Agency for Healthcare Research and Quality

Evidence Report/Technology Assessment

Number 76

Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects

Summary

Overview

At the direction of the funding agencies (the National Institutes of Health Office of Dietary Supplements (ODS), the National Center for Complementary and Alternative Medicine (NCCAM), and the Agency for Healthcare Research and Quality (AHRQ)), and in consultation with our Technical Expert Panel, we addressed research questions regarding the efficacy of herbal ephedra and ephedrine for weight loss and athletic performance through a comprehensive literature review and synthesis of evidence. We assessed the safety of these products through review of clinical trials. Meta-analysis was performed where appropriate. In addition, we reviewed herbal ephedra- and ephedrine-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-containing products. It is expected that the results of this review will be used to direct further research.

Reporting the Evidence

The following questions were provided to us by the funding agencies and guided this evidence report.

Weight Loss

1. What is the evidence for efficacy of ephedra-containing dietary supplement products in weight loss, over a sustained period of time?
2. Can efficacy for weight loss be attributed to ephedra alone, or ephedra in combination with other ingredients (e.g., caffeine)?
3. Does ephedra have additive effects with other agents?
4. What dosage levels of ephedra are necessary to achieve weight loss?

Athletic Performance

1. What is the evidence for efficacy of ephedra-containing dietary supplement products in terms of energy enhancement and enhancement of athletic performance, over a sustained period of time?
2. Can efficacy for energy enhancement and enhancement of athletic performance be attributed to ephedra alone, or ephedra in combination with other ingredients (e.g., caffeine) that produce energy enhancement and/or enhancement of athletic performance?
3. Does ephedra have additive effects with other agents?
4. What dosage levels of ephedra are necessary to achieve energy enhancement and enhancement of athletic performance?

Safety Assessment

1. Does use of ephedra-containing dietary supplement products over a sustained period of time increase the risk of cardiovascular disease (CVD) or other serious and life-threatening events in specific populations?
2. What populations are at risk of CVD and other life-threatening events through use of ephedra over a sustained period of time?
3. Can the risk for adverse events in these populations be attributed to ephedra alone, or in combination with other ingredients (e.g., caffeine)?
4. Does ephedra have additive effects with other agents?
5. What dosage levels of ephedra produce risk of CVD or other life-threatening events?

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6. Do ephedra-containing dietary supplement products alter physiologic markers of cardiovascular function?
7. What are the metabolic actions of ephedra, so as to explain its beneficial and adverse effects?

In addition to answering these 15 questions about ephedra-containing dietary supplement products, we were also asked to synthesize the available information on the same questions for the purified alkaloid, ephedrine.

After searching published reports, journal articles, conference presentations, and various sources of unpublished studies, we identified 52 controlled clinical trials of ephedrine or herbal ephedra for weight loss or athletic performance in humans. The FDA provided us with copies of over 1,000 adverse event reports (AERs) related to herbal ephedra and 125 AERs related to ephedrine. These reports often included interviews with patients and/or family members, extensive medical records, and copies of product labels. We identified 65 case reports in the literature and received a disk of 15,951 reports containing 18,502 cases from Metabolife, a manufacturer of ephedra products.

Methodology

Efficacy. Data for the efficacy analysis were abstracted from reports of controlled trials onto a specially designed form containing questions about the study design, the number of patients and comorbidities, dosage, adverse events, the types of outcome measures, and the time from intervention until outcome measurement. We selected the variables for abstraction with input from the project's technical experts. Two physicians, working independently, each extracted data from the same reports and resolved disagreements by consensus.

In selecting studies for the meta-analysis of weight loss efficacy, we considered only those trials of at least 8 weeks treatment duration. Our technical expert panel judged that shorter treatment durations were insufficient to assess weight loss. In selecting studies on athletic performance, we found that these studies varied widely with respect to intervention. Because of this heterogeneity, we compared and contrasted these studies in a narrative review, rather than performing a statistical synthesis.

The effects of ephedra/ephedrine on weight loss were examined in six different types of comparisons: (1)ephedrine versus placebo; (2) ephedrine plus caffeine versus placebo; (3) ephedrine plus caffeine versus ephedrine; (4) ephedrine versus other active treatment; (5)ephedra versus placebo; and (6) ephedra plus herbs containing caffeine versus placebo. The last comparison subgroup contained only a single trial; thus, effect sizes were estimated only for the first five. The effect size was calculated by dividing the outcome of a study (e.g., difference in weight loss per month between the two groups) by its standard deviation, which produces a unitless measure that is useful when comparing studies that assess outcomes (such as weight) that are similar but are measured differently (e.g., weight loss in pounds versus change in body mass index). Effect sizes were pooled separately for each of the five comparison subgroups. In addition, we used meta-regression to conduct a cross-subgroup synthesis on the effect sizes of the subgroups with a placebo comparison: ephedrine versus placebo; ephedrine plus caffeine versus placebo; and ephedra plus herbs containing caffeine versus placebo.

Safety. We reviewed each report of a controlled trial (regardless of treatment duration) for data on adverse events. Adverse events were recorded onto a spreadsheet that identified each study arm, the description of the adverse event as listed in the original article, and the numbers of subjects and adverse events in each arm. We then compared event rates in the ephedra or ephedrine groups to those in the placebo groups. We conducted a meta-analysis on those adverse event symptoms for which appreciable numbers of events were noted in the controlled trials.

Adverse event reports compiled by the FDA concerning ephedra or ephedrine were also reviewed by our physician reviewers. Within the time and resource constraints of this report, we reviewed all available reports of death, myocardial infarction (heart attack), cerebral vascular accident (stroke), seizure, and serious psychiatric illness filed prior to September 30, 2001. We also reviewed published case reports as well as event reports filed with Metabolife, a manufacturer of ephedra-containing products. After screening, all case reports were subjected to a review.

Based on input from our technical expert panel and the literature on methods to assess adverse event reports, we identified three important criteria for inclusion of such reports:

1. Documentation of an adverse event that met our selection criteria.
2. Documentation that the person having the adverse event took an ephedra-containing supplement or ephedrine within 24 hours prior to the event (for cases of death, myocardial infarction, stroke, or seizure).
3. Documentation that alternative explanations for the adverse event were investigated and were excluded with reasonable certainty.

We classified cases that met all three of these criteria as "sentinel events." Cases in which the event might have had other possible causes but the pharmacology of ephedrine could have contributed were classified as "possible sentinel events." Cases of death, myocardial infarction, cerebral vascular accident, and seizure were reviewed by internists, with additional review (as indicated) by a cardiologist, neurologist, or rheumatologist. Psychiatric cases were reviewed by a psychiatrist specializing in addictions and a psychologist with expertise in substance abuse. The criterion for use within 24 hours was not required for psychiatric cases.

Findings

Efficacy for Weight Loss. We identified 44 controlled trials that assessed use of ephedra or ephedrine used for weight loss. Of these, 18 were excluded from pooled analysis because they had a treatment duration of less than 8 weeks. Six additional trials were excluded for a variety of other reasons. Of the remaining 20 trials included in the meta-analysis, only five tested herbal ephedra-containing products. Together, these 20 trials assessed 678 persons who consumed either ephedra or ephedrine. The majority of studies of both ephedra and ephedrine are plagued by methodological problems (particularly, high attrition rates) that might contribute to bias. These methodological limitations must be considered when interpreting any conclusions regarding the efficacy of these products. Nevertheless, the evidence we identified and assessed supports an association between short-term use of ephedrine, ephedrine plus caffeine, or dietary supplements that contain ephedra with or without herbs containing caffeine and a statistically significant increase in short-term weight loss (compared to placebo). Adding caffeine to ephedrine modestly increases the amount of weight loss. There is no evidence that the effect of ephedra-containing dietary supplements with herbs containing caffeine differs from that of ephedrine plus caffeine: Both result in weight loss that is approximately 2 pounds per month greater than that with placebo, for up to 4 to 6 months. No studies have assessed the long-term effects of ephedra-containing dietary supplements or ephedrine on weight loss; the longest duration of treatment in a published study was 6 months.

Efficacy for Physical Performance Enhancement. The effect of ephedrine on athletic performance was assessed in seven studies. No studies have assessed the effect of herbal ephedra-containing dietary supplements on athletic performance. The few studies that assessed the effect of ephedrine on athletic performance have, in general, included only small samples of fit individuals (young male military recruits) and have assessed the effects only on very short-term immediate performance. Thus, these studies did not assess ephedrine as it is used in the general population. The data support a modest effect of ephedrine plus caffeine on very short-term athletic performance. No studies have assessed the sustained use of ephedrine on performance over time. The only study that assessed the additive effects of these agents reported that ephedrine must be supplemented with caffeine to affect athletic performance.

Safety Issues. The data on adverse events were drawn from clinical trials and case reports published in the literature, submitted to the FDA, and reported to Metabolife, a manufacturer of ephedra-containing supplement products. The strongest evidence for causality should come from clinical trials; however, in most circumstances, such trials do not enroll sufficient numbers of patients to adequately assess the possibility of rare outcomes. Such was the case with our review of ephedrine and ephedra-containing dietary supplements. Even in aggregate, the clinical trials enrolled only enough patients to detect a serious adverse event rate of at least 1.0 per 1,000. For rare outcomes, we reviewed case reports, but a causal relationship between ephedra or ephedrine use and these events cannot be assumed or proven.

Evidence from controlled trials was sufficient to conclude that the use of ephedrine and/or the use of ephedra-containing dietary supplements or ephedrine plus caffeine is associated with two to three times the risk of nausea, vomiting, psychiatric symptoms such as anxiety and change in mood, autonomic hyperactivity, and palpitations.

The majority of case reports are insufficiently documented to make an informed judgment about a relationship between the use of ephedrine or ephedra-containing dietary supplements and the adverse event in question. For prior consumption of ephedra-containing products, we identified two deaths, three myocardial infarctions, nine cerebrovascular accidents, three seizures, and five psychiatric cases as sentinel events; for prior consumption of ephedrine, we identified three deaths, two myocardial infarctions, two cerebrovascular accidents, one seizure, and three psychiatric cases as sentinel events. We identified 43 additional cases as possible sentinel events with prior ephedra consumption and seven additional cases as possible sentinel events for prior ephedrine consumption. About half the sentinel events occurred in persons aged 30 years or younger. Classification as a sentinel event does not imply a proven cause and effect relationship.

We did not assess the plethora of additional symptoms that have been reported in the published literature and the FDA Medwatch file for ephedra-containing dietary supplements and ephedrine products.

Future Research

Our analysis of the evidence reveals numerous gaps in the literature regarding the efficacy and safety of ephedra-containing dietary supplements. First, long-term assessments of the effectiveness of herbal ephedra or ephedrine for promoting weight loss are lacking. We identified no study with a treatment duration longer than 6 months. To improve health outcomes and reduce the risk of morbidities associated with being overweight, sufficient weight loss (5 to 10 percent of body weight) and long-term weight maintenance are necessary. Therefore, the benefit of ephedrine or herbal ephedra-containing dietary supplements for health outcomes is unknown.

Evidence regarding the effect of herbal ephedra or ephedrine on physical performance that reflects its use in the general population (repeated or long-term use by a representative sample) is also needed.

In order to assess a causal relationship between ephedra or ephedrine consumption and serious adverse events, a

hypothesis-testing study is needed. Continued analysis of case reports cannot substitute for a properly designed study to assess causality. A case-control study would probably be the study design of choice.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Southern California-RAND Evidence-based Practice Center, under Contract No. 290-97-0001. It is expected to be available in March 2003. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 76, *Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects*. . In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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