[Tein tämän artikkelin *Muscular Development* –lehteen, mutta efedraa koskevan myyntikieltopäätöksen vuoksi siitä tuli “hyödytön”. -AM-].

**Supplement Performance**

**Ephedra: Innocent Until Proven Guilty**

**By Anssi Manninen**

In 1972, Dr. Erikson, a Danish general practitioner in Elsinore, Denmark noted unintentional weight loss when he prescribed a compound containing ephedrine, caffeine and Phenobarbital to patients he was treating asthma.\(^1\) By 1977, over 70,000 patients were taking the “Elsinore Pill”, and one Danish pharmaceutical house was producing one million tablets a week.\(^1\)

Initial human studies with ephedrine and caffeine were with the Elsinore Pill which contained 40 mg of ephedrine and 100 mg of caffeine given three times a day. During the time that Elsinore Pill was used for the treatment of obesity, there was skin rashes, some serious, reported. However, these were most likely due to the Phenobarbital in the Elsinore Pill.\(^1\) The long history using ephedrine in combination with methylxanthines, both for treatment of asthma and obesity, makes the present concern over the safety of herbal products somewhat surprising.

Recently, Dr. Stephen Bent and coworkers published questionable paper on ephedra in respected *Annals of Internal Medicine*.\(^2\) They concluded that the risk for an adverse reaction after the use of ephedra is substantially greater than with other herbal products. Further, Dr. Bent and coworkers suggested that the sale of ephedra as a dietary supplement should be restricted or banned to prevent serious adverse reactions in the general population. However, there was serious methodological flaws, negative bias, and failure of peer review on this article. Thus, three rebuttals were recently published in *Annals of Internal Medicine*.\(^3,4,5\)

**Whitaker Letter**
According to Dr. Julian Whitaker, Bent’s data were extremely inaccurate. To estimate ephedra consumption, Dr. Bent and colleagues used marketing data from SPINS, Inc. on ephedra consumed in the category "Herbal Formulas and Singles," which accounted for 403,976 units per year. However, as pointed out by Dr. Whitaker, “they ignored the ephedra-containing products used for weight loss or energy—their stated concern—categorized by SPINS as "Vitamins and Supplements." This category accounted for 12,568,641 units per year, which is 31 times the amount on which Bent and colleagues based their conclusions. This oversight grossly exaggerates the relative risks of ephedra.”

Further, “faulty data are the least important flaw of this study. First, the ephedra products generating concern are combination products used for weight loss or energy. These products contain 10 to 15 active ingredients, including other stimulants such as caffeine, guarana, and green tea extract. To single out ephedra is clear bias. Second, and most important, to compare reports of adverse reactions from ephedra with those from other herbal products is absurd. Ephedra is a known stimulant, and most ephedra products carry warnings to that effect... The contributions of Bent and colleagues do not enlighten, they obscure. Yet they will be viewed as justification for purging U.S. culture of an herbal ingestant that has been in constant use for 5000 years.”

Kingston & Borrow Letter

According to Drs. Richard Kingston and Stephen W. Borron, ”Bent and colleagues do not make clear that most of the ephedra cases described in TESS [American Association of Poison Control Centers Toxic Exposure Surveillance System] involve botanicals with many active ingredients. There is no consideration of severity, ephedra dose, duration of use, purity, contaminants, underlying health status, or other substances contemporaneously consumed. Comparing ephedra with "other herbs," the actions and indications of which are distinct, is toxicologic nonsense... The authors also ignored the difficulties of assigning a cause-and-effect relationship to events spontaneously reported to poison centers. These incidents are rarely authenticated by independent medical practitioners but rather represent reports from the general public, which are often made anonymously and are typically accepted at face value. Although valid questions about the safety of ephedra have been raised in many venues, the report by Bent and colleagues adds
nothing to defining the incidence and integrity of adverse event reports potentially associated with this substance.”

Dickinson Letter

The article by Dr. Bent and colleagues purported to show that ephedra products account for less than 1% of the market for herbal supplements, yet are associated with a high percentage of adverse events reported to poison control centers. However, as pointed out by Dr. Annette Dickinson, “the authors relied on sales data that fail to encompass the bulk of the ephedra market, and therefore their calculations of relative risk are severely flawed... More comprehensive data compiled by the Nutrition Business Journal indicate that in 2001, ephedra accounted for about 7.5% of total dietary supplement sales and about 33% of sales of herbal products. Using 35% rather than 0.82% as the denominator would of course drastically change the calculation of the relative risk for an adverse event.”

Bent & Colleagues Respond

“We stand by our conclusions that ephedra supplements pose a disproportionate health risk and that their use should be restricted. Our findings are in agreement with the RAND Corporation’s analysis of case reports, which suggests a link between ephedra products and such catastrophic events as sudden death, heart attack, stroke, seizures, and serious psychiatric symptoms.” However, their “findings” are certainly not agreement with RAND report. According to RAND report, “Our study could not prove with scientific certainty that ephedra is unsafe”. Further, it should be noted that Dr. Bent and colleagues (Tiedt and Shlipak) have a clear financial conflicts of interest: “Expert Testimony: S. Bent (Livsey vs. Metabolife; Neumann vs. Herbalife), T.N. Tiedt (cases involving Metabolife International, Cytodyne, MuscleTech, Next Nutrition, TwinLabs, Dorsey Labs, Enrich, E’Ola, GNC, Phoenix Labs, Chemins Labs), M.G. Shlipak (Livsey vs. Metabolife; McDonald vs. TwinLabs).”

Let’s Face the Facts
Certainly, the most objective method of assessing risks and benefits is by evaluating the randomized double blind, placebo-controlled trials in the peer-reviewed literature. Studies of ephedrine with caffeine suggest that the risks (elevation of blood pressure, agitation, dizziness, headache, insomnia, etc.) are usually mild and transient, existing primarily during the first few days to weeks of treatment. For example, Dr. Boozer and colleagues recently examined long-term safety and efficacy for weight loss of an herbal Ma huang and Kola nut supplement:

**Source:** International Journal of Obesity 26:593-604, 2002.

**Design:** Six-month randomized, double-blind placebo controlled trial.

**Subjects:** A total of 167 subjects randomized to placebo (n=84) or herbal treatment (n=83) at two outpatient weight control research units.

**Measurements:** Primary outcome measurements were changes in blood pressure, heart function and body weight. Secondary variables included body composition and metabolic changes.

**Results:**

**Body composition-related effects:** The increased weight reduction with the Ma Huang/Kola nut combination in this study is consistent with results form two previous 8 weeks studies of Ma Huang formulations. According to authors, the reductions in body fat, waist and hip circumferences and the favorable changes in serum HDL and LDL cholesterol levels are probable consequences of the greater reduction in body weight in the subjects treated with the Ma Huang/caffeine combinations. However, it has been suggested that ephedrine/caffeine combinations have specific effects to increase lipolysis and improve blood lipid profile.

**Cardiovascular effects:** The effects of herbal ephedrine/caffeine combinations on blood pressure appears to be small, with previous reports of either no increase or small, transitory increases. These effects on blood pressure are less than those reported with sibutramine treatment. Increased heart rate is consistent with the known effect of this combination to stimulate energy expenditure. Although there have been speculation of a
link between consumption of low levels of ephedra alkaloids and arrhythmias, the findings of no cause and effect relationship in this placebo-controlled study is consistent with the lack of any research data linking synthetic ephedrine to cardiac arrhythmias.  

**Conclusions**: This study demonstrated significant beneficial effects on body weight, body fat and blood lipids of herbal Ma Huang/Kola nut mixture (90/192 mg/day ephedrine alkaloids/caffeine) in overweight men and women who were otherwise healthy. Compared with placebo, the tested product produced no adverse events and minimal side effects that are consistent with the known mechanisms of action of ephedrine and caffeine

How can the absence of treatment-related adverse events in this and previous trials of ephedra combinations be reconciled with the adverse event reports collected by the FDA from users of these products? According to Dr. Boozer and colleagues, possible explanations include coincidence, pre-existing pathology, non-recommended usage and increased individual sensitivity. *Certainly, ephedrine/ephedra is not for everyone and must be used responsibly. It is very important that you read products labels, warnings and cautions, and follow the directions.*

**Citrus Aurantium: A Replacement for Ephedra?**

Many supplement companies are now substituting Citrus aurantium for ephedra in their diet formulations. Citrus aurantium, an agent containing beta agonists, has been reported to aid in weight loss in two studies and increase thermogenesis, at least to some extent, in three studies.

The purpose of recent study by Dr. Carlon Colker and coworkers was to determine the effects of Citrus aurantium extract, caffeine, and St. John's wort on body composition, metabolic variables, plasma lipid levels, and mood states in overweight healthy adults. In a double-masked, randomized, placebo-controlled study, 23 subjects were assigned to 1 of 3 groups. Group A received Citrus aurantium extract 975 mg, caffeine 528 mg, and St. John's wort 900 mg daily; group B received a maltodextrin placebo; and group C received nothing and served as the control group. For 6 weeks, subjects were instructed by a registered dietician on how to follow an 1,800-kcal/day American Heart Association (AHA) Step One diet
and performed a 3-day/week circuit training exercise program under the supervision of an exercise physiologist.

Compared with subjects in the placebo and control groups, subjects in the treatment group lost a significant amount of body weight (1.4 kg). They also lost a significant amount of body fat (an average change of 2.9%). In terms of actual fat loss, group A lost a significant amount (3.1 kg), whereas the control group demonstrated a tendency toward fat loss. Group A experienced a decrease, which did not reach statistical significance, of both plasma cholesterol and triglycerides. No significant changes in blood pressure, heart rate, electrocardiographic findings, serum chemistries, or urinalysis findings were noted in any of the groups.

Based on these results, it was concluded that the combination of Citrus aurantium extract, caffeine, and St. John's wort is safe and effective when combined with mild caloric restriction and exercise for promoting both body weight and fat loss in healthy overweight adults. Thus, Citrus aurantium may be the best thermogenic substitute for ephedra. However, more studies are needed to establish this definitively. For more detailed review on Citrus aurantium and weight loss, see the recent review by Dr. Greus and coworkers in *Journal of Medicine*.

**Serving Limits, Warnings and Precautions for Taking Ephedra Products**

- Do not take more than 25 mg ephedrine alkaloids per serving and not more than 100 mg per day.
- Consult a health care professional before consuming an Ephedra-containing dietary supplement if you have heart disease, thyroid disease, diabetes, high blood pressure, depression or other psychiatric condition, glaucoma, difficulty in urinating, prostate enlargement, or seizure disorder, if you are using a monoamine oxidase inhibitor (MAoI) or any other prescription drug, or you are using an over-the-counter drug containing ephedrine, pseudoephedrine or phenylpropanolamine (ingredients found in certain allergy, asthma, cough/cold and weight control products).
- Do not use Ephedra products if you are under the age of 18. Do not use Ephedra products if you are pregnant or nursing.
- Discontinue use and call a health care professional immediately if you experience rapid heartbeat, dizziness, severe headache, shortness of breath, or other similar symptoms.
- Exceeding recommended serving will not improve results and may result in serious adverse health effects

Source: Ephedra Education Council, Washington, DC. www.epherafacts.com
References


