

Evidence Report

Chapter 1. Introduction

Purpose

This evidence report details the methodology, results, and conclusions of a comprehensive literature review and synthesis of evidence on the efficacy and safety of ephedra and ephedrine, either alone or in combination with other substances, to promote weight loss or to enhance athletic performance. Meta-analysis was performed where appropriate.

Scope of Work

At the direction of the funding agencies (National Institutes of Health Office of Dietary Supplements (ODS), National Centers for Complementary and Alternative Medicine (NCCAM), and Agency for Healthcare Research and Quality (AHRQ) and in consultation with our Technical Expert Panel (see Table 2, Chapter 2), we addressed research questions regarding the efficacy of herbal ephedra and synthetic ephedrine for weight loss and athletic performance. We assessed the safety of these products through review of clinical trials. In addition, we reviewed herbal ephedra-related adverse events reports on file with the U.S. Food and Drug Administration (FDA), published case reports, and reports to a manufacturer of ephedra products. It is expected that the results of this review will be used to direct further research.

In searching for evidence of efficacy and safety, we were directed to assess studies using both the isolated alkaloid, ephedrine, and whole herb or extracts of the herb ephedra.

Background

A 2000 survey by manufacturers of ephedra-containing supplement products estimated that three billion servings of these products were consumed in the prior year; these findings were revealed during testimony at a Public Meeting on the Safety of Dietary Supplements Containing Ephedrine Alkaloids held August 8, 2000. According to Michael McGuffin, an industry spokesperson, this figure represented a 65 percent increase in sales volume over the previous five years and would correspond to approximately \$6.8 billion in total sales.¹ Use of ephedrine alkaloid-containing products to promote weight loss or enhance athletic performance has garnered a great deal of media attention over the last year. This attention is due in part to a number of well-publicized adverse events reportedly associated with the use of ephedra or ephedrine alkaloid-containing products.²⁻⁷

Herbal ephedra has been used in China to treat respiratory conditions for over 5,000 years;⁸ however, the herb is not used for weight loss or physical performance enhancement in eastern medicine. Its active alkaloid, ephedrine, was first used in western medicine as an asthma treatment in the 1930s. Since then, ephedrine and other sympathomimetic alkaloids have been used in many over-the-counter (OTC) decongestants and cold medicines. It was not until the

early 1990s that herbal ephedra and other products containing ephedrine began to be promoted as weight loss aids in the United States.

Federal regulation of dietary supplement products differs considerably from that of products that are deemed drugs. Dietary supplement products, including those that contain herbal ephedra (as distinct from the purified alkaloid ephedrine), are regulated by the Dietary Supplement Health and Education Act (DSHEA) of 1994. Under DSHEA, new products that contain only supplement ingredients that were sold in the United States before October 15, 1994 do not require FDA review before they are marketed, because they are presumed to be safe based on their history of use by humans. Manufacturers of a dietary supplement that contains a new ingredient not sold as a dietary supplement before 1994 must notify FDA of their intent to market that product and must demonstrate reasonable evidence for the safety of the product to humans. In turn, FDA can bar the new ingredient from the marketplace for safety reasons. However, manufacturers are not required to perform clinical or other studies to establish the safety of their products before marketing. Once a dietary supplement is marketed, FDA can restrict its use or order its removal from the marketplace only if it can prove that the product is not safe. In contrast to the rules for dietary supplements, before a drug product can be marketed, the manufacturer must obtain FDA approval by providing convincing evidence that it is both safe and effective.

On October 11, 1995, in response to a growing number of adverse event reports submitted to the FDA about ephedra-containing products (more than 300 at the time), the FDA convened an open meeting of the Special Working Group on Food Products Containing Ephedrine Alkaloids (a working group of the Food Advisory Committee) to assess the potential public health problems associated with dietary supplements and other food products that contained botanical sources of ephedrine alkaloids (that is, ephedra). The reported adverse events involved primarily the cardiovascular and central nervous systems. Most events occurred in young to middle-aged women, often those using the products for weight loss or to increase energy. Based on the reports and the evidence they heard, the working group found sufficient evidence to suggest that adverse effects were associated with the use of ephedrine alkaloids, that safe levels should be established and that warning labels should appear on products containing the ephedrine alkaloids, regardless of their source.

In August 1996, the FDA convened a meeting of its Food Advisory Committee to continue the discussion of the safety of ephedrine alkaloid-containing foods and supplements. By that time, the number of adverse events reported to the FDA had doubled from the year before to over 600. As a result of that meeting, some members recommended removal of dietary supplements containing ephedra from the market.⁹ Other members suggested that the FDA develop rules on use that would help reduce the risk of adverse events. In 1997, the FDA published a proposed rule on use of dietary supplements containing ephedrine alkaloids. It proposed a dose limit of 8 mg ephedrine alkaloid per serving, a daily limit of 24 mg, a duration limit of 7 days, and various label warnings. After the rule was published in the Federal Register, the FDA received a large number of comments from consumers, physicians, scientists, and supplement manufacturers. In response, the General Accounting Office (GAO) audited the methods used by the FDA to develop the proposed rules. In July 1999, the GAO reported that the FDA had insufficient

evidence to support dosage and duration limits. As a result, in early 2000, the FDA withdrew a large part of the 1997 proposal.

However, the controversy over ephedra has continued. From 2000 to 2002, more than 100 people sued makers of ephedra products,⁷ and from 1992 through 2002, more than 1000 health problems were reported to FDA. These reports led a nonprofit consumer group, Public Citizen, to file a lengthy petition in 2001, asking the FDA to ban the production and sale of ephedra products. In the fall of 2001, the National Football League banned the substance following the deaths of several high school and college athletes after alleged use of ephedrine-containing products, and in January 2002, the Canadian government issued a warning against use of ephedra.

On June 14, 2002, the U.S. Department of Health and Human Services proposed an expanded scientific evaluation of ephedra. The agenda for that research will be based on the findings of the current report.

The Problem of Obesity

From 1999 through 2002, the prevalence of obesity in the United States increased by 1 percent per year, reaching a level of 19.8 percent among the adult population. This increase represents a 65 percent rise in the prevalence of obesity from 1991 to 2002 (from 12 percent to 19.8 percent), although a precise comparison is difficult because of changing definitions of obesity.¹⁰⁻¹² Obesity is currently defined as a body mass index of 30 or greater: BMI is obtained by dividing body weight (in kilograms) by the height (in meters) squared. Overweight individuals are those whose BMI falls between 25 and 29.9. According to that definition, by the year 2000, the majority of Americans (56 percent) were overweight.¹⁰ Moreover, according to the 1999 National Health and Nutrition Examination Survey (NHANES), 13 percent of children and adolescents are currently seriously overweight and are displaying increasing rates of obesity-related chronic diseases such as Type II diabetes, not previously seen in children.¹³ Attempts to meet the body weight goal of the Healthy People 2000 Initiative¹⁴ (reducing the prevalence of overweight among adults to less than 20 percent of the population) have failed.

The United States is not alone in facing rising rates of obesity. In Canada, between 1985 and 1998, the overall prevalence of obesity increased in adults from 5.6 percent to 14.8 percent and from 1981 to 1996, it tripled in children.^{15, 16} The World Health Organization reports that there are more than 300 million obese people in the world, and the rising rate of obesity is no longer solely a problem of industrialized countries, but one that is rapidly appearing in developing countries.^{17, 18}

In addition to Type 2 diabetes, other serious health risks are associated with obesity. Rates and severity of hypertension, dyslipidemia, insulin resistance (Syndrome X), coronary artery disease, stroke, sleep apnea, osteoarthritis, certain cancers, and other conditions increase with increasing weight.^{19, 20} Further, obesity increases the rate of mortality as well as morbidity, especially mortality associated with heart disease and diabetes.²¹ Using data from five large prospective cohorts, Allison and colleagues estimated that in 1991, 280,000 deaths were attributable to excess weight.²² Patients with a BMI greater than 30 accounted for more than 80 percent of the obesity-attributable deaths.

The costs of obesity to the health care system are large and growing with the increasing rates of obesity. In 1986, when only 34 million Americans were clinically obese, a conservative estimate of the economic costs related to obesity was \$39.3 billion.²³ By 1995, one study²⁴ estimated direct cost for obesity at \$70 billion, although another study estimated these costs at 25 percent lower.²⁵ The costs of obesity are estimated to be higher than those for either smoking or excessive drinking.²⁶

Intentional weight loss by obese persons leads to reductions in risk factors for disease. A minimum loss of 5 percent to 10 percent of body weight followed by long-term weight maintenance can improve health outcomes.²⁷ Despite this finding, only 42 percent of obese people surveyed by Galuska and colleagues reported that their doctor recommended weight loss.^{28, 29} Still, much of the population reports that they are actively trying to lose weight: a 2000 survey showed that one third (38 percent) of subjects were actively trying to lose weight and another third (36 percent) were trying to maintain their weight.¹¹ Furthermore, among those who were overweight, 45 percent of subjects were actively trying to lose weight, and 35 percent were trying to maintain their weight. Among those who were obese, 66 percent of subjects were actively trying to lose weight, and 21 percent were trying to maintain their weight.¹¹ In a population-based study of 14,679 U.S. adults in 5 states using the 1998 BRFSS data, seven percent reported using nonprescription weight loss products; 2 percent reported using phenylpropanolamine and one percent reported using ephedra products from 1996 to 1998. More women used ephedra products than men; 1.6 percent of women and 0.4 percent of men reported using weight loss products containing ephedra. Extrapolated nationally, this study estimated that during 1996–1998, 2.5 million Americans used weight loss products containing ephedra. This study also has data to suggest that many individuals are not aware they are taking weight loss products that contain ephedra. Of the 183 respondents in Michigan who responded to the questions about using ephedra and reported that they took “other” nonprescription weight loss products, 33 percent reported using name-brand products that claim to contain both ephedra products and chromium picolinate.³⁰

This estimate of use of ephedra-containing products may be low. Heber and Greenway state that the most widely used herbal products for weight loss contain ephedrine alkaloids.³¹ Among 230 (61 percent) of 376 adults in the St. Paul/Minneapolis area who reported using an herbal product during the past 12 months, 44 (19 percent) used ephedra. Of these 44, 20 (45 percent) used ephedra for weight loss. Therefore, 5.3 percent of these adults (20 of 376) reported using ephedra for weight loss.³²

Enhancing Physical Performance

Stimulants have a long history of use in athletic performance, dating back to the early 1900s.³³ Several serious accidents in the late 1960s, including the death of a cyclist using amphetamines, spurred the International Olympic Committee (IOC) to ban stimulants from use during competition. However, this ban was not fully enforceable until a reliable screening test became available in 1972.³⁴ Use of OTC stimulants is regulated somewhat differently than that of stimulants available only by prescription, because OTC stimulants are widely available in products used to treat common conditions such as colds or congestion. Therefore, these

compounds are not banned outright, but athletes whose use of these substances exceeds some reporting threshold are subject to censure.³⁴

Use of dietary supplements by athletes is common and somewhat more frequent than that of the general public. In a review of 51 studies, Sobal and Marquart³⁵ found that 56 percent of athletes used one or more supplements. Another study of college athletes reports a 42 percent prevalence of supplement use.³⁶ Supplement use was higher among men than among women, and higher among elite athletes and in particular sports such as body building, weight lifting, and ultramarathon running.³⁵ A survey among elite Australian swimmers supports this finding: 94 percent of them reported using dietary supplements. All participants reported using vitamins and/or minerals, and 61 percent reported using herbal preparations.³⁷ Supplement use is prevalent even among younger athletes: 20 to 25 percent of adolescents are reportedly using supplements. For all athletes, performance enhancement is cited as a common reason for use, and multi-vitamins are the most frequently used dietary supplements.³⁵

OTC stimulants, particularly ephedrine or its related alkaloids, are among the substances most frequently detected on drug screens or reported in surveys. In a series of 1,256 positive drug screens identified by IOC laboratories in 1989, 40 percent involved stimulants. Ephedrine alkaloids accounted for 75 percent of the stimulants reported.³⁸ Evaluation of drug use by student athletes in the most recent National Collegiate Athletic Association (NCAA) survey (2001) showed that ephedrine and amphetamine use increased from 1997 to 2001, at a time when use of many other substances was declining.³⁹ Ephedrine was used by 3.5 percent of responders in 1997, a figure that increased to 3.9 percent by 2001. In a survey of 511 subjects attending a gymnasium, self-reported use of ephedrine exceeded that of anabolic steroids (25 percent versus 18 percent for men; 13 percent versus 3 percent for women).⁴⁰ The authors asserted that extrapolating these figures to the general public would suggest that 2.8 million people have used ephedrine-containing products to improve athletic performance within the last three years. Further, there may be a subset of committed users of ephedrine products who take high doses for extended periods of time. Gruber and Pope⁴¹ reported on a cohort of female weightlifters, 56 percent of whom were using doses of 120 mg ephedrine daily for over one year. Some individuals had been using such doses continuously for over five years, and the majority of these women continued to use ephedrine despite the presence of adverse symptoms.

History and Pharmacology

Ephedra species have a long history of medicinal use, documented in medical treatises from China and India. Some experts have called it the oldest medicinal plant in continuous use.⁴² A species of ephedra was found in a Neanderthal grave and was presumably used medicinally.⁴³ Use by Dioscorides, the famous Hellenistic herbalist, has been documented, as has use in Europe from the 15th to the 19th centuries.⁴⁴ Use of ephedrine, the principal alkaloid in ephedra, gained notoriety during modern times when it was learned that the drug was given parenterally to Japanese kamikaze pilots during World War II.⁴⁵ Over 40 species of ephedra are found throughout Asia, Europe, and the Mediterranean area, as well in North and South America.

Botany

Ephedra, or ma huang, is the common name for any one of three species grown medicinally in China and recognized in the Chinese Materia Medica: *Ephedra sinica*, *Ephedra equisetina* and *Ephedra intermedia*.⁴⁶

The branches of this small twiggy shrub have been used in the practice of traditional Chinese medicine to treat colds, fevers, and wheezing and as a diaphoretic and diuretic.⁴⁷ Botanically related species have also been used in traditional Indian and Tibetan medicine for similar indications.⁴⁸ In the modern discipline of phytomedicine, ephedra has been approved by the German Commission E to treat diseases of the respiratory tract with mild bronchospasm in patients over 6 years of age.⁴⁹ In addition to the three species mentioned above, others, such as *Ephedra distachya* or *Ephedra gerardiana* may be used for preparation of commercial products.⁴⁹ North American ephedra species, such as *Ephedra nevadensis*, commonly known as mormon tea, reportedly contain little or no ephedrine.^{50, 51}

Phytochemistry

The active components of ephedra (about 1.32 percent by weight) are the phenylalanine-derived alkaloids such as (-)-ephedrine, (+)-pseudoephedrine, (-)-norephedrine, and (+)-norpseudoephedrine, which is also called cathine.^{45, 52} Alkaloid content and composition may vary based on species and growing conditions such as geographic location, altitude, and soil pH.⁵³⁻⁵⁶ Ephedra is harvested in the fall, when the alkaloid content is highest.⁵⁷ Even though the total alkaloid content can vary from 0.5 percent to 2.3 percent, ephedrine accounts for the majority of the alkaloids (up to 90 percent of total), followed by pseudoephedrine (generally up to 27 percent of total).^{45, 58, 59} One species of ephedra, *Ephedra intermedia*, has been reported to have reversed ratios of ephedrine to pseudoephedrine, with approximately 30 percent ephedrine and up to 75 percent pseudoephedrine.^{57, 60} Norephedrine content is generally very low in commercial ephedra species.⁶⁰ Ratios of the most common alkaloids vary in commercial preparations, but ephedrine and pseudoephedrine account for 90 to 100 percent of the alkaloids measured.⁶¹ The relative potency of the alkaloids is discussed below.

Pharmacology of Ephedrine/ Ephedra

Although ephedrine was first isolated from ma huang in 1887, it was not until early in the twentieth century that the pharmacology of ephedrine and its related alkaloids was considered by Western medicine.^{44, 62-64} Ephedrine is defined as a mixed sympathomimetic agent, which acts indirectly by enhancing the release of norepinephrine from sympathetic neurons and directly by stimulating alpha and beta adrenergic receptors.⁶⁵ The other, related, alkaloids have similar activities, although they are less potent than ephedrine.⁶² Thus, the pharmacologic activity of a given ephedra sample depends on its alkaloid composition.

In the cardiovascular system, ephedrine increases heart rate and therefore cardiac output.^{65, 66} Because of its peripheral vasoconstriction activity, ephedrine increases peripheral resistance and can lead to a sustained rise in blood pressure. As a result, parenteral ephedrine has been used to treat shock and hypotension associated with cesarean section. Elevations in blood pressure appear to be dose dependent in humans.⁶⁷ However, there appears to be a threshold effect: doses under 50 mg do not necessarily result in increased blood pressure.

In the lung, ephedrine acts via the beta (2) adrenergic receptors to relax bronchial smooth muscle.^{65, 66} However, ephedrine's use as a bronchodilator (which began in 1924),⁶³ has largely been supplanted by more selective agents for chronic use. Currently, ephedrine is used as a decongestant and for the temporary relief of shortness of breath due to bronchial asthma.

Because of its lipid solubility, ephedrine crosses the blood-brain barrier where it acts as a central nervous system stimulant.^{65, 66} Immediate effects are attributable to stimulation of dopamine release, but ephedrine also acts on central adrenergic receptors, which increases release of central norepinephrine. This combination of adrenergic and dopaminergic effects leads, in the short term, to improved mood and heightened alertness with decreased fatigue and desire for sleep. Physical activity also increases. Concern exists that because of its chemical similarity to amphetamines, ephedrine may have potential for abuse. Ephedrine has demonstrated reinforcing effects in humans that are similar to those of amphetamines but not as strong.⁶⁸ At higher doses, the release of norepinephrine causes anxiety, restlessness, and insomnia.

Ephedrine and its alkaloids may promote weight loss via several mechanisms. First, ephedrine may exert an anorexic effect via central effects of norepinephrine on satiety centers in the hypothalamus.⁶⁹ Second, stimulation of beta (3) receptors in brown fat, via release of catecholamines, leads to increased lipogenesis.⁷⁰ Third, of the three principal alkaloids of ephedra (ephedrine, pseudoephedrine, and phenylpropanolamine), ephedrine is the most potent thermogenic agent (a substance that increases the portion of ingested calories that are dissipated as heat, at the expense of energy storage).

Pharmacokinetics

Ephedrine is readily absorbed from the gastrointestinal tract, with peak concentrations of an oral, immediate-release dose achieved at approximately two to three hours.⁷¹⁻⁷³ It is distributed widely throughout the body, crossing the blood-brain barrier, as mentioned above, as well as the placenta. The half-life of ephedrine in the blood (the time required to reach half the peak concentration) is six hours.⁷³ Metabolism does occur in the liver, but the majority of ephedrine (60–97 percent) is excreted unchanged via the urine.^{74, 75} The pharmacokinetics of pseudoephedrine and phenylpropanolamine (norephedrine) are similar.⁷³

The disposition of a pharmaceutical preparation of ephedrine (25 mg) in ten healthy volunteers was compared with that of three botanical preparations that contained a roughly equivalent alkaloid dose.⁷⁶ Among the four products tested, the time to achieve peak concentration ranged from 2.61 to 3.05 hours, and the elimination half-life (time that was required for half of the ingested product to be eliminated) varied from 4.85 to 6.47 hours. None of the botanical preparations tested was found to have statistically different pharmacokinetics from the purified ephedrine. These results are not completely confirmed by a second study, which compared purified ephedrine with a botanical preparation.⁷⁷ This study found that the absorption of the botanical preparation was slower and took almost twice as long as the pharmaceutical preparation to reach maximal concentration (3.90 versus 1.69 hours). However, maximal concentration of ephedrine was actually higher for the botanical preparation. Elimination half-life was between five and six hours for both preparations.

Combination Formulas Used for Weight Loss

Pharmaceutical preparations of ephedrine for weight loss often include caffeine and/or aspirin. Caffeine alone has been shown to stimulate thermogenesis and weight loss, both as an isolated alkaloid and as a botanical tea.^{67, 78, 79} Further, caffeine potentiates the thermogenic effects of ephedrine by acting as an adenosine receptor antagonist and inhibiting cellular phosphodiesterase activity.^{80, 81} Botanical preparations often mimic these combined formulations by including caffeine- or salicylic acid-containing herbs or those that contain sympathomimetic amines such as *Sida cordifolia* (country mallow) or *Citrus aurantium* (bitter orange) (see Table 1). Other herbs frequently included in botanical weight loss formulas include those with diuretic or laxative actions.