Ephedrine and Other Stimulants As Ergogenic Aids

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Introduction
A wide range of recreational, prescription, and illicit drugs have psychotropic effects that may be perceived to be ergogenic. The ephedra alkaloids have received recent attention for their widespread use by athletes and their potential serious side effects, despite the lack of evidence regarding any ergogenic or performance benefit. Some prescription drugs (eg, methylphenidate and bupropion) raise complex issues regarding their appropriate therapeutic use in athletes. Recreational drugs, some of which are illegal (eg, cocaine), are commonly used by athletes and cause a wide range of potentially ergolytic effects. In total, these drugs are important for their frequent use, the frequency with which they are mentioned in the media, and their potential for causing significant adverse effects.

Ephedrine
Ephedra alkaloids are popular components of many nutritional supplements, with approximately 3 billion doses sold in 1999 [2]. They are found in several plant species, including Ephedra sinica, E. intermedia, and E. equisetina, collectively known as Chinese ephedra or ma huang, and Sida cordifolia [3••,4]. Purified forms of these substances include ephedrine, pseudoephedrine, norephedrine, methylephedrine, norpseudoephedrine, and methylpseudoephedrine. Phenylpropanolamine is a synthetic compound functionally similar to the ephedra alkaloids in effect and use.

Epidemiology
One study of commercial fitness center clients reported ephedrine use within the past 3 years in 109 of 511 subjects, which would extrapolate to a national use by 2.8 million American recreational athletes [5]. A National Collegiate Athletic Association (NCAA) study of the drug and supplement use habits of 21,000 college students from 713 NCAA member institutions in 2001 [6] showed an increase in ephedrine use from 3.5% to 3.9% compared with rates in 1997. Men's lacrosse (5.5%) and women's gymnastics (8.3%) had the highest rate of ephedrine use among NCAA athletes. The major reasons to use supplements as reported by athletes are improved athletic performance (27.3%), improved physical appearance (27.3%), and weight control (19.7%). More than half of these college athletes started using nutritional supplements before finishing high school.

Pharmacology and clinical uses
Ephedra alkaloids are sympathomimetic agents that act as both α and β adrenergic agonists, and enhance the release of norepinephrine from sympathetic neurons [7]. Ephedra alkaloids cross the blood-brain barrier and are a potent central nervous system (CNS) stimulator. Functionally, the ephedra alkaloids are similar to amphetamines, although weaker. The relative balance of α and β receptors determines their net effect. Sympathetic stimulation can cause excitatory effects in some tissues, and inhibitory effects in others. Stimulation of α receptors in vascular smooth muscle leads to contraction and vasoconstriction. β1 receptors, primarily found in cardiac tissue, may lead to increased heart rate and myocardial strength when stimulated. Stimulation of β2 receptors in bronchial smooth muscle causes bronchodilatation, and vasodilatation in skeletal muscle [8].
Clinically, ephedrine has been used in the past for the treatment of asthma, but has no current common therapeutic use. Pseudoephedrine can be found in many prescription and over-the-counter preparations (used mostly for the treatment of congestion) that may be associated with respiratory infections or allergies. Until its recent voluntary removal from the market because of reports of increased risk for stroke in women, phenylephrine was also used similarly to pseudoephedrine and in over-the-counter diet pills. Ephedra alkaloids have been used for both asthma and allergies in China for more than 5000 years [9].

Ephedrine is excreted largely unchanged in the urine and the usual elimination half-life is 3 to 6 hours, which can be prolonged with increased urine pH [10]. Gas chromatography coupled with mass spectrometry of a urine sample is the standard test for the purpose of detecting unapproved use. A urine concentration of greater than 10 µg/mL is considered positive by the NCAA, the International Olympic Committee (IOC), and the National Football League (NFL). Hair analysis can be valuable as a complement to urinalysis for providing a more accurate history of drug use, but has yet to be standardized [11].

Athletic applications

With their stimulant properties and sympathomimetic actions, ephedra alkaloids have been perceived as lending unfair advantages to athletes when used in supplement form. Many athletes use substances containing ephedra alkaloids because of perceived benefits of increased energy, decreased time to exhaustion, and potential sympathomimetic properties with increased metabolism, increased fat loss, and improved muscle strength. Studies investigating the use of ephedra alkaloids at standard dosages have not supported their perceived performance-enhancing properties. However, some studies looking at the use of ephedrine and caffeine together have supported potential ergogenic effects [12,13,14–18].

Sidney and Lefcoe [12] studied the use of ephedrine and the effect on cardiorespiratory endurance, maximal oxygen uptake, ratings of perceived exertion, lung function, anaerobic capacity, speed, reaction time, hand-eye coordination, and muscle function. When compared with placebo, there were no statistically significant differences. They did, however, find that blood pressure and heart rate were significantly elevated.

DeMeersman et al. [13,14] evaluated the effects of ephedrine use on 10 subjects during a cycle ergometer test. They assessed various cardiorespiratory variables, as well as ratings of perceived exhaustion and found no statistically significant advantage for ephedrine use over placebo. Interestingly, their research was prompted by an IOC investigation of an American athlete who tested positive for ephedrine use from incidental inhaler use for asthma during the 1972 Olympics. He was forced to return his gold medal based on the assumption that the ephedrine offered him an unfair advantage, a decision challenged by DeMeersman et al. [13] on the basis of this research.

Similar studies have evaluated the potential effects of pseudoephedrine at both standard doses and doses that are higher than recommended. Gill et al. [14] evaluated the effect of a 180-mg dose of pseudoephedrine administered 45 minutes prior to exercise on short-term maximal exercise performance. Subjects completed a series of tests, including isometric knee extension, bench press at one repetition maximum (1RM) and 70% of 1RM, and a 30-second maximal cycle ergometry test. Subjects taking pseudoephedrine experienced increased maximum torque during isometric knee extension, improved peak power during cycle performance, and improved lung function when compared with placebo. Bench press tasks and total work during the cycle test were not significantly changed [14].

Most studies, however, have evaluated pseudoephedrine at more standard dosages and could not show evidence of performance enhancement. Clemons and Crosby [15] investigated the effects of 60 mg of pseudoephedrine on heart rate, respiratory exchange ratio, ventilation, oxygen consumption, respiratory rate, tidal volume, systolic and diastolic blood pressure, total exercise time, core temperature, and ratings of perceived exertion during graded exercise tests with the Bruce protocol. Their only significant findings were of increased heart rate during each stage and at 8 minutes of recovery. Gillies et al. [16] also found that pseudoephedrine at a dose of 120 mg did not produce measurable ergogenic effects during high-intensity exercise of 1 hour duration with cycle ergometry. Bright et al. [17] evaluated heart rate, blood pressure, glucose, and insulin after administration of pseudoephedrine at 60 and 120 mg during submaximal exercise. They found no significant changes in these variables, but did report an increased risk of sinus arrhythmias at the 120-mg dose. Finally, Swain et al. [18] looked at the effects of both pseudoephedrine and phenylpropanolamine at standard dosages during cycle ergometry. They found no significant changes for either substance with measurements of VO2max, rating of perceived exertion, maximal systolic and diastolic blood pressure, heart rate, or time to exhaustion, with the exception of peak systolic blood pressure after administration of pseudoephedrine.

In summary, it appears that the isolated use of ephedrine, pseudoephedrine and phenylpropanolamine at usual dosages has an inconsistent, and probably insignificant, ergogenic benefit for power, endurance, strength, or speed.

A series of studies by Bell et al. and Bell and Jacobs [19,20–24] evaluated the effects of ephedrine in combination with caffeine and found the combination to enhance performance. In a study of 5 mg/kg of caffeine and 1 mg/kg of ephedrine, administered separately and together, the combination resulted in an increased time to exhaustion and decreased rating of perceived exhaustion on cycle ergometry compared with either drug alone or placebo. A quarter of the subjects experienced nausea and vomiting with exercise after the combination of caffeine and ephedrine [19]. Doses as
low as 4 mg/kg of caffeine and 0.8 mg/kg of ephedrine in combination were equally as effective as the higher doses, and caused fewer gastrointestinal side effects [23]. Similarly, the combination of 375 mg of caffeine and 75 mg of ephedrine given prior to a Canadian Forces Warrior Test, a 3.2-km run wearing a helmet, rifle, webbing, full canteen, back pack, and combat boots, resulted in significantly faster race times and higher heart rates [21].

The findings regarding the effect of ephedrine on weight loss are equivocal. Theoretically, ephedrine can increase metabolic rate and suppress appetite. In a randomized study on 167 subjects, Boozer et al. [25] showed that herbal ephedra/caffeine (90–192 mg/d) can promote body weight and body fat reduction. Average weight loss was 5.3 ± 5 kg with herbal treatment and 2.6 ± 3.2 kg with placebo in a 6-month trial (P < 0.001). However, the results in less selected populations and less controlled settings are far less impressive, and the use of ephedrine for weight loss has been mostly discounted.

Adverse effects
There are serious concerns regarding the safety of supplements containing ephedra alkaloids. In 1994, the Dietary Supplement Health and Education Act excluded dietary supplements from rigorous US Food and Drug Administration (FDA) regulation. Because supplements are not considered therapeutic, they are not held to the same level of rigor in claiming efficacy and safety as that required of prescribed and over-the-counter medications [26]. Since the 1994 deregulation, an increasing number of reports of adverse events, including hypertension, arrhythmias, myocardial infarction, seizure, cerebrovascular accidents, and death [27], has prompted the FDA to recommend a limit on the use of ephedra alkaloids of 24 mg/d for no more than 7 days.

In addition to the more serious adverse events described above, commonly used dosages of ephedrine can cause headache, dizziness, irritability, anxiety, tremor, and psychosis. Caffeine can augment the adverse cardiovascular and CNS effects of ephedrine. The deaths of several high school and college students have been blamed on the use of ephedra [28]. Acute myocardial infarction (probably secondary to vasospasm), cardiac arrhythmias, and stroke are the cause of death in a majority of cases [29–31,32••]. Pre-existing cardiovascular disease is not a prerequisite for adverse events, and the cardiovascular toxic effects associated with ma huang are not necessarily dose-dependent [30,31]. Haller and Benowitz [32••] reviewed 140 reported adverse events from dietary supplements containing ephedra alkaloids submitted to the FDA between 1997 and 1999. Using a standardized rating system to assess causation, 31% of cases were definitely or probably related to ephedra alkaloids, and 31% were possibly related. Of these two groups, 47% involved cardiovascular events, with the majority related to hypertension (17 cases) and tachycardia or palpitations (13 cases), whereas 18% involved CNS events, with stroke (10 cases) and seizures (seven cases) being most prevalent; 10 events resulted in death and 13 in permanent disability.

Many case reports have identified substances containing ephedra alkaloids as possible causative factors in adverse events occurring in otherwise healthy adults. Wooten et al. [33] reported a case of a 20-year-old man who developed an intracerebral hemorrhage and vasculitis after the ingestion of “speed” containing ephedrine. Kockler et al. [34] reported the hospitalization of a 22-year-old man after seizure-like activity believed to be related to ephedrine ingestion. Bruno et al. [35] reported three cases involving patients who developed a cerebrovascular accident believed to be linked to ephedrine use. Vahedi et al. [36] reported a case of ischemic stroke in a 33-year-old sportsman after ingestion of ma huang, and Theoharis et al. [37] reported sudden death of a healthy college student after ingestion of a ma huang-containing beverage.

In a landmark study, Kernan et al. [38] collaborated with the FDA and manufacturers of phenylpropanolamine to evaluate the risk of hemorrhagic stroke associated with its use. In a case-control study assessing the risk in both men and women ages 18 to 49 years recruited from 43 US hospitals, phenylpropanolamine use was an independent risk factor for hemorrhagic stroke in women. This study prompted the voluntary removal of phenylpropanolamine from the market, including the removal of many over-the-counter appetite suppressants and cold remedies.

Ephedrine has been banned by the IOC for years, the NCAA since 1997, and most recently by the NFL. Recently, the US armed forces also banned ephedra products from commissaries and military exchanges worldwide. Ephedra-containing products, including a wide range of weight-loss products, are not regulated by FDA. Gurley et al. [39] found dramatic mislabeling and inconsistencies among many ephedra-containing dietary supplement products. In 1997, the FDA proposed a limit for ephedrine alkaloids in dietary supplements of 8 mg per serving within a 6-hour period, or 24 mg/d [27]. The current maximum dose of nonprescription ephedrine is 25 mg, with a maximum daily dose of 100 mg [39].

Athletes are forever searching for the one element that will give them a competitive edge, but they are often less clear about the cost they are willing to bear from trying the many supplements promising to provide them with performance enhancement. Ephedra alkaloids taken alone and at standard dosages have not been proven to have ergogenic properties. Not only do athletes risk disqualification at the elite level when using supplements containing ephedra alkaloids, they may be risking their lives. Because of recent highly publicized tragedies, various athletic associations have focused on further evaluations of the use of these substances and on trying to educate athletes about potential health risks associated with their use. In September 2001, shortly after the death of the Minnesota Vikings’ Corey Stringer, NFL commissioner Paul Tagliabue announced the league’s ban on ephedrine usage. Year-round random drug testing was initiated in July 2002 as the NFL became the first professional league to institute such a ban. Continued
evaluation of the use of these substances is necessary, as is continued education of athletes, parents, coaches, and trainers regarding the health risks associated with ephedrine alkaloids.

Amphetamines, Including Methylphenidate
The use of methylphenidate and related amphetamine stimulants for the treatment of attention deficit and hyperactivity disorder (ADHD) has increased significantly in recent years, probably due to both increased accuracy of diagnosis and increased demand by parents for stimulant treatment [1]. This increased prevalence of use has resulted in sports and team physicians being faced with an increasing number of athletes asking about its use, regulation, and effects on athletic performance. In addition, methylphenidate in particular is commonly abused by adolescents, through crushing tablets for sublingual mucosal absorption, usually for recreational purposes, and this use could lead to detection during drug testing by regulatory agencies such as the NCAA.

Amphetamine was synthesized in 1920 and used to reduce fatigue and increase alertness during World War II. Its effect on well-rested subjects is unclear, with claims of more rapid learning of new tasks, and increased physical energy, confidence, and well-being [40]. Its effects on sleep-deprived subjects are more clear, and more controversial, with regard to improved attention deployment, focus, and concentration. There are several proposed mechanisms, most of which involve the increased turnover of neurotransmitters such as dopamine and norepinephrine. It may be ergogenic in short-term power performance, possibly through tolerance of longer periods of anaerobic metabolism, although controlled data are scant. What is more clear is the increased risk of serious, sometimes fatal, side effects of amphetamine use, including heatstroke due to shunting of blood to the core and away from skin. Impaired judgement may cause the athlete to compete while injured, as well as possibly harming other athletes through inappropriate behavior. All amphetamines are banned by the IOC, and the NCAA requires substantial and current documentation of the medical indication for their use, with concern that it may be inappropriately justified by an inaccurate, falsified, or outdated diagnosis of ADHD. The recent release of a new, nonstimulating medication for the treatment of ADHD will raise new questions about the appropriate approach to ADHD in athletes, as well as stimulate studies assessing the possible ergogenic effect of this and future new medications.

Cocaine
Cocaine has been used by soldiers since the late 1800s to decrease fatigue, but unlike amphetamines, it currently has no legitimate medical use except as a local anesthesia for nasal and laryngeal procedures. Its recreational use is widespread, and it is highly addictive, with its effect mediated through dopamine release [40,41]. Withdrawal produces fatigue and depression. It is most notable for distorting the user’s perception of reality; in an athlete, for example, the perception of increased levels of performance, decreased fatigue, and increased strength, despite objective measures to the contrary [42]. Its vasoconstrictive effect can be fatal through the induction of cardiac arrhythmias and coronary artery ischemia [43], and it is banned by both the NCAA and IOC, including its use as a local anesthetic.

Bupropion
Bupropion is an antidepressant without serotoninergic or noradrenergic effect that is presumed to act through blockade of dopamine reuptake [41]. However, bupropion and its metabolites are actually fairly weak inhibitors of dopamine, as well as serotonin and norepinephrine, so its actual mechanism of action is unclear. Studies of its clinical pharmacology are conflicting and equivocal. It is believed to have a stimulating effect through its dopaminergic blockage, and presumably for this reason was recently banned by the IOC. It is often used in adolescents with a dual diagnosis of ADHD and unipolar depression, because it is perceived to have a beneficial additive effect in ADHD, again because of its possible dopaminergic effect. The IOC ban may also be related to the fact that bupropion can have an anxiolytic effect for athletes involved in shooting and archery, as well as because other serotoninergic and noradrenergic antidepressants may be banned for certain sports and by certain sports federations because of their anxiolytic effect. Because the use of any stimulant in patients with ADHD, such as methylphenidate, has come under new and more intense scrutiny, bupropion use may be subject to more intense investigation by sports federations and authorities for this reason as well. There is no known ergogenic benefit from the use of bupropion with regard to strength or endurance exercise.

Conclusions
The actual ergogenic benefits of ephedrine, methylphenidate and other amphetamines, cocaine, and bupropion are unclear, but all are banned or suspect to varying degrees and by different sporting federations and associations. This discrepancy between actual benefit and banned status highlights the difficulty sports physicians have in advising athletes, parents, coaches, and athletic administrators about the proper approach to monitoring, education, and testing for these medications. As is true for the approach to many potential ergogenic substances, good judgement and up-to-date information are essential to appropriate decisions and guidance.

Addendum
At the time this manuscript went to press, Major League Baseball proposed a ban on the use of ephedrine by certain minor league baseball players. The ban was proposed because of
concerns about the highly publicized death of a major league baseball player, possibly due to the vasoconstrictive and heat intolerance effects of ephedrine. The FDA was also exploring restrictions on the use and marketing of ephedrine by the general public, and commissioned a meta-analysis of the risks and benefits of ephedrine [44]. There will likely be continued active discussion of ephedrine and its adverse effects, and readers should seek up-to-date information in making appropriate decisions about its use or potential ban.

References and Recommended Reading
Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance
   This thorough review explores the scientific evidence for use of supplements containing herbs and herbal extracts as ergogenic aids. Ephedra alkaloids are summarized in detail, including the major studies evaluating their potential ergogenic properties.
   The authors present one of the earliest investigations into the potential ergogenic effects of ephedrine. It was borne out of unsubstantiated claims of its ergogenic effects, which resulted in the disqualification of an Olympic athlete. Their data show that the use of ephedrine offers no advantage to performance.
   This detailed review of 140 reports of adverse events involving supplements containing ephedra alkaloids used a standardized rating system for assessing causation, and nicely organizes and validates the concerns regarding the supplement’s safety.