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Ephedra and Ephedrine Alkaloids for Weight Loss and Athletic Performance  
Fact Sheet for Health Professionals  
  
This document summarizes the results of an evidence-based review on the efficacy and safety of ephedra and ephedrine alkaloids for weight loss or to enhance athletic performance (power and endurance). The report was prepared by the Southern California Evidence-based Practice Center-RAND (RAND) under contract to the Agency for Healthcare Research and Quality (AHRQ) of the U.S. Department of Health and Human Services. This work was sponsored by the Office of Dietary Supplements (ODS) and the National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health, U.S. Department of Health and Human Services. A summary of this report was published in JAMA and the data described here are drawn from that article [1].  
  
Key points  
The Chinese botanical ephedra, or ma-huang, is sold as a dietary supplement in the United States. It is a natural source of the alkaloids ephedrine and pseudoephedrine. Some dietary supplement products used for weight loss and to enhance athletic performance contain these alkaloids.  
Synthetic ephedrine and pseudoephedrine are found in over-the-counter decongestants and cold medicines and are used to treat asthma. Ephedrine is not approved in the United States as a drug for weight loss or to enhance athletic performance.  
The use of ephedrine, ephedrine plus caffeine, or dietary supplements containing ephedra and botanicals with caffeine is associated with a modest but statistically significant increase in weight loss over a relatively short time (less than or equal to 6 months). No studies have assessed their long-term effects (greater than 6 months).  
No studies have assessed the effect of dietary supplements containing ephedra and botanicals on athletic performance. The few studies that assessed the effect of ephedrine support a modest effect of ephedrine plus caffeine on very-short-term (1-2 hours after a single dose) athletic performance in a highly selected physically fit population.  
Results of controlled trials show that the use of synthetic ephedrine, ephedrine plus caffeine, or ephedra plus botanicals containing caffeine is associated with 2-3 times the risk of nausea, vomiting, psychiatric symptoms such as anxiety and change in mood, autonomic hyperactivity, and palpitations compared with placebo.  
RAND analyzed adverse event reports filed with the U.S. Food and Drug Administration (FDA) and with a manufacturer of ephedra-containing dietary supplements as well as published case reports. Although this analysis raises concerns about the safety of botanical dietary supplements containing ephedra, most of these case reports are not documented sufficiently to support an informed judgment about the relationship between the use of ephedra-containing dietary supplements or ephedrine and the adverse event in question.  
According to the RAND report, the number of deaths, myocardial infarctions, cerebrovascular accidents, seizures, and serious psychiatric illnesses in young adults is sufficient to warrant further evaluation of the safety of these products in a controlled manner (such as a hypothesis-testing case-control study) to test the possibility that consumption of ephedra or ephedrine causes these serious adverse events.  
Introduction to ephedra and ephedrine alkaloids  
The Chinese botanical ephedra, or ma-huang, is sold as a dietary supplement in the United States. Ephedra is the common name for three principal species: Ephedra sinica, Ephedra equisentina, and Ephedra intermedia [2]. The active compounds in the plant s stem (about 1.32% by weight) are the phenylalanine-derived alkaloids ephedrine, pseudoephedrine, phenylpropanolamine (norephedrine), and cathine (norpseudoephedrine) [3,4].  
  
Alkaloid content and composition vary by species and growth conditions [5-7]; total alkaloid content can vary from 0.5% to 2.3%. Ephedrine, the most potent alkaloid, can account for up to 90% of the total alkaloid content and pseudoephedrine can account for up to 27% [3,8,9]. The pharmacologic activity of an ephedra sample depends on its alkaloid composition. North American ephedra species, such as E. nevadensis (known as Mormon tea), contain little or no ephedrine or other alkaloids [10].  
  
Ephedrine is a mixed sympathomimetic agent that enhances the release of norepinephrine from sympathetic neurons and stimulates alpha and beta receptors [11]. Ephedrine stimulates heart rate, thereby increasing cardiac output [11,12]. It causes peripheral constriction resulting in an increase in peripheral resistance that can lead to a sustained rise in blood pressure [13]. It relaxes bronchial smooth muscle [11,12] and is used as a decongestant and for temporary relief of shortness of breath caused by asthma.  
  
Ephedrine acts as a stimulant in the central nervous system [11,12]. Of the ephedra alkaloids, ephedrine is the most potent thermogenic agent. It may function as an anorectic by acting on the satiety center in the hypothalamus [14].  
  
Products available for weight loss or athletic enhancement  
Ephedrine or products containing combinations of ephedrine and caffeine are not approved in the United States as drugs for weight loss. Botanical dietary supplements for weight loss may include ephedra (a natural source of ephedrine) and other botanicals that are natural sources of caffeine and salicylic acid. In place of ephedra, manufacturers sometimes substitute botanicals that contain sympathomimetic amines, such as country mallow or bitter orange. Botanicals with diuretic or cathartic action are sometimes also included.  
  
Although ephedrine is not approved in the United States as a drug for athletic performance, athletes have used over-the-counter stimulants containing ephedrine or its related alkaloids to enhance athletic performance. Products containing ephedra alone or combined with vitamins, minerals, or other botanicals are marketed to increase energy and enhance athletic performance.  
  
Overview of the RAND evidence-based review of ephedra and ephedrine alkaloids  
ODS and NCCAM sponsored an evidence-based review by RAND to assess the clinical efficacy and safety of products containing ephedra or synthesized ephedrine alkaloids used for weight loss or to enhance athletic performance. RAND, one of 12 centers participating in the AHRQ Evidence-based Practice Program, prepared a report for AHRQ that was released in March 2003. A technical expert panel that included basic scientists and clinicians with a wide range of expertise provided input for the report.  
  
RAND conducted a comprehensive search of published and unpublished sources for controlled clinical trials on ephedra and ephedrine used for weight loss and athletic performance in humans. Each study considered for the review was evaluated according to preestablished criteria. RAND identified 52 controlled clinical trials of synthetic ephedrine or botanical ephedra used for weight loss or athletic performance in humans. Weight-loss studies with at least 8 weeks of follow-up data were reviewed for inclusion in a meta-analysis. Studies of athletic performance used a wide variety of interventions and were not synthesized through meta-analysis.  
  
The strongest level of evidence to show that an adverse event was caused by a particular exposure comes from placebo-controlled randomized trials. Data on adverse events associated with the use of ephedrine or ephedra-containing dietary supplements were collected from 52 randomized controlled trials identified in the literature search. The number of events or people (depending on how the study reported the events) was abstracted for each treatment and placebo group. A meta-analysis was conducted on data from 50 trials for subgroups of adverse events, including psychiatric symptoms, autonomic hyperactivity, nausea/vomiting, palpitations, hypertension, and tachycardia. No serious adverse events (death, myocardial infarction, cerebrovascular/stroke events, seizure, or serious psychiatric events) were reported in the clinical trials. However, because participants in clinical trials must meet eligibility criteria, including the absence of specific underlying health risks, they may not represent the general population.  
  
Case reports were assessed in this review because the total number of patients in the clinical trials was not sufficient for adequately assessing the possibility of rare outcomes. Although such adverse event reports are not conclusive evidence of a cause-and-effect relationship, they can indicate the potential for such a relationship.  
  
The cases came from the published case reports identified in the literature search; case reports from the FDA through September 30, 2001; and case reports from a manufacturer of ephedra-containing dietary supplements. The reports were coded for the type of adverse event; serious adverse events were analyzed further. The goal of the analysis was to identify cases that would be classified medically as idiopathic in etiology (i.e., cause unknown). If use of ephedra or ephedrine-containing products was documented for such cases, then the possibility that ephedra or ephedrine caused the event was considered.  
  
Cases were classified as sentinel events if 1) documentation existed that an adverse event meeting the selection criteria occurred, 2) documentation existed that the person having the adverse event took an ephedra-containing supplement within 24 hours before the event (for cases of death, myocardial infarction, stroke, or seizure), and 3) alternative explanations were investigated and excluded with reasonable certainty. If another condition existed that by itself could have caused the adverse event but may have been precipitated by ephedra or ephedrine, it was classified as a possible sentinel event.  
  
Findings  
Efficacy of ephedra and ephedrine alkaloids used for weight loss  
  
RAND identified 44 controlled trials assessing ephedra and ephedrine alkaloids used in combination with other compounds for weight loss [1]; 20 of these trials met the criteria for inclusion in the meta-analysis. Meta-regressions were used to assess the effect of ephedrine, ephedrine plus caffeine, and ephedra plus herbs containing caffeine. Five pairs of treatment regimens were compared:  
  
Ephedrine vs. placebo: 5 studies. Ephedrine was associated with a statistically significant weight loss of 1.3 pounds/month more than was associated with placebo for up to 4 months of use.  
Ephedrine plus caffeine vs. placebo: 12 studies. Ephedrine plus caffeine was associated with a statistically significant weight loss of 2.2 pounds/month more than was associated with placebo for up to 4 months of use.  
Ephedrine plus caffeine vs. ephedrine: 3 studies. Ephedrine plus caffeine was associated with a statistically significant weight loss of 0.8 pounds/month more than was associated with ephedrine alone.  
Ephedrine vs. other active weight loss products: 2 studies. No conclusions could be drawn because of the small sample size in each of these studies.  
Ephedra plus herbs containing caffeine vs. placebo: 4 studies. Ephedra plus herbs containing caffeine was associated with a statistically significant weight loss of 2.1 pounds/month more than was associated with placebo for up to 4 months of use.  
The use of ephedrine, ephedrine plus caffeine, or dietary supplements containing ephedra and herbs with caffeine was associated with a statistically significant increase in weight loss over a relatively short time. Both ephedrine plus caffeine and ephedra plus herbs containing caffeine were somewhat more effective than ephedrine alone in promoting weight loss.  
  
Only one study compared ephedra plus other herbs (but without caffeine) with a placebo. The ephedra-containing product was associated with a weight loss of 1.8 pounds/month more than was associated with a placebo for up to 3 months of use.  
  
Overall, the effects on weight loss of synthetic ephedrine plus caffeine and ephedra plus herbs containing caffeine were equivalent: weight loss of approximately 2 pounds/month more than was associated with placebo for up to 4 or 6 months of use. No studies assessed the long-term effects on weight loss; the longest published follow-up was 6 months.  
  
Efficacy of ephedra and ephedra alkaloids used to enhance athletic performance  
  
No studies assessed the effect of dietary supplements containing ephedra with or without herbs containing caffeine on athletic performance. The effects of ephedrine on athletic performance have not been well studied; RAND identified 8 published controlled trials of the effects of synthetic ephedrine on athletic performance, all but 1 of which also included caffeine. These trials were not appropriate for a pooled analysis because they used a wide variety of interventions.  
  
A few studies assessed the effect of ephedrine on athletic performance in small samples for short times (1-2 hours after a single dose) and showed a modest effect of ephedrine plus caffeine on very-short-term athletic performance in a highly selected physically fit population. This use does not reflect that of the general population. No studies assessed the sustained use of ephedrine on performance.  
  
Safety assessment  
  
RAND reviewed adverse events reported in 52 published randomized controlled clinical trials. No serious adverse events (death, myocardial infarction, cerebrovascular/stroke events, seizure, or serious psychiatric events) were reported in the clinical trials. However, evidence from the trials was sufficient to support the conclusion that the use of ephedrine, ephedrine plus caffeine, or ephedra plus caffeine is associated with 2-3 times the risk of nausea, vomiting, psychiatric symptoms such as anxiety and change in mood, autonomic hyperactivity, and palpitations. The contribution of caffeine to these symptoms cannot be determined.  
  
RAND also reviewed 71 cases reported in the published medical literature, 1820 case reports provided by FDA, and more than 18,000 consumer complaints reported to a manufacturer of ephedra-containing dietary supplements. Most of the cases were not well documented so decisions could not be made about the potential relationship between the use of ephedra-containing dietary supplements or ephedrine and the adverse event. A total of 65 cases from the published literature, 241 cases from FDA, and 43 cases from a manufacturer of ephedra-containing dietary supplements were included in the adverse event analysis.  
  
Sentinel events with prior ephedra consumption included 2 deaths, 3 myocardial infarctions, 9 cerebrovascular/stroke events, 3 seizures, and 5 psychiatric cases. Sentinel events with prior ephedrine consumption included 3 deaths, 2 myocardial infarctions, 2 cerebrovascular/stroke events, 1 seizure, and 3 psychiatric cases. About half of the sentinel events occurred in individuals 30 years of age or younger. An additional 43 cases were identified as possible sentinel events with prior ephedra consumption and an additional 7 cases were identified as possible sentinel events with prior ephedrine consumption.  
  
References  
Shekelle PG, Hardy ML, Morton SC, et al.: Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance. A meta-analysis. JAMA 289:1537-1545, 2003. [PubMed abstract]  
Hu SY: Ephedra (ma-huang) in the new Chinese materia medica. Economic Botany 23:346-351, 1969.  
Karch SB: Ma huang and the ephedra alkaloids. In: Cupp MJ, ed. Toxicology and Clinical Pharmacology of Herbal Products. Totowa, NJ: Humana Press, 2000:11-30.  
Leung AY, Foster S: Encyclopedia of Common Natural Ingredients Used in Foods, Drugs, and Cosmetics. New York: John Wiley, 1996.  
5. Kajimura K, Iwamoto Y, Yamasaki K, et al.: Variation of growth and contents in ephedrine type alkaloids in Ephedra distachya. Natural Medicines 48:122-125, 1994.  
Tanaka T, Obha K, Lawaahara K, Sakai E.: Comparison of the constituents of ephedra herbs from various countries on ephedrine type alkaloids. Natural Medicines 49:418-424, 1995.  
Kondo N, Mikage M, Idaka K: Medico-botanical studies of ephedra plants from the Himalayan region, part III: causative factors of variations of alkaloid content in herbal stems. Natural Medicines 53:194-200, 1999.  
Evans WC: Trease and Evans Pharmacognosy. London: WB Saunders, 1989.  
McKenna DJ, Jones K, Hughes K: Botanical Medicines. The Desk Reference for Major Herbal Supplements, 2nd edition. New York: Haworth Herbal Press, 2002.  
Caveney S, Charlet DA, Freitag H, Maier-Stolte M, Starratt AN: New observations on the secondary chemistry of world Ephedra (Ephedraceae). American Journal of Botany 88:1199-1208, 2001. [PubMed abstract]  
Hardman JG, Limbird LE, Gilman A, eds.: Goodman and Gilman s The Pharmacological Basis of Disease. New York: McGraw-Hill, 2001.  
Burnham TH, Novak KK, Bell WI, eds.: Ephedrine. In: Drug Facts and Comparisons, 57th edition. St. Louis: Facts and Comparisons, 2003.  
Astrup A, Toubro S: Thermogenic, metabolic, and cardiovascular responses to ephedrine and caffeine in man. International Journal of Obesity and Related Metabolic Disorders 17:S41-S43, 1993. [PubMed abstract]  
Astrup A, Toubro S, Christensen NJ, Quaade F: Pharmacology of thermogenic drugs. American Journal of Clinical Nutrition 55:246S-248S, 1993. [PubMed abstract]  
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