Supplements and drugs used to enhance athletic performance

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Our society is founded on competition and places immense value on success. A brief look at the salaries of our professional athletes in recent years supports this. At the highest levels, winning or losing can be the difference in multi-million-dollar salaries, product endorsements, and scholarships. These pressures have led to a “win at all costs” mentality. Millions of athletes at every level of competition look for that “edge,” sometimes even illegally and without much regard to safety. In a survey of Olympic hopefuls, 98% reported they would use a banned substance if it were absolutely undetectable and guaranteed victory [14,112]. In fact, greater than 50% reported they would use the same undetectable substance if it would allow them a winning edge for 5 years but then resulted in death.

Adolescents are not immune from these pressures. Winning brings admiration from their peers, praise from their parents and coach, and opportunities to compete at the next level. They also see their heroes on television returning gold medals because of banned-substance use or breaking home run records after supplement use. Perhaps this is why more and more adolescents are trying performance-enhancing drugs. Adolescents often hope that performance-enhancing drugs will increase their competitive edge or make them more attractive [11].

Numerous substances claim performance-enhancing qualities. Some are illegal, and many are banned by major sports governing bodies. A large number are sold as dietary supplements. Since the passage of the Dietary Supplement Health and Education Act in 1994, the US Food and Drug Administration (FDA) is no longer responsible for guaranteeing the purity or safety of these substances. Often, supplements have very little proof of efficacy for their claims. Persons of any age can easily purchase these “natural” substances at health food stores.
Unfortunately, many people equate “natural” with “safe” and practice the philosophy of “if some is good, then more is better.” Despite the popularity of dietary supplements, it is imperative to remember that neither the performance-enhancing effects nor the safety of these substances has been studied in the pediatric and adolescent populations. This article covers four of the more popular performance-enhancing drugs: anabolic-androgenic steroids, prohormones, creatine and ephedra alkaloids (see Table 1).

**Anabolic–androgenic steroids**

*Physiology*

Anabolic–androgenic steroids (AASs) are synthetic derivatives of the natural hormone testosterone and represent some of the oldest performance-enhancing drugs. AASs have three proposed mechanisms of performance enhancement: anabolic, anticatabolic, and motivational. At physiologic doses, AASs have anabolic effects much like natural testosterone. AASs bind to testosterone receptors within the cell cytoplasm, enter the cell nucleus, and bind to specific sites on the DNA. This binding influences the type of enzymes and proteins ultimately produced by the cell [135]. In skeletal muscle cells, this binding promotes a positive nitrogen balance [135], which in turn may increase muscle mass and strength. However, this mechanism does not account for all of AAS effects because normal adult male testosterone levels nearly saturate their receptors [135]. At supra-physiologic doses, the anticatabolic effects of AAS are thought to be more important [62,136]. As the stress of training increases, the body releases higher levels of glucocorticoids [3,15]. In an “overtrained” state, this promotes a negative nitrogen balance within skeletal muscle that diminishes the anabolic benefits of training. In other words, strength gains “plateau” as the stress of training reaches a certain intensity. At high levels, AASs have saturated the anabolic binding site and begin to compete with glucocorticoids. Displacement of glucocorticoids from their binding sites reduces their catabolic effect and once again a positive nitrogen balance is promoted [135,136]. Lastly, AAS use is believed to cause increased aggression that may lead to motivational effects. Increased aggression may allow the user to train harder and longer and hence see more benefit than the nonuser.

*Clinical use*

Historically, AASs have had clinical usefulness in a limited number of settings. One of the earliest uses was to promote positive nitrogen balance in concentration camp survivors [90]. Since then, AASs have been used to treat refractory anemias, hereditary angioneurotic edema, breast cancer, and even osteoporosis [90,135]. To date, the most practical use of AASs is replacement therapy in males with congenital hypogonadism [90,135]. Unfortunately, some individuals use AASs solely for performance or body image enhancement.
Efficacy in performance enhancement

After initial skepticism, the medical community has come to agree that AASs can increase both muscle mass and strength [6,20,62,67,112]. Early studies of AAS effects on muscle mass and strength had equivocal results, and many in the medical community doubted any performance-enhancing effect [5]. On the other hand, athletes using AASs insisted that their performance was improved [43,62]. Haupt and Rovere [62] reviewed the early studies and found that differences in the subjects might have biased the results. Studies in which the subjects had trained heavily before AAS use and continued to train during AAS use were more likely to show significant increases in strength and body weight. Individuals involved in weight training are more likely to be in an overtrained state with a negative nitrogen balance before starting AAS use. Therefore, they would see the greatest benefit from the AAS antistriatal effects. In addition, more recent research demonstrates that supraphysiologic AAS doses do indeed increase muscle mass and strength. Bhasin et al. [19] controlled the diet and training intensity of men with previous weight-training experience and randomized them into groups of supraphysiologic AAS doses or placebo. They found a significant increase in body weight and lower extremity strength in the AAS group undergoing weight training. They also found that supraphysiological doses of AAS have anabolic effects without weight training. Nevertheless, the most profound effect seems to occur when high doses are used by individuals who have trained heavily before use, continue to train during use, and maintain a diet adequate in calories and protein [6,19,62]. Therefore, if strength and body mass are important to an athlete’s sport, then AAS use will theoretically enhance their performance. However, only an increase in maximal single lift strength has been shown, and improvement in performance during actual competition has never been studied. In addition, aerobic and endurance activities are not enhanced [5,6,62], and any strength gains are lost after a period of cessation [63].

Adolescent use

Despite AASs being illegal and having potential health risks, adolescents continue to report using them. The first report of adolescent AAS use was in 1959 by a high school football player [112]. Since then, there have been dozens of surveys documenting self-reported AAS use at the college, high school, and even junior high levels [30,40,46,68,107,115,139]. Through the early 1980s, one in five National Collegiate Athletic Association (NCAA) Division I athletes reported AAS use [39]. Since the NCAA began testing players for AAS use in 1986, the prevalence of reported use among NCAA athletes has decreased [92]. Prevalence of AAS use in US high schools ranges from 4% to 11% in males [4,11,30,40,68,107,115,139] and up to 2.5% in females [11,40,46,115]. A nationwide survey in 1987 found that 6.6% of male high school seniors have used AASs [30]. Two thirds of adolescent users started by age 16 years [30]. Trends from national data between 1991 and 1995 had shown that high school AAS use
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<th>Benefits</th>
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<td><strong>AAS</strong></td>
<td><strong>Cardiovascular</strong> — adverse changes in lipid profile and elevation of blood pressure</td>
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<td></td>
<td><strong>Hepatic</strong> — enzyme elevation, jaundice and possibly malignancy</td>
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<td></td>
<td><strong>Musculoskeletal</strong> — epiphyseal fusion and decreased tensile strength of tendons</td>
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<td></td>
<td><strong>Psychiatric</strong> — multiple effects including potential addiction and dependence</td>
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<td><strong>Banned by all major sports governing organizations</strong></td>
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<tr>
<td></td>
<td><strong>Purchased OTC as dietary supplement</strong></td>
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<td><strong>Not recommended</strong></td>
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**Andro/DHEA**
- **Andro** — Doses up to 100 mg do NOT increase testosterone production or strength.
- **Andro** — Higher doses might increase androgens at higher doses.
- **DHEA** — Does NOT increase testosterone.

**Side effects**
- Adverse changes in lipid profile.
- Effects of increased estrogens.
- Possibly cause effects of increased androgens at higher doses.
- May promote growth of hormone sensitive malignancies.

**Current recommendations and legal issues**
- **ILLEGAL and punishable as a felony**
- **Banned by IOC, NCAA, NFL and recently NBA**
- **Purchased OTC as dietary supplement**
- **Not recommended**
<table>
<thead>
<tr>
<th>Supplement</th>
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<tr>
<td>Creatine</td>
<td>- DOES increase work capability over brief, repetitive, maximal exertion&lt;br&gt;- Does NOT improve endurance or maximal exertion over 60 seconds&lt;br&gt;- Individual response varies with “responders” and “non-responders”&lt;br&gt;- No additional benefit for doses above 20 g/d x 4 day load or 2 g/d maintenance&lt;br&gt;- Appears relatively safe in small number of studies&lt;br&gt;- No good information of long-term use, especially on heart and brain&lt;br&gt;- No information in growing adolescents&lt;br&gt;- Early weight gain from water retention&lt;br&gt;- Anecdotal reports of cramping and hydration issues&lt;br&gt;- Sporadic reports of reversible renal problems&lt;br&gt;- NOT banned by many sports governing organizations&lt;br&gt;- Purchased OTC as dietary supplement&lt;br&gt;- ACSM does NOT recommend for adolescent population&lt;br&gt;- Use with caution in adults</td>
</tr>
<tr>
<td>Ephedra</td>
<td>- Does NOT improve endurance or weight loss when used alone&lt;br&gt;- Seems to improve endurance when combined with caffeine&lt;br&gt;- Seems to improve weight combined with caffeine in obese persons on dietary restrictions&lt;br&gt;- No studies of weight loss when combined with caffeine in lean athletes&lt;br&gt;- Linked to serious adverse cardiovascular and CNS events such as hypertension, stroke and sudden death&lt;br&gt;- Effects potentiated by addition of caffeine&lt;br&gt;- Combination of ephedrine and caffeine considered unsafe by FDA&lt;br&gt;- Systematic use banned by IOC and NCAA&lt;br&gt;- Combinations of herbal forms of ephedra and caffeine found in OTC supplements NOT recommended</td>
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AAP = American Academy of Pediatrics; AAS = anabolic–androgenic steroids; ACSM = American College of Sports Medicine; Andro = androstenedione; CNS = central nervous system; DHEA = dehydroepiandrosterone; FDA = US Food and Drug Administration; IOC = International Olympic Committee; NBA = National Basketball Association; NCAA = National Collegiate Athletic Association; NFL = National Football League; OTC = over the counter.
by males had been stable, whereas female use had increased and in some cases was statistically significant [139]. However, more recent data suggest that AAS use by males is again on the rise [11]. At the junior high level, AAS use among seventh graders is approximately 2.5% [46,107].

A “partial profile” of the adolescent AAS user has been described [11]. Some risk factors are clearly associated with AAS use. First, males are two- to threefold more likely to use AASs [11,40,107,115], and users are significantly more likely to use other illegal drugs, including injected substances [11,40]. In addition, users are more likely to participate in school sports, especially strength-dependent sports, such as football and wrestling [11,30,107,115,140]. Nevertheless, a surprising 30% to 40% do not participate in a school sport [11,30,40,68]. The most common reasons for AAS use are to enhance sports performance and improve appearance [11]. Other risk factors have been proposed but are less clear. These include a higher socioeconomic status, poorer academic performance, poorer body image, and higher rates of self-reported violence and aggression [11]. In addition, there may be a family history of substance abuse [86] and less parental influence not to use drugs [44].

**Dosage**

AASs used by individuals for performance-enhancing reasons most commonly come in two forms: oral and injectable (see Table 2). Transdermal forms also exist, but there are no reports of their use by athletes. Oral preparations are quickly absorbed over several hours and relatively quickly eliminated over several days. Injectable forms are longer acting but may be detectable for several months. AASs are often used in the off-season to avoid detection at competition. Typically, users

<table>
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<tr>
<td>Methandrostenolone</td>
<td>Dianabol</td>
</tr>
<tr>
<td>Stanozol</td>
<td>Winstrol</td>
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<tr>
<td>Oxandrolone</td>
<td>Oxandrin</td>
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<tr>
<td>Methyltestosterone</td>
<td>Android, Virilon, Testred</td>
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<tr>
<td>Fluoxymesterone</td>
<td>Halotestin</td>
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<tr>
<td>Oxymetholone</td>
<td>Anadrol, Anapolon</td>
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<tr>
<td><strong>Generic names</strong></td>
<td><strong>Trade names</strong></td>
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<tr>
<td></td>
<td>Deca-durabolin, Neo-durabolin, Hybolin decanoate, Androlone-D, Durabolin, Hybolin</td>
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<tr>
<td></td>
<td>Testosterone enanthate, Delatestyl, Andro LA, Durathate, Everone, Testex</td>
</tr>
<tr>
<td></td>
<td>Testosterone propionate, Testcortic, Depo-testosterone, Duratext</td>
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take AASs in 4- to 12-week cycles to minimize side effects [90,138]. In addition, they often use several different oral and intramuscular preparations simultaneously in a practice referred to as stacking. The goal of stacking is to maximize AAS receptor binding in hopes of improving overall effect, but this has not been scientifically proven [138]. As a user feels strength gains beginning to plateau, they may increase the total dose or change the combination of AASs as the cycle progresses. Then, near the end of a cycle, the user will taper the dose. This practice is referred to as pyramiding, and the tapering may help to reduce withdrawal symptoms [67,138]. Medically indicated testosterone replacement for hypogonadal males is 6 to 10 mg/d [135]. Abusers can reach 40 to 100 times larger doses during a cycle [90,138].

Clinical presentation

Because puberty is a time of increased endogenous testosterone production, detecting outward signs of AAS use in a male adolescent may be difficult. Acne, deepening voice, weight gain, and gynecomastia are similar to that seen in puberty. Red flags include hypertension, receding hairline, prolonged gynecomastia, aggressive behavior, depression, and testicular atrophy. In females, menstrual irregularities and virilization should raise the index of suspicion. Unfortunately, commonly ordered laboratory tests cannot reliably confirm AAS use.

Adverse effects

AASs have been associated with a vast number of adverse effects. A lot of data about adverse effects in AAS abusers are from case reports or from performance studies. The bottom line is that no one knows the extent of adverse effects of AASs taken in the doses and duration by abusers.

Endocrine/reproductive

Being synthetic “male” hormones, AASs have obvious endocrinologic effects. In males, increased levels of AASs cause feedback inhibition of gonadotropin-releasing hormone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) release from the hypothalamus and pituitary [20,62,135]. Therefore, although there are high levels of androgenic substances in the blood, the decreasing LH and FSH levels cause testicular atrophy, altered spermatogenesis, and infertility. These changes are directly related to the dose and duration of AAS use but also appear to be reversible after several months’ cessation [20]. In addition, when levels of AASs are elevated, they begin to undergo aromatization to estrogens in peripheral tissues [90,135]. These rising estrogen levels can cause irreversible gynecomastia [4,112,135]. In females, increased levels of AASs cause menstrual irregularities and breast atrophy. They also have virilizing effects, such as male-pattern baldness, deepened voice, hirsutism, and clitoromegaly. Some of the virilizing effects are irreversible [4,135]. In prepubertal male users, AAS
can trigger precocious puberty [112]. In skeletally immature users, after an initial acceleration of linear skeletal growth, a premature fusion of growth plates and a reduced final height can occur [4,135].

Cardiovascular

AASs have been associated with significant cardiac adverse effects, ranging from altered lipid levels and hypertension to myocardial infarction and sudden death. AAS use clearly causes adverse lipid changes [4,20,90,101,135]. High-density lipoprotein can be decreased up to 52%, and low-density lipoprotein, increased up to 36% [49]. Both systolic and diastolic blood pressure at rest and during exertion may be elevated [104]. The heart undergoes structural changes during AAS use: The left ventricle is seen thickened on echocardiography, but the cause of this change is unknown [20,38]. AAS use has been associated with an increased risk for thromboembolism, although no direct evidence shows that they are thrombogenic [20].

Hepatic

Oral forms of AAS are particularly likely to cause hepatic damage. They can cause cholestasis [67,135] with increases in alkaline phosphatase, liver isozymes of lactate dehydrogenase (LDH), and conjugated bilirubin [67]. Increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) also can occur but are nonspecific because aggressive weight training alone can be the cause [62,112]. More severe hepatic effects from prolonged use of oral AASs, such as peliosis hepatis (blood-filled cysts within the liver) and liver tumors, have been reported but are rare [5,6,62].

Musculoskeletal

AAS use has led to structural dysplasia of collagen fibrils resulting in decreased tensile strength of muscle–tendon units in animal studies. This effect seems augmented when coupled with the increased tendon stresses of regular exercise [87,88]. Therefore, athletes using AASs may suffer more strains or ruptures, and cases of significant tendon rupture have been associated with use [35,127].

Psychological

The most concerning societal effect of AAS abuse is increased aggression. This occurs on the playing field, in the weight room, and in the athlete’s personal life [84,113]. Libido changes, coupled with aggression, might result in aggressive
sexual behavior [113]. AASs have been shown to affect positive mood (euphoria, energy, sexual arousal), negative mood (irritability, mood swings, hostility, depression), and cognitive impairment (distractibility, forgetfulness, confusion) [20,113]. Finally, AAS use can lead to dependence and addiction. When users’ motivation is enhanced performance or appearance, they often become distressed as improvements from AAS diminish after cessation. This can lead to and reinforce repeated use just to maintain initial AAS effects [24,74,140]. In a study of Australian bodybuilders using AASs, 23% met DSM-IV criteria for dependence, and another 25%, for abuse [33]. In addition, a withdrawal syndrome characterized by depression is well recognized [25,74].

Legal aspects

Nonmedical AAS use or possession has been illegal since 1988. In 1990, the Anabolic Steroids Control Act made AASs a Schedule III substance, making it easier to investigate and prosecute offenders [139]. Nonmedical possession is punishable with 1-year incarceration with or without a minimum $1000 fine, and intent to sell is a felony [8,139]. AAS use has been banned by all of the major sports governing organizations, including the International Olympic Committee (IOC), NCAA, and National Amateur Bodybuilders Association. The American Academy of Pediatrics and the American College of Sports Medicine (ACSM) both condemn the use of AASs for enhancement of athletic performance [4,6]. Despite this, AAS use continues among adolescents.

Prevention

Attempts to prevent adolescents and young athletes from the use and abuse of AASs require a balanced approach, including the following.

Education

Athletes are more likely to change their attitudes regarding AAS use if both the risks and the benefits are discussed rather than stressing only the adverse events [50]. Educational programs are important within the medical community as well. The most common medical contact for the user is the general practitioner (family practitioner, pediatrician, internist). Unfortunately, knowledge among medical practitioners is limited, and thus credibility among athlete and AAS users is compromised [55,106].

Research

Many questions about dosages, effect on performance, and side effects are still unclear. Continued studies will allow physicians to more confidently address education issues with athletes with the support of the scientific community.
Drug testing

More questions than answers exist as to how and when to use drug testing as a deterrent to the use of illegal performance-enhancing drugs and supplements. Detection of anabolic steroids in urine sample is a difficult task. The only accepted method for AAS analysis is gas chromatography/mass spectrometry. In 1996, the IOC introduced the use of high-resolution mass spectrometry. This combination is both sensitive and specific [21]. Because the imposition of sanctions is dependent on accurate drug testing, the use of witnessed urine samples and chain of custody is standard procedure in the collection of random drug-test samples.

Sanctions

For drug testing to be effective as a deterrent, sports governing organizations must set up penalties for violations. It is essential for these governing bodies to have policies for procedures and an appeals process. Punishment often includes rehabilitation programming at some level.

Current medical recommendations

AASs have a very unfavorable risk–benefit ratio with both reversible and irreversible side effects proven through scientific research. Outward clinical signs make the use of AASs recognizable to knowledgeable clinicians. Further nonmedical use of AASs is illegal and punishable as a significant offense. Finally, drug testing and athletic sanctions make its use in athletic competition a form of unethical cheating at all levels of sports participation.

Androstenedione and dehydroepiandosterone

Physiology

Androstenedione (“andro”) and dehydroepiandrosterone (DHEA) are precursors in the endogenous production of testosterone and sometimes referred to as prohormones (see box). DHEA is converted into androstenedione, which in turn can be converted into testosterone (Fig. 1). By themselves, andro and DHEA have very few anabolic–androgenic properties [2,135] and therefore are not considered AASs. The theory behind their use as performance-enhancing agents is to boost the body’s production of testosterone by increasing the concentration of testosterone precursors. In this manner, the user should gain anabolic benefits similar to those of AASs. The extent of prohormone use among adolescents is not known, but given their over-the-counter (OTC) availability as a dietary supplement, the prevalence is likely greater than reported AAS use. In addition, the popularity of prohormones skyrocketed after slugger Mark McGwire broke the major league home run record while admitting to using andro.
**Efficacy in performance enhancement**

Studies of androstenedione do not demonstrate any performance enhancement yet. An initial study in 1962 showed an increase in serum testosterone levels in two females [85]. Since then, several studies have shown that andro supplementation in men does increase serum androstenedione levels but does not significantly change testosterone levels [12,23,26,76,103,130]. Although andro had no effect on testosterone, many studies found significant increases in estrogen levels [12,23,26,76,83,103], presumably from peripheral conversion via aromatase enzymes. Moreover, andro supplementation did not increase muscle strength.

![Steroid syntheses pathway](image)

**Fig. 1.** Steroid syntheses pathway. (DHEA = Dehydroepiandrosterone).
and showed a trend toward a net negative skeletal muscle protein balance [103]. Even a study of an OTC supplement containing androstenedione, DHEA, and inhibitors of aromatase enzymes still showed an increase in estrogens without any effect on testosterone, muscle strength, or muscle histochemistry [26].

Still, the medical community must not make the same mistakes it did with early AAS studies and dismiss the effect of androstenedione yet. One study has shown that higher doses of andro (300 mg) did produce significant increases in testosterone over an 8-hour period [83]. However, the absolute increase in testosterone was to the upper limits of normal for men (only 4 of 14 with values slightly above normal), and their estrogen levels were even greater than those of the low-dose group (100 mg/dose). This study did not look at strength changes at higher doses. Another potential problem with current studies is the selection of subjects without recent weight-training experience [23,26,76]. Starting supplementation at a strength gain “plateau” is known to be important for detecting significant strength changes with AAS use [62]. However, the bottom line is that current evidence shows only significantly increased estrogen levels with no changes in testosterone or strength from andro use. Even if larger andro doses do increase testosterone levels, the mild effect is doubtful to be of any significance to performance.

DHEA has even less convincing data for performance enhancement. Most studies have been done on aged populations whose DHEA levels are naturally lower [1]. Studies of DHEA supplementation in young individuals show a significant increase in both DHEA and androstenedione levels but no change in testosterone levels [26,27,93,130]. In addition, DHEA supplementation of up to 150 mg/d does not significantly change muscle mass or strength [26,27,93,130,133].

Adverse effects

Adverse effects of androstenedione and DHEA, especially with long-term use, are not well known. Short-term use of andro has caused adverse changes in lipid profile [23,26,76]. Reports of virilizing effects in women have been reported with DHEA use [1]. With clear proof that even relatively low doses of andro significantly increase estrogen levels, side effects of elevated estrogen should be expected. Concern has been raised that long-term use could induce hormone-sensitive malignancies [1,2,26]. Also, if higher doses of prohormones were to significantly increase endogenous androgens, adverse effects similar to AAS use, such as irreversible gynecomastia, virilization, and premature epiphyseal fusion, would be expected [2]. Lastly, impurities in the preparation or metabolic products from prohormones themselves can cause an individual to test positive for anabolic steroid use [41,122].

Legal aspects

Because prohormones do not meet criteria for true AASs, they are not illegal. However, several major sports governing bodies ban the use of prohormones.
This list includes the IOC, NCAA, National Football League, and National Basketball Association. In addition, the FDA has not approved either androstenedione or DHEA for any indication [1,2]. Despite this, the 1994 Dietary Supplement Health and Education Act allows both of these prohormones to be sold over the counter as dietary supplements. Therefore, these substances are readily available to adolescent populations.

**Current medical recommendations**

Prohormones do not work “as advertised.” At best, andro transiently increases testosterone levels to the upper limits of normal. However, both andro and DHEA have consistently failed to improve performance in any study. The only effect that prohormones are proven to have is a substantial increase in female hormones. In addition, impurities in prohormone preparations have led to positive AAS testing. Current evidence shows that andro and DHEA do not enhance performance.

**Creatine**

*Physiology*

Creatine (see box) is a nonessential protein derived from arginine, glycine, and methionine. The liver, kidneys, and pancreas endogenously synthesize creatine at a rate of 1 to 2 g/d [13,132]. An additional 1 to 2 g/d is obtained in the average diet, mostly from fish and meat. These endogenous and exogenous routes combine to meet the average person’s daily requirement of 2 g/d [61,78]. Approximately 95% of the total body creatine is found in skeletal muscle, and the rest is found in the heart, brain, testes, retina, and other tissues [131]. Creatine is converted to creatinine in skeletal muscle, which in turn is excreted by the kidneys at a rate of 2 g/d [132]. It is important not to confuse creatine with creatinine.

Within skeletal muscle, creatine plays an essential role as an initial energy source for muscle contraction. Creatine is in reversible equilibrium with phos-

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phosphocreatine (PCr) as shown in Fig. 2. Muscle requires adenosine triphosphate (ATP) for energy but maintains only enough ATP stores for approximately two seconds of contraction [31]. As ATP stores are depleted during intense muscle contraction, phosphocreatine is sacrificed into creatine and ATP. This conversion is the major contributor to muscle energy during the first 10 to 20 seconds of maximal anaerobic exertion [65,110]. After 10 to 20 seconds, anaerobic glycolysis and aerobic oxidative phosphorylation become more important sources of ATP [7,65]. During recovery from exertion, aerobic pathways predominate, and large amounts of ATP are generated. In this environment, the equilibrium is reversed, and phosphocreatine is replenished relatively quickly. In fact, more than 90% of PCr is resynthesized after 3 or 4 minutes [60,116]. In summary, PCr is an important source of energy during the initial seconds of maximal anaerobic exertion and is quickly replenished by aerobic pathways during recovery.

The goal of creatine supplementation is to maximize muscle stores of creatine and phosphocreatine. Higher PCr stores create higher substrate availability and should allow for quicker generation of ATP during the first 10 to 20 seconds of maximal exertion [7,31,110]. Also, higher creatine levels should allow quicker replenishment of PCr during recovery [31,53]. There is also a potential for buffering of lactic acid and thereby delaying fatigue [7].

**Efficacy in performance enhancement**

Reviews of creatine supplementation found some performance-enhancing qualities in certain situations [7,31,70,72,78]. The most consistent benefits are in repetitive, brief, high-power exercise [7,70,72]. Specifically, an increased total work and power can be generated over repeated 6- to 30-second bouts of maximal exertion interspaced with 20 seconds to 5 minutes recovery under laboratory conditions [72]. However, the effect of creatine use on initial, single-bout performance has been inconsistent [70,72]. The few studies that demonstrate an improvement in first-bout exertion were actually designed to assess performance over multiple bouts [72]. In addition, creatine shows no enhancement of maximal exercise lasting longer than 60 seconds [7,31,70,72,78], likely because phosphocreatine becomes an insignificant source of energy after the first 20 seconds [72,110]. Likewise, the exertion must be anaerobic and maximal. Endurance and submaximal exercise are not improved because the aerobic pathway supplies the majority of energy [7,31,70,72,78]. Still, short bursts of maximal exertion during longer endurance activities may benefit [45,70,126]. Finally, creatine supplementation during weight training has been shown to improve strength in some studies [42,54,79,129]. Specifically, creatine users have been able to perform more repetitions, sometimes at quicker rates. However, creatine itself is not anabolic.

\[
\text{PCr} + \text{ADP} + \text{H}^+ \rightleftharpoons \text{ATP} + \text{Cr}
\]

Fig. 2. Reversible equilibrium of creatine and phosphocreatine.
and has not been shown to alter protein synthesis [7,98,111]. It is hypothesized that creatine can help users to improve the volume and quality of weight training and thus indirectly increase strength and lean mass gains more than in nonusers [42,78,128,129].

To summarize, creatine has a very specific range for potential performance enhancement. First, the exercise to be performed must be maximal and anaerobic. Submaximal exercise does not rely as significantly on PCr for energy. Second, the duration of exercise should be long enough to take advantage of the increased PCr stores. If the bout is too short, then PCr stores are not depleted below what nonusers can supply. Third, the duration of exercise should be short enough to prevent glycolysis and aerobic pathways from becoming major energy sources. If the bout is too long, then these other sources dilute any initial benefit from PCr. Fourth, there must be adequate recovery time between exertion bouts. If recovery is too short, then not enough PCr stores are replenished to aid energy delivery for the next bout. Finally, creatine supplementation does not directly increase muscle strength or mass. However, it may improve the quality of weight training and indirectly improve strength gains.

Skepticism remains regarding creatine’s ability to enhance performance in actual competition [70,78]. Most studies have measured performance in laboratory conditions. Repetitive stationary cycling is the most common exercise to show beneficial effect, but competitive cycling has not been studied. Other exercises showing benefit include repetitive jumping, repetitive knee extensions, repetitive weight lifting, and rowing. Results of running and swimming under conditions similar to competition are mixed with almost an equal number of studies showing no benefit as showing benefit. No effect was found on tennis-stroke performance or sprint power in matchlike situations [95]. Juhn and Tarnopolsky [72] hypothesized that weight gain from water retention may negate any benefits from increased creatine stores in these weight-dependent sports. Still, some sports, such as football and hockey, have periods of brief, maximal, repetitive exertion during competition, and weight gain may not be detrimental. In fact, a recent study showed significantly faster on-ice sprints in elite hockey players after supplementation [69]. Therefore, although creatine supplementation has improved performance in certain situations in laboratory conditions, it may not translate into improved competition performance in all sports.

In addition, response to creatine supplementation is variable, and not everyone profits. Creatine concentration in skeletal muscle ranges between 90 and 160 mmol/kg dry weight [61,70,72]. An individual’s creatine concentration seems to be related to the amount of meat protein in their diet because vegetarians tend to have lower values [36,53,61]. Individuals with lower initial creatine values show the greatest increase in concentration and also show the greatest improvements in performance [31,61]. This has led to the idea of creatine “responders” and “nonresponders.” Responders have lower initial creatine stores, and therefore supplementation may produce a measurable increase in performance. On the other hand, nonresponders are already at near maximal creatine stores, and therefore additional supplementation has no effect.
Statistics

Creatine is one of the more commonly used performance-enhancing supplements. Approximately 2500 metric tons of creatine was consumed in 1999 [91]. In 1997, a national survey of NCAA athletes revealed that more than 30% used creatine supplementation within the preceding 12 months [92]. User rates among male athletes at individual NCAA programs were as high as 56% [56,109]. Approximately 10% of high school athletes use creatine [82,109]. Males users greatly outnumber female users [56,81,82,109]. The majority of creatine users subjectively believed that supplementation improved their performance [56,109]. Nevertheless, creatine users are not well informed. The majority of users obtain information about creatine from friends and teammates [81,109]. Also, more than 75% of users either did not know how much creatine they were using or were exceeding the recommended maintenance dose [71,109].

Dosing

Creatine supplementation starts with a loading dose to maximize creatine stores, followed by a maintenance dose. The usual loading dosage is 5 g of creatine monohydrate four times a day for 4 to 6 days [7,70,78]. After a 5-day load at 20 g/d, creatine stores gradually decrease to baseline over approximately 4 weeks [66]. A maintenance dose as low as 2 g once a day is sufficient to prevent loss [66]. It is important to realize that loading doses above 20 g/d do not provide any additional benefit. In fact, skeletal muscle has an upper limit as to how much creatine it can store. Any excess creatine ingested is excreted unchanged into the urine [61,70,98,99]. Actually, the usual 20-g/d loading dose itself may be excessive. At this dose, the majority of creatine uptake into skeletal muscle occurs during the first 48 hours [61]. In addition, 20 g/d for 2 days has shown creatine stores and performance benefits similar to longer loading durations [70]. Finally, “slow loads,” at 3 g/d for 28 days, have similarly increased PCR stores [66,72].

Certain factors can influence creatine uptake into muscles. First, persons with lower initial stores will have a greater increase (i.e., responders). Second, creatine ingested after submaximal exercise increases accumulation approximately 10% but with large variations in results [7,61,105]. However, use after prolonged exercise can decrease accumulation [7]. Also, because of concerns that creatine causes dehydration, creatine use before or during exercise is not recommended [7]. Third, creatine ingested with relatively large doses of simple carbohydrate can increase creatine accumulation more consistently [51,52]. However, the 90 to 100 g of glucose per 5 g creatine necessary to see this effect is difficult to tolerate [7]. Fourth, creatine taken with caffeine may hinder its effect [124].

Adverse effects

Currently, the majority of creatine’s short-term side effects are anecdotal or isolated case reports, and the long-term effects are unknown.
Weight gain

The only proven side effect is weight gain, up to 1.6 kg after the loading phase and 2.4 kg with more prolonged use [61,70,79,125,129]. Weight gain after the loading phase is mostly from water retention [70,72,129].

Gastrointestinal distress and muscle cramping

Other frequently cited side effects are gastrointestinal distress, muscle cramps, and muscle stiffness. Most of these reports are anecdotal, and several studies of creatine use have not found them to be limiting or common [7,31,70,73,98]. On the other hand, many of these studies primarily investigated performance effects and not specifically side effects. Also, these studies contained relatively small numbers of creatine users, and only a few looked at supplementation beyond 1 to 3 months.

Renal

Because of the increased protein load from creatine use, renal side effects have been the most concerning. Creatine loading increases the urinary creatine concentration 90-fold [73,97] and the urinary creatinine concentration by 20% to 40% [66,73,125]. Serum creatinine can also be increased approximately 20% [73,79]. Poortmans et al. [97,100] have published the only studies specifically investigating creatine’s effect on renal function in previously healthy individuals. They found that neither a 5-day loading dose nor an additional 58 days’ maintenance at 2 g/d significantly altered glomerular filtration rate in creatine users. In addition, they found no impairment of renal function with up to 5 years of self-reported creatine use [99]. However, these studies included no more than 10 subjects each and have been criticized for the parameters chosen to study renal function under creatine supplementation [80]. Only one report of “strong circumstantial evidence” of decreased renal function related to creatine supplementation is found in the literature [102]. After a normal load and 7 weeks’ maintenance at 2 g/d, an individual with a long-term history of focal segmental glomerulosclerosis had a 50% reduction in glomerular filtration rate that resolved 1 month after discontinuing use [102]. Likewise, only one case of an adverse renal effect in a previously healthy person has been reported [77]. The individual developed biopsy-proven interstitial nephritis after taking 20 g/d of creatine for 4 weeks, which resolved after discontinuing use. Currently, the ACSM recommends that persons with renal disease or a high risk for renal disease (diabetes or strong family history) not use creatine [7]. Likewise, healthy persons taking creatine should take measures to stay well hydrated during use [70]. Recently, three wrestlers died from rapid weight loss measures while taking creatine. Although creatine use was not directly linked to their deaths, the ACSM recommends that individuals using rapid weight loss techniques or performing under increased heat stress avoid taking creatine [7].
Unknown effects

Once again, there are no good studies of long-term adverse effects from creatine use [31,73,78]. Concern also has been raised that almost nothing is known regarding effects on other tissues that utilize creatine, such as the heart, brain, and testes [70,73]. Lastly, almost no data about the effects in teenagers are available [7,57,70,78]. Thus, the ACSM does not advise creatine supplementation in persons less than age 18 years [7].

Legal aspects

Creatine is not illegal, and supplementation is allowed by many major sports governing bodies. However, the FDA has not approved the use of creatine for any indication [2]. Creatine is easily obtained over the counter as a dietary supplement as a part of the 1994 Dietary Supplement Health and Education Act.

Current medical recommendations

Creatine has not been studied in adolescents. Therefore, neither the safety nor the effect on performance is known in adolescents. Even in adults, the range of activity that seems to be enhanced is narrow. The exertion must be brief, maximal, and repetitive, with significant time for recovery. Creatine does not improve endurance performance. In fact, performance in some sports may be adversely affected because of water retention and weight gain. In addition, creatine supplementation does not benefit everyone. Responders tend to have lower creatine stores, whereas nonresponders have higher stores. Nonresponders are already operating at near-maximal creatine benefits. Nonresponders also tend to have adequate amounts of meat and fish in their diets. Therefore, although it is not recommended that adolescents use creatine supplementation, they could be encouraged to maintain a diet with adequate amounts of meat or fish. Also, little is known about the effects of creatine use in settings often seen in athletics, such as heat stress, chronic use of nonsteroidal anti-inflammatory drugs, voluntary dehydration, and others. No studies have examined adverse effects with large numbers of subjects, especially to organs such as the heart and brain. In summary, creatine use is not recommended for adolescents, and it should be used only with caution in adult athletes. Individuals who still choose to supplement need to know that higher-than-recommended doses are lost in the urine without any added benefit and that they must make extra efforts to increase hydration during use.

Ephedra alkaloids

Physiology

Ephedra alkaloids (see box) are found naturally in certain plants. Common sources include Chinese Ephedra (also called Ephedra sinica or MaHuang) and Sida cordifolia [29]. Purified forms include ephedrine, pseudoephedrine, and...
phenylpropanolamine (PPA), which are commonly sold over the counter as cold remedies or appetite suppressants. Ephedra alkaloids act as α- and β-adrenergic agonists and enhance the release of norepinephrine from sympathetic neurons [64]. They also can be potent CNS stimulants [64]. However, when manufactured in herbal or extract form, they can be sold as dietary supplements without FDA regulation and marketed as a “natural” way to increase energy and burn fat. Their popularity is booming, with an estimated 3 billion doses sold in 1999 [9]. Athletes often have one of two goals when using ephedra alkaloids. One goal is decreased fatigue and increased energy for training and competition. Another goal is increased metabolism to aid in reducing fat mass for more muscular definition.

<table>
<thead>
<tr>
<th>List of several ephedra preparations</th>
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<tr>
<td>Adipo-Kinetix</td>
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<td>Animal Cuts</td>
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<td>Bete-Lean</td>
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<td>Beta-Trim</td>
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<td>Biotest MD6</td>
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<td>Burn Stack</td>
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<td>Clenbutrx</td>
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<td>Diurlean</td>
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<td>Dyma-Burn Xtreme</td>
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<td>Power Cuts</td>
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<td>Yellow Jackets</td>
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<td>Zenotrope</td>
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**Efficacy in performance enhancement**

Most studies of ephedra alkaloids by themselves demonstrate no performance-enhancing effects. Ephedrine, pseudoephedrine, and PPA all have been studied at therapeutic and twofold therapeutic doses. None of the studies showed any significant change in strength, time until exhaustion, oxygen uptake, or perceived fatigue [22,32,37,48,108,114]. The most common single finding was a significantly increased heart rate [32,108]. Still, a recent study of pseudoephedrine at threefold therapeutic dose (180 mg) showed a significant increase in knee extension strength and peak power during 30 seconds of maximal cycling [47]. However, bench-press strength and total work produced during cycling were not changed. Although the results of this recent study are mixed, ephedra alkaloids may prove to enhance performance at higher doses.
Other recent evidence by Bell et al. [18] demonstrates potential endurance benefits of ephedrine when combined with caffeine. Time to exhaustion was significantly increased, and perceived fatigue was significantly decreased during high-intensity stationary cycling within 2 hours of taking ephedrine and caffeine (E+C). No significant changes in performance were found while taking either ephedrine or caffeine alone. There was no change in oxygen consumption or minute ventilation, but heart rate was significantly increased in the E+C group. However, two of eight subjects taking 1 mg/kg of ephedrine plus 5 mg/kg of caffeine experienced nausea or vomiting during the intense exercise. In a second study, lower doses (0.8 mg/kg of ephedrine plus 4 mg/kg of caffeine) were shown to still improve time to exhaustion and perceived fatigue but without gastrointestinal distress [17]. In fact, a third study showed improvements under field conditions [16]. The E+C group had significantly reduced their time to complete a military-style outdoors run but, once again, had a significantly increased heart rate.

The E+C combination also seems to be more potent for reducing body weight in obese individuals. Several studies have shown a significant decrease in total body weight in obese patients taking 20 mg of ephedrine plus 200 mg of caffeine three times a day while restricting caloric intake [10,89,119,120]. One study found both an increased weight loss and body fat loss in obese adolescents taking E+C while on dietary restrictions [89]. Another study found a significant weight loss with E+C use in obese adults even without caloric restrictions [34]. However, the effect on body composition in athletes or other “lean” individuals has not been studied.

Adverse effects

There are considerable concerns regarding the safety of ephedra alkaloids and especially about the combination of ephedrine and caffeine. The FDA has been trying since 1996 to place tighter restrictions on products containing ephedra alkaloids. A recent independent review of 140 adverse reactions reported to the FDA by persons taking ephedra alkaloids found that 31% were either definitely or probably related to use [59]. An additional 31% were possibly related. There were 10 deaths and 13 permanent disabilities among users as young as age 15 years. Most events were related to hypertension, arrhythmia, stroke, or seizure. There are multiple reports of similar noteworthy adverse events related to ephedra use in the literature [28,96,117,118,121,123,134,137]. In fact, PPA, an ephedra alkaloid, recently was removed from all OTC medications after its use as an appetite suppressant was found to increase the risk for hemorrhagic stroke in women [75]. PPA was present in numerous OTC cold preparations and appetite suppressants for years before this link was discovered. In addition, the combination of ephedra alkaloids and caffeine might be even more dangerous. Caffeine is known to potentiate the stimulant effects of ephedra alkaloids [141]. In fact, the FDA has banned the combination of ephedra alkaloids and caffeine since 1983 [94]. Despite this, many dietary supplements combine “natural” sources of Ephedra with
guarana, an herbal form of caffeine. The purity of the extracts in dietary supplements is also questionable. A study of 20 herbal supplements showed that many contained multiple ephedra alkaloids and that the actual ephedra content can vary from 0% to 154% of their label claims [58]. Also, five products studied contained norpseudoephedrine, a Schedule IV controlled substance [58].

**Legal aspects**

Ephedra alkaloids are legal but banned by many major sports governing organizations. Currently, the IOC and NCAA ban all systemic use of ephedrine-related products, including simple cold remedies. In addition, both organizations place limits on acceptable urinary caffeine levels. Despite an FDA ban on combining ephedra alkaloids with caffeine, several OTC dietary supplements contain such combinations in herbal extract form. In addition, some herbal extracts can contain substantial amounts of controlled substances [58].

**Current medical recommendations**

The use of certain ephedra alkaloids has been linked to severe cardiovascular and CNS adverse effects, such as arrhythmia and stroke. The combination of ephedra and caffeine may be even more dangerous. Some OTC products already have been removed from the market, but similar dietary supplements are not under the same regulations. By themselves, ephedra alkaloids do not enhance performance or weight loss, and ephedra alkaloids should not be used because they are potentially dangerous.

**Summary**

The temptation of using drugs and supplements as shortcuts to improving athletic performance or even to enhance appearance is very seductive to adolescents. This age group is often characterized by a desire for quick results and a lack of concern for future consequences. Preventing the use of drugs to enhance athletic performance is difficult even when we have good medical and scientific evidence to prove a dangerous risk–benefit ratio, such as with AASs.

The use of “nutritional supplements” is even more difficult to control. The protection of these substances by the Dietary Supplement Health and Education Act of 1994 removed control of these substances from the FDA. Therefore, release and widespread use of new supplements occurs before significant clinical study of benefit and adverse effects takes place. The distributors’ financial interest, the products’ promotional claims, and the athletes’ and coaches’ insatiable desire to win at all costs are a volatile combination. This spawns the production of a huge number of “natural” products, making it even more difficult to assess efficacy, safety, legality, and purity of these substances. Health care professionals need to rely on research when available, stay current on trends in athletes’ drug and supplement use, and discuss the individual athlete’s concerns.
when they arise. The preparticipation physical examination can be a good opportunity for discussion. Finally, physicians need to educate athletes, parents, coaches, trainers, and other physicians. A reasonable strength and conditioning program and a well-balanced diet must be presented as a sensible alternative to a riskier, shortcut mindset.

References

[22] Bright TP, Sandage BW, Fletcher HP. Selected cardiac and metabolic responses to pseudophe- 


