Ephedra and ephedrine for weight loss and athletic performance enhancement: clinical efficacy and side effects


CRD summary
This review assessed the effectiveness and safety of using ephedrine or ephedra for weight loss or improving athletic performance. The authors concluded that ephedra and ephedrine provide modest, short-term improvements in weight loss, but that they are associated with increased rates of side-effects. These conclusions reflected the limited evidence available and are likely to be reliable.

Authors' objectives
To assess the efficacy and safety of ephedra and ephedrine on weight loss and athletic performance.

Searching
MEDLINE, EMBASE, BIOSIS Previews, AMED, MANTIS, the Cochrane Controlled Trials Register, International Pharmaceutical Abstracts, Pascal and SciSearch were searched from their inception to March and April 2001; the search terms were reported. The reference lists of each retrieved article were also checked. Unpublished studies and grey literature were sought through notices in two journals and by contacting regulatory bodies and experts. Reports of adverse events were obtained from the U.S. Food and Drug Administration and Metabolife, the manufacturer of ephedra products. No language restrictions were employed.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) or controlled clinical trials (CCTs) of weight loss were eligible for the assessment of efficacy if there was a minimum treatment period of 8 weeks. Controlled trials of athletic performance were eligible for the assessment of efficacy, irrespective of follow-up. All controlled trials were eligible for the assessment of safety. Case reports were eligible for the safety analysis if ephedra or ephedrine was reported to have been consumed within 24 hours before an adverse event occurred, or if ephedrine or an associated product was found in the blood or urine and other potential causes were excluded.

Specific interventions included in the review
Studies including ephedra (a herbal dietary supplement) or ephedrine (an alkaloid derived from herbal ephedra) were eligible for inclusion. Both ephedra and ephedrine, at a variety of dosages, were included in the review. They were either given alone or in combination with other treatments, most commonly caffeine.

Participants included in the review
The inclusion criteria for the participants were not stated clearly, but appeared to be individuals using ephedra or ephedrine to promote weight loss or enhance athletic performance.

Outcomes assessed in the review
Studies that assessed weight loss, athletic performance or information on adverse events were eligible for inclusion. Weight loss became the primary outcome for the review.

How were decisions on the relevance of primary studies made?
Three reviewers independently assessed studies for inclusion in the review. Any disagreements were resolved by consensus.

Assessment of study quality
The validity of controlled trials was assessed using the Jadad scale, which assesses randomisation, blinding and the handling of withdrawals. A score of at least 3 out of 5 was used to identify trials considered to be of higher quality. The authors did not state how many reviewers performed the validity assessment.

**Data extraction**

Two reviewers independently extracted the data, and any disagreements were resolved by consensus. Data on the study design and execution, participants, therapies, weight loss, follow-up times and adverse events were extracted. Effect sizes (standardised mean differences) were calculated from the mean and standard deviation for every comparison of interest with respect to weight loss. Odds ratios (ORs) were calculated for adverse events.

**Methods of synthesis**

How were the studies combined?

Studies of weight loss were combined in random-effects meta-analyses. Trials assessing athletic performance were too heterogeneous to be pooled statistically, so these were combined in a narrative summary. Pooled ORs for some adverse events with sufficient data were estimated by meta-analysis. Publication bias was assessed by evaluating funnel plots, and by conducting an adjusted rank correlation test and a regression asymmetry test.

How were differences between studies investigated?

Subgroups were identified based on the comparison employed in the trials. A chi-squared test for heterogeneity was carried out. Sensitivity analyses were also conducted to investigate the effects of attrition and quality, and a meta-regression was performed to compare the monthly weight loss effect sizes across comparisons.

**Results of the review**

Twenty trials were included in the assessment of weight loss and eight in the assessment of athletic performance. It was unclear how many trials were RCTs or CCTs, or how many participants were included. A total of 117 studies were included in the review of adverse events: 52 controlled trials and 65 case reports or case series.

Weight loss.

Trials of ephedrine or ephedra for weight loss involved up to 6 months of treatment.

Five trials, which received quality scores between 1 and 3, compared ephedrine with placebo. The pooled estimate of the rate of weight loss was an effect size of -0.50 (95% confidence interval, CI: -0.85, -0.15), which translated to a monthly weight loss of 1.3 pounds more for ephedrine than for placebo. An analysis including only high-quality trials found a pooled estimate significantly lower than the main analysis (effect size -0.20, P=0.049). No statistical heterogeneity was identified (P=0.185).

Twelve trials compared ephedrine plus caffeine with placebo, of which six had a quality score of 3 or more. The pooled estimate of the rate of weight loss was an effect size of -0.85 (95% CI: -1.1, -0.61), which translated to a loss of 2.2 pounds more in the treatment group than in the placebo group. The results of the sensitivity analyses were not significantly different from the main analysis. There was no evidence of publication bias. The P-value from the chi-squared test for heterogeneity was 0.073, although the directions of the effect sizes of the individual trials were consistent.

Three trials compared ephedrine plus caffeine with ephedrine alone, and the quality scores were between 1 and 3. The pooled estimate of the rate of weight loss for the combined group was an effect size of -0.31 (95% CI: -0.60, -0.02), which equated to a weight loss of 0.8 pounds per month more for ephedrine plus caffeine compared with ephedrine alone. No statistical heterogeneity was identified (P=0.966).

Two trials compared ephedrine with another active weight loss therapy. There were no statistically significant differences between the groups in either trial.

One trial, which received a quality score of 4, compared ephedra with placebo. This trial found a weight loss rate of 1.8...
pounds per month greater in the ephedra group than in the placebo group (95% CI: -2.7, -1.0).

Four trials compared ephedra plus caffeine-containing herbs with placebo; two of the trials received a quality score of 5 and two received a score of 2. The pooled estimate of the rate of weight loss was an effect size of -0.81 (95% CI: -1.12, -0.51), which translated to a weight loss of 2.1 pounds more in the treatment group than in the placebo group. There was no evidence of publication bias and no statistical heterogeneity was identified (P=0.689).

The meta-regression across all trials showed that all effect sizes for each comparison were significantly different from zero (i.e. all treatments were associated with significantly increased weight loss compared with placebo), with ephedrine plus caffeine and ephedra plus caffeine-containing herbs being somewhat more effective for weight loss than ephedrine alone.

Athletic performance.

Six small trials (with fewer than 24 participants) compared the effects of synthetic ephedrine with or without caffeine to caffeine and placebo on exercise parameters in healthy males. One of these trials assessed strength training and found a significant improvement in muscle endurance during the first of three repetitions. No other statistically significant differences were identified. One trial assessed the effects of ephedrine versus placebo or no treatment on 21 healthy young men. No statistical differences in athletic performance were identified.

Adverse events.

The pooled estimates showed that the treatment groups experienced significantly higher rates of psychiatric symptoms (8 trials; OR 3.64, 95% CI: 1.91, 7.31), autonomic hyperactivity (13 trials; OR 3.37, 95% CI: 2.19, 5.31), heart palpitations (11 trials; OR 2.29, 95% CI: 1.27, 4.32) and upper gastrointestinal symptoms (10 trials; OR 2.15, 95% CI: 1.39, 3.38).

Authors' conclusions
Ephedrine and ephedra promote modest short-term weight loss. However, there were no data regarding long-term weight loss. The use of ephedra or ephedrine and caffeine was associated with an increased risk of heart palpitations or psychiatric, autonomic, or upper gastrointestinal symptoms.

CRD commentary
The inclusion criteria were clear in terms of the interventions, outcomes and study designs eligible for inclusion in the review. The search was extensive with attempts to minimise language and publication bias. The authors used appropriate measures to minimise bias and error in the study selection and data extraction processes of the review. The quality of the included studies was assessed using a validated measure (although not the most informative) and the findings were incorporated into sensitivity analyses of the results. Meta-analytic methods were employed where appropriate, and the methods of analyses and the assumptions employed were explicit. The authors' cautious conclusions accurately reflect the limitations of the evidence available to the review, and are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that long-term assessments of the efficacy of ephedra or ephedrine for promoting weight loss are required. Studies evaluating the effect of repeated use of ephedra or ephedrine on athletic performance in women and adolescents, and in individuals who represent the general population, are needed. There is also a need for a study assessing the possible association of ephedra or ephedrine and the occurrence of serious adverse events.

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