Landmark Study!

Ephedra & Caffeine Safe and Effective

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This NIH funded study was conducted by some of the leading obesity researchers in America at St. Luke's-Roosevelt Hospital, Columbia University in New York and the Beth Israel-Deaconess Medical Center, Harvard Medical School in Boston

Some time ago, I suggested the media hype about the dangers of taking herbal ephedra supplements was overblown. I described a number of clinical studies indicating that use of synthetic ephedrine or herbal ephedra supplements (with or without caffeine) appeared to be among the most effective and safe strategies to promote fat loss in apparently healthy populations.[1-13] Despite this efficacy and safety record, several groups have warned the public about the safety of ephedra-containing supplements.[14,15] In addition, herbal ephedra supplements have been on the FDA's watch list for some time.[15] For example, Dr. Paul Coates, Director of the Office of Dietary Supplements (ODS) at the National Institutes of Health (NIH), indicated at the recent Performance Enhancement Products conference that "we will not enter the ephedra controversy unarmed." So, what's new? A landmark study funded by the NIH has just been published that reports data from a six-month clinical trial examining the efficacy and safety of herbal ephedra supplementation.[16] This discussion overviews the results of this study to see if the concerns raised about herbal ephedra supplements are real or have been overblown.

Background: Getting Up to Speed

Ephedrine and caffeine (EC) have been shown to stimulate metabolism, increase energy expenditure and promote fat loss.[1-13] For example, Boozer and associates[1] reported that eight weeks of ephedrine (72 mg/day) and caffeine (240 mg/day) supplementation promoted a 4.0 kilogram loss (8.8 pounds) in body mass and a 2.1 percent loss in body fat with minor side effects. Molnar and colleagues[2] reported that overweight children treated for 20 weeks with ephedrine and caffeine observed a 14.4 percent loss in body mass and a 6.6 percent decrease in body fat with no differences in side effects when compared to placebo. Greenway and colleagues[3] reported that ephedrine/caffeine was a more cost-effective and safer treatment for reducing weight, cardiac risk, and low density lipoprotein (LDL) cholesterol than several commonly prescribed weight loss drugs (fenfluramine with mazindol or phentermine). These findings and others have led a number of investigators to conclude that EC supplementation can serve as a safe and effective treatment for obesity.[3,12,13]

Thermogenic (fat-burning) supplements typically contain naturally derived sources of ephedrine (e.g., Ma Haung, Sida Cordifolia), caffeine (e.g., Gaurana, Bissey Nut, Kola), and/or other ingredients believed to increase energy expenditure and lipolysis, and/or promote fat loss (e.g., aspirin/salicin [Willow Bark Extract], synephrine [Citrus Aurantium, Bitter Orange], forskolin [Coleus Forskohlii]; calcium & sodium phosphate, thyroid stimulators [e.g., guggulsterones, L-tyrosine], cayenne & black pepper, ginger root, etc). Thermogenic weight loss supplements represent one of the largest segments in the weight loss/fat loss supplement category. In 1999 alone, an estimated 12 million people used herbal thermogenic supplements.[17]

Concerns over the safety of ephedra-containing supplements have been voiced for years. The basis of this concern has primarily come from case reports submitted to the FDA's Adverse Event Monitoring System (AEMS). The AEMS is a voluntary system of reporting perceived side effects related to taking nutritional supplements. A number of reports to the AEMS have indicated that individuals who were taking ephedra-containing supplements (with or without other supplements) experienced some type of symptom, side effect or adverse event. Based on these reports, the FDA issued a warning about ingesting ephedrine-containing dietary supplements[14] and attempted to ban sale of ephedra-containing supplements. The attempt to ban sale of ephedra supplements was quickly rescinded by Congress, which found there was insufficient data to support FDA claims that ephedra was not a safe nutritional supplement.

However, a paper published in the *New England Journal of Medicine* in the fall of 2000 renewed warnings about ephedra supplements.[18] This study evaluated 141 cases reported to the AEMS from 1997 to 1999 that involved ephedra supplements. The researchers reported that it was their view that 31 percent of cases were considered definitely or probably related to the use of supplements containing ephedra alkaloids and 31 percent were deemed possibly related. Of these, 47 percent involved cardiovascular symptoms and 18 percent involved the central nervous system. Hypertension was the single most frequent adverse effect (17 reports), followed by palpitations and/or tachycardia (13); stroke (10); and seizures (7). According to these reviewers, 10 events resulted in death and 13 produced permanent disability. In most instances, excessive amounts of ephedra or ephedrine were apparently consumed (i.e., more than the apparent upper limit of safety of 90 mg/day). The authors concluded that use of dietary supplements containing ephedra alkaloids may pose a health risk to some persons. This report renewed efforts to call for a ban on the sale of herbal ephedra supplements and provided rationale for the NIH to fund a comprehensive study.

Landmark NIH-Sponsored Study

The background information on ephedra was meant to offer a full appreciation of the significance of the results of the latest study on herbal ephedra/caffeine. As you will see, results weren't exactly what the anti-ephedra establishment had hoped for. The study was conducted by some of the leading obesity researchers in America at St. Luke's-Roosevelt Hospital, Columbia University in New York and the Beth Israel-Deaconess Medical Center, Harvard Medical School in Boston.[16] In the study, 167 overweight but otherwise healthy men and women were randomized to participate in a double blind and placebo controlled study to determine the safety and efficacy of herbal EC supplementation.

Subjects ingested a placebo or an herbal EC supplement 30 minutes prior to eating each of three meals per day for six months. This provided a total of 90 milligrams per day of ephedrine alkaloids (from Ma Huang) with 192 milligrams per day of caffeine (from Kola nut). Compliance in taking the supplements was closely monitored and was reported to be approximately 90 percent for the placebo and EC groups. Subjects were given nutritional education and exercise counseling.

In addition, subjects underwent a comprehensive medical exam and a battery of tests that included determination of body mass; bioimpedance-determined body composition; waist and hip circumference measurements; a comprehensive blood profile (including glucose, blood lipids, liver and renal function tests, electrolytes, complete blood counts, and thyroid stimulating hormone); toxicological analysis of urine; a 12-lead ECG analysis; a 24-hour Holter monitor analysis to assess heart rate and cardiac arrhythmias; ambulatory blood pressure analysis to assess blood pressure throughout the day; and a symptom/side effect review. Subjects underwent testing following one, two, four, 12, and 24 weeks of supplementation.

Results revealed that herbal EC supplementation promoted a significantly greater decrease in body weight (-11.7 vs -5.7 pounds), body fat (-9.5 vs -5.9 pounds) and LDL cholesterol (-8 vs -0 mg/dl) while increasing HDL-cholesterol (+2.7 vs -0.3 mg/dl). These findings support previous research indicating that ephedra/caffeine supplementation promotes weight loss/fat loss and may improve blood lipid profiles. Although these findings are not new, the landmark nature of this study was the comprehensive manner in which side effects were monitored. Safety analysis revealed that herbal EC supplementation promoted small changes in mean heart rate (+4 vs -3 beats/minute) and mean 24-hour blood pressure responses obtained at one, two and four weeks of supplementation (+3 vs -5 mmHg).

However, no significant differences were observed in mean, minimum or maximum systolic or diastolic blood pressure, mean arterial pressure, resting 12-lead ECGs, or the prevalence of

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cardiac arrhythmia following six months of supplementation. The researchers concluded that the changes in heart rate and blood pressure were marginal and not of clinical significance in a healthy population. Additionally, herbal EC supplementation had no effects on markers of liver function, kidney function, thyroid function, electrolyte levels, or complete blood counts. Analysis of self-reported symptoms revealed that subjects taking herbal EC experienced a slightly greater incidence of dry mouth, heart burn and insomnia, while reporting less incidence of diarrhea. No differences were seen in the incidence of irritability, nausea, chest pain, palpitations, or the number and/or reasons that subjects withdrew from the study. The researchers concluded that "herbal ephedra/caffeine supplementation, when used as directed by healthy overweight men and women in combination with healthy diet and exercise habits, may be beneficial for weight reduction without significantly increased risk of adverse events."

Analysis of the Controversy

When I read this study, I kept thinking— here we go again, another study showing efficacy and safety of EC supplementation. So far, a number of clinical trials have been conducted to determine whether synthetic or herbal EC supplementation affects body composition and various markers of health. Moreover, a number of studies[10,11] have evaluated the efficacy and safety of over-the-counter (OTC) thermogenic supplement formulations (e.g. Hydroxycut®, Xenedrine®, Norexin® and Ripped Fuel® etc). Most studies report positive effects on weight loss/fat loss and body composition with relatively few, if any, side effects reported. Yet, few supplements have created such a whirlwind of controversy.

Some researchers contend that most clinical trials were conducted using synthetic or pharmacological grade EC rather that herbal EC preparations found in dietary supplements that may lack quality control and/or purity.[17] Therefore, results from well-controlled clinical trials using synthetic EC cannot be extrapolated to use of herbal EC preparations. Additionally, since naturally occurring ephedra may contain different types of ephedrine alkaloids, which are believed to have different physiological properties, it's possible some individuals may be more sensitive to having adverse reactions to these various types of ephedrine alkaloids.[17] Others contend that since these studies have been conducted on healthy individuals, possible adverse reactions to taking these supplements are unknown in individuals with underlying medical problems that may be contraindicated.[16,17] While these concerns are valid, they are based more on speculation rather than any scientific evidence from controlled research studies.

The recent Boozer et al study[16] provides the strongest evidence to date that herbal EC supplements are effective and apparently safe when used properly in a healthy but overweight population. Although subjects taking herbal EC experienced some minor side effects, the incidence of occurrence was relatively small and similar to subjects taking placebos in most cases. There was no evidence of an increased risk of significant adverse events such as cardiac arrhythmia, tachycardia, or severe hypertension. This is an important point because concerns are often raised about the safety of taking various supplements (e.g., ephedra, creatine, etc.) based on anecdotal reports of side effects. However, unless the incidence of side effects observed while taking a nutritional supplement is greater than that observed in individuals taking placebos, these side effects may simply reflect a normal rate of occurrence in a given population.

Interestingly, in 1997, the FDA pro-

posed label restrictions for dietary supplements containing ephedrine alkaloids to no more than eight milligrams in a six-hour period, a total daily intake of no more than 24 milligrams per day, and use of ephedrine-containing supplements for no more than seven consecutive days. The FDA indicated that these safety measures were "based on the fact that long-term intake of ephedrine alkaloids increases the likelihood of serious adverse events."[14]

In contrast, Cantox Health Sciences International, an independent research group commissioned to evaluate the literature on the safety and efficacy of ephedra by the Center for Responsible Nutrition, concluded that the upper tolerable safety limit for ephedrine was 90 milligrams per day.[19] The Boozer et al study[16] clearly indicates that ingesting 30 milligrams of ephedrine alkaloids (from Ma Huang) with 63 milligrams of caffeine (from Kola nut) three times per day (a total of 90 mg/day of ephedrine alkaloids and 192 mg/day of caffeine) for six months promoted fat loss and improved lipid profiles without serious adverse events. Obviously, this study and others have not supported the FDA's position on the safety of dietary supplements containing ephedrine alkaloids. One is left to wonder why the FDA has focused so much attention on these supplements when they allow sale of compounds known to be of greater health risk— like tobacco, alcohol, and OTC cold medications (containing pseudoephedrine) and analgesics such as aspirin and acetaminophen.[20-22]

Bottom Line

This landmark research study clearly indicates that herbal EC supplementation can promote fat loss and improve blood lipid levels without significant adverse events. These findings add to the growing body of evidence indicating that EC supplementation can serve as an effective fat loss tool when used in a prudent manner in apparently healthy populations. However, herbal EC supplementation may not be for everyone and can be potentially dangerous if misused. Individuals considering use of thermogenic supplements containing EC should carefully consider the potential side effects, discuss possible use with a knowledgeable physician, and not exceed recommended dosages (typically 60-90 mg/day of ephedrine alkaloids and 100-200 mg/day of caffeine). Finally, recommendations about EC-containing dietary supplements (as with any other supplement) should be based on a rational analysis of the scientific and medical literature, not unfounded speculation. ■

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