions are uncontrolled, although in one study an attempt was made to compare men taking and not taking androgens [20]. One hundred sixty men recruited from gymnasia responded to a questionnaire about androgen use and psychiatric symptoms. Psychiatric symptoms, including major mood disorders and aggressive behavior, were more common in the men who had taken androgens than in those who had never taken androgens, and among the former the symptoms were more common when they were taking androgens.

**Cardiac disease** — The effect of high doses of androgens on cardiac function is uncertain. Several case reports describe sudden death in young athletes who had no previously known heart disease but who were taking androgens; cardiac hypertrophy or myocarditis were found at autopsy [21,22]. It is not possible to establish causality in these sporadic cases. (See "Risk of sudden death in athletes").

There are also reports of left ventricular hypertrophy in body builders and power lifters, but most of these studies have not been randomized or controlled for degree of exercise, which itself can affect the degree of cardiac hypertrophy [23]. In one randomized, placebo-controlled trial, eight body builders treated with nandrolone decanoate showed no difference in several echocardiographic parameters at the end of eight weeks from those treated with placebo, but this study was limited by the small numbers of subjects and short duration [24].

**Serum lipids** — Although physiologic doses of testosterone have no consistent effects upon serum lipid concentrations, pharmacologic doses of androgens, especially 17-alpha-alkylated androgens, decrease serum high-density-lipoprotein (HDL) cholesterol and increase low-density-lipoprotein (LDL) cholesterol
concentrations [16]. In a study of normal men aged 30 to 56 years given androstenedione (300 mg/day for 28 days), serum HDL cholesterol concentrations decreased by 15 percent, a change that would predict an increase in risk of coronary heart disease [12].

**Coagulation activation**— Androgen administration is associated with activation of the hemostatic system. As an example, in one study of 49 weight lifters in whom androgen use was ascertained by history and urine testing, the confirmed steroid users had a higher percentage of abnormally high thrombin–antithrombin complexes in plasma than nonusers (16 versus 6 percent, p=0.01), higher plasma concentrations of prothrombin fragment 1 (44 versus 24 percent, p<0.001), antithrombin III (22 versus 6 percent, p=0.005), and protein S (19 versus 0 percent), and lower plasma concentrations of tissue plasminogen activator and its inhibitor [25]. The importance of hemostatic system activation with regard to risk of thrombosis is unclear.

**Virilization**— Because men are maximally virilized by physiologic amounts of testosterone, only women athletes are virilized by taking androgens. Specifically, they have facial and body hirsutism, temporal hair recession in a male pattern, acne, and clitoral enlargement.

**Premature epiphyseal fusion and stunting of growth**— Pharmacologic doses of testosterone hasten epiphyseal closure if taken by adolescents whose epiphyses have not yet closed naturally. The number at risk is illustrated by a survey of 873 Indiana high school football players randomly selected from 27 high schools throughout the state [26]. Six percent reported that they were current or former users of androgens; 50 percent first used the drugs before age 14 years and 15 percent before age 10 years.

**Infections**— Sporadic case reports describe infections due to injection of androgens, including local abscess at the site of injection, septic arthritis, and HIV infection from sharing of needles.

**Detection of use**— Exogenous administration of pharmacologic doses of androgens might be suspected in a man who competes in a sport in which excess androgens are perceived as improving performance and who have small testes, low sperm counts, high hematocrit and hemoglobin values, and low serum sex hormone-binding globulin concentrations. In a woman, androgen abuse might be
suspected in an athlete with hirsutism, balding, or acne. The diagnosis can be confirmed by one of several tests, depending upon the compound to be tested.

- Androgens other than testosterone can be detected by gas chromatography and mass spectroscopy if the athlete is still taking the compound(s) at the time of the testing.

- Testosterone taken exogenously cannot be distinguished from that produced endogenously, so other methods must be used. The conventional method is to determine the urinary ratio of testosterone to its endogenous epimer, epitestosterone. Normally the ratio is <6:1, but subjects taking exogenous testosterone, which suppresses the production of both testosterone and epitestosterone and replaces it only with testosterone, have higher ratios [27]. Another proposed method uses the ratio of testosterone to LH in the urine, which is high (>30) in subjects taking testosterone because it suppresses LH secretion [28].

- Athletes and those who supply them with androgens are ever attempting ways to avoid detection. The most common way is to discontinue the drug before testing will occur. Another way was first reported in the lay press in the fall of 2003 [29]. According to these reports, a private laboratory in the San Francisco area synthesized an androgenic steroid specifically designed to avoid detection. The drug was identified when a syringe filled with it was provided to the United States Anti-Doping Agency, which eventually determined that the drug was tetrahydrogestrinone. In February 2004, the president of the laboratory, a personal trainer of well-known athletes, and others were indicted by a grand jury for providing athletes with these drugs [30].

**OTHER DRUGS** — Some athletes take several other drugs in addition to androgens to enhance performance.

**Stimulants** — Stimulants, including amphetamines and caffeine, have been taken for years, but are not used commonly in competitions in which testing occurs since they are detected by standard tests. They still may be taken in less regulated events. Ephedra, which is banned by the United States Food and Drug Administration, is discussed in detail elsewhere. (See "Drug therapy of obesity").

**Erythropoietin** — Athletes have used recombinant erythropoietin because it
increases hemoglobin concentrations and therefore oxygen-carrying capacity. They hope that it will also improve performance. It was reported to be the "booster of choice" during the 1998 Tour de France bicycling race [31]. Both erythropoietin administration and blood doping increase exercise performance [32,33].

No side effects have yet been reported, but thrombotic events might be expected with long-term therapy, especially if the hematocrit is well above 50 percent, and is exacerbated by the dehydration associated with endurance sports [34].

The use of recombinant erythropoietin should be suspected in athletes if the hematocrit is above 50 percent in males and above 47 percent in females; however, there is substantial overlap with healthy controls [35]. As a result, tests for confirming erythropoietin use have been proposed:

- Elevation of the serum ratio of the soluble transferrin receptor to ferritin [36]
- The glycosylation pattern of commercially available recombinant erythropoietin differs from that of human serum erythropoietin, and can be detected by electrophoretic techniques [34,37]

**Growth hormone** — Athletes take recombinant human growth hormone because of its demonstrated effects on body composition (more muscle, less fat) and because it is not yet often tested for. Efficacy has not been demonstrated [38]. It would be expected to cause acromegaly if given in high doses long enough, but no such cases have been reported. In addition, epidemiologic data suggest an association between serum concentrations of insulin-like growth factor 1 (IGF-1) and cancer risk. (See "Risk factors for prostate cancer" section on Insulin like growth factor). Other adverse effects of growth hormone therapy in adults are discussed elsewhere. (See "Growth hormone deficiency in adults", section on Side effects).

Little information is available about the detection of growth hormone use by athletes. In a study in which two doses of growth hormone were administered to normal men and women for one month, the serum concentration of IGF-1 was a more sensitive indicator of the treatment than IGF binding protein-3 and was more sensitive in men than in women [39]. Two weeks after the end of treatment, however, the serum IGF-1 was only barely elevated in men and not at all in
women.

Biochemical markers of bone and collagen turnover may also be useful for detection of exogenous growth hormone use. As an example, in normal subjects, the recombinant growth hormone-induced increase in procollagen type III and osteocalcin persists for up to two months after treatment withdrawal [40].

**Insulin** — Athletes have also begun to use insulin because of its anabolic effects on muscle. In one survey of 20 men who were recruited from gyms and admitted to using androgens, 5 reported that they also used insulin [41]. They reported ingesting large amounts of sugar after insulin injection, but there have been reports of hypoglycemia in athletes who have taken insulin.

**Creatine** — The nutritional supplement creatine is taken by many professional, collegiate, and high school athletes. At one university, 48 percent of male and 4 percent of female athletes were chronically ingesting creatine supplements [42]. In a study of 328 male and female high school athletes, 27 (8 percent) reported taking creatine [43].

Some small studies suggest that creatine enhances performance in short-duration, high-intensity exercise, but other studies suggest it does not [44]. No studies suggest that it enhances performance in endurance sports. In a meta-analysis of 16 studies, creatine supplements combined with resistance training increased the maximal weight that young men (<36 years old) were able to lift (bench press and squats) [45]. There was no effect in women and older men, and performance of other types of muscular effort did not improve.

Side effects include weight gain, and possibly acute interstitial nephritis and more rapid progression of renal disease [46,47].

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**REFERENCES**


