Evidence Report/Technology Assessment
Number 76

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

U.S. Department of Health and Human Services
Agency for Healthcare Research and Quality

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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Structured Abstract

Objectives. To assess the efficacy of herbal ephedra-containing dietary supplements and ephedrine on weight loss and athletic performance, through comprehensive literature review and synthesis of evidence. We also assessed safety of these products through review of adverse events reported in clinical trials, published case reports of adverse events, reports on file with the U.S. Food and Drug Administration (FDA), and a file of reports kept by a manufacturer of ephedra products, Metabolife.

Search Strategy. We searched for studies of herbal ephedra and ephedrine using the following electronic databases: Medline, EmBase, BIOSIS, Allied & Complementary Medicine Database (AMED), MANTIS, the Cochrane Controlled Clinical Trials Register Database, International Pharmaceutical Abstracts, Pascal, and SciSearch. We were able to obtain unpublished studies by posting notices in relevant journals and through contacts on our Technical Expert Panel. The FDA provided us with copies of over 1,000 adverse event reports (AERs) related to herbal ephedra and 125 adverse event reports related to ephedrine. The Metabolife files contained 18,502 cases.

Selection Criteria. Only studies of weight loss that were controlled trials of human subjects with treatment of at least eight weeks duration were accepted to assess efficacy. For assessment of athletic performance, only controlled trials of human subjects were accepted, but no minimum follow-up was specified. Reports of adverse events from controlled trials were included regardless of treatment duration. We reviewed all available reports of death, myocardial infarction (heart attack), cerebral vascular accident (stroke), seizure, and serious psychiatric illness reported to the FDA prior to September 30, 2001 and contained in their ephedra or ephedrine files, and all case reports identified in our literature search .

Data Collection and Analysis. We found 59 articles that corresponded to 52 controlled clinical trials of ephedrine or herbal ephedra for weight loss or athletic performance. Forty-four were controlled trials assessing ephedra or ephedrine for weight loss. Of these, 18 were excluded from pooled analysis because they had treatment durations of less than eight weeks. Thirteen articles corresponding to six trials were excluded for a variety of reasons. For the outcome of weight loss the effects of ephedra/ephedrine 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. Only four placebo-controlled trials assessed the combination of ephedra plus herbs containing caffeine, and only one trial assessed ephedra without herbs containing caffeine. Because of their small number and heterogeneity, eight athletic performance trials were compared and contrasted using only a narrative review and were not synthesized statistically. We also conducted a pooled meta-analysis on those adverse event symptoms that occurred frequently in the controlled trials.

In reviewing the individual adverse event reports, we searched for documentation that an adverse event had occurred, documentation that the subject had consumed ephedra within 24 hours prior to the adverse event, or a toxicological examination revealing ephedrine or one of its associated products in the blood or urine. We also sought evidence that an adequate investigation

had assessed and excluded other potential causes. Cases that met all these criteria were labeled "sentinel events." Cases that met the first two criteria but had other possible causes of the event were labeled "possible sentinel events." Classification as a sentinel event does not imply a proven cause and effect relationship. We used clinical judgment of expert clinicians to assess whether other causes had been adequately evaluated and excluded.

Main Results. *Weight Loss.* Short-term use of ephedrine, ephedrine plus caffeine, or dietary supplements containing ephedra with or without herbs containing caffeine is associated with a statistically significant increase in short-term weight loss (compared to placebo). The addition of caffeine to ephedrine is associated with a statistically significant modest increase in short-term weight loss. The observed effects on weight loss of ephedrine plus caffeine and ephedra-containing dietary supplements with or without herbs containing caffeine are approximately equivalent: a weight loss approximately two pounds per month greater than that with placebo, for up to four to six months. No studies have assessed the long-term effects of ephedrine or ephedra-containing dietary supplements on weight loss; the longest published treatment duration was six months.

Athletic Performance. The effect of herbal ephedra–containing dietary supplements on athletic performance has not been assessed. The few studies that assess the effect of ephedrine on athletic performance have included only small samples of fit individuals (young male military recruits) and have assessed its effect only on very short-term immediate performance. These data support a modest effect of ephedrine plus caffeine on very short-term athletic performance. One study reported the addition of caffeine to ephedrine is necessary to produce an effect on athletic performance. No studies have assessed the sustained use of ephedrine on performance over time.

Safety Issues. There is sufficient evidence from controlled trials to conclude that the use of ephedrine and/ or the use of ephedra-containing herbal 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 controlled trials studied relatively few people and in aggregate were insufficient to evaluate events with a risk of less than 1.0 per one thousand.

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. Prior ephedra consumption was associated with two deaths, three myocardial infarctions, nine cerebrovascular accidents, three seizures, and five psychiatric cases as sentinel events. Prior consumption of ephedrine was associated with 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 with prior ephedrine consumption. About half the sentinel events occurred in persons aged 30 years or younger.

Conclusions. Ephedrine, ephedrine plus caffeine, and ephedra-containing dietary supplements with or without herbs containing caffeine all promote modest amounts of weight loss over the short term. There are no data regarding long-term effects on weight loss. Single-dose ephedrine plus caffeine has a modest effect on athletic performance. The available trials do not provide any evidence about ephedrine or ephedra-containing dietary supplements, as they are used by the general population, to enhance athletic performance. Use of ephedra or ephedrine plus caffeine is

associated with an increased risk of gastrointestinal, psychiatric, and autonomic symptoms. The adverse event reports contain a sufficient number of cases of death, myocardial infarction, cerebrovascular accident, seizure, or serious psychiatric illness in young adults to warrant a hypothesis-testing study, such as a case-control study, to support or refute the hypothesis that consumption of ephedra or ephedrine may be causally related to these serious adverse events.

Contents

Tables

Figures