The safety and efficacy of pharmaceutical and herbal caffeine and ephedrine use as a weight loss agent

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Summary

Since passage of the Dietary Supplement Health and Education Act of 1994, the sale of herbal dietary supplements containing caffeine and ephedrine for weight loss has become widespread in the United States. Reports of adverse events associated with the use of these non-prescription supplements have raised concerns in the United States regulatory community. Restricting the use of these products is now being considered. Such restriction should be based upon controlled clinical trials. This review of the literature in Medline relative to the use of caffeine and ephedrine in the treatment of obesity concludes that caffeine and ephedrine are effective in causing weight loss. Caffeine and ephedrine give equivalent weight loss to Diethylpropion and superior weight loss compared to dexfenfluramine. Caffeine and ephedrine have a long history of safe, non-prescription use. The adverse events accompanying acute dosing are mild and transient. Adverse events with caffeine and ephedrine reach and remain at placebo levels after 4–12 weeks of continuous treatment, but data from randomized trials up to 6 months only are available. Obesity is chronic, requires chronic treatment, its incidence is increasing and it has few effective treatments. The benefits of caffeine and ephedrine in treating obesity appear to outweigh the small associated risks. Restriction of dietary herbal supplements containing caffeine and ephedrine, often with other ingredients, should be based on controlled clinical trials of these products.

Keywords: Caffeine, Ephedrine, Obesity

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Introduction

Herbal forms of caffeine and ephedrine fall under the Dietary Supplement Health and Education Act of 1994. Selling caffeine and ephedrine, in herbal form, for weight loss, is now a large industry. The widespread use of this herbal combination has lead to reports of serious adverse events and raised safety concerns in the regulatory community (1). The United States Food and Drug Administration (FDA) published a proposed ruling in 1997 to restrict the use of herbal caffeine and ephedrine products. The Government Accounting Office's review of that ruling prompted the FDA to withdraw portions of its proposal.

Reports of serious adverse events associated with the use of herbal caffeine and ephedrine have continued, however, and the FDA is re-exploring the need to intervene to protect the public. This need to protect the public should be based upon the determination of the relative risks and benefits of taking herbal caffeine and ephedrine for weight loss. Such a determination requires knowledge of the incidence of these serious adverse events and the efficacy of caffeine and ephedrine for weight loss, things that cannot be determined from a voluntary reporting system. Prospective studies with appropriate controls can make this determination and such studies do exist in the peer-reviewed scientific literature. A review of this scientific literature is therefore the best resource upon which to make these regulatory decisions.

This review of the peer-reviewed literature was compiled by reviewing the articles in the Medline database published in English from 1966 through to 2000 using the terms

caffeine and ephedrine, each cross-referenced to the term obesity as a search criteria. In reviewing this literature, particular emphasis has been given to the efficacy of caffeine and ephedrine in causing weight loss, the benefits that can be expected from that weight loss and the incidence of adverse events placed in the context of an appropriate control group.

Since the concern of the FDA has been relative to herbal products and the literature deals almost exclusively with pharmaceutical grade caffeine or other methylxanthines with ephedrine, one might question the applicability of this literature review. Caffeine in the herbal products is the same chemical contained in pharmaceutical caffeine. Herbal ephedrine has 4 isomers, but the pharmaceutical grade product contains the most potent of these (2). Therefore, the herbal form of ephedrine should be even safer than equivalent doses of the pharmaceutical grade product, because it contains less of the most potent isomer.

Background

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 for asthma. As he pursued his observation, rumour spread from his patients to the rest of the country. By 1977, over 70 000 patients were taking the 'Elsinore Pill', and one Danish pharmaceutical house was producing one million tablets a week.

During the time that the 'Elsinore Pill' was used for the treatment of obesity, there were skin rashes, some serious, reported. These were most likely due to the Phenobarbital in the 'Elsinore Pill'. In 1977, the Danish Institute of Health issued a warning to doctors not to prescribe the compound due to the increased incidence of skin rashes, and Dr Erikson was pilloried in the public and scientific press.

On that background the 'Elsinore Pill' without phenobarbital was compared with the appetite suppressant diethylpropion and to a placebo in 132 subjects in a 12-week double-blind trial. In subjects given 25 mg of diethylpropion three-times-a-day (tid) and the 'Elsinore Pill' without Phenobarbital (100 mg of caffeine and 40 mg of ephedrine tid) weight loss of 8.4 kg and 8.1 kg was noted, respectively, which was not significantly different from each other, but which was greater than the placebo weight loss of 4.1 kg ($P < 0.01$). Tremor and agitation were more frequently noted with subjects on the 'Elsinore Pill', but were transient and the withdrawal for side-effects was equal in the diethylpropion and 'Elsinore Pill' groups. There was no increase in blood pressure, pulse rate or laboratory parameters. The authors concluded that ephedrine and caffeine had the advantage over diethylpropion because of its lower cost with equivalent safety and efficacy (3).

Other early studies of ephedrine and caffeine also used commercial asthma preparations. Theophylline and caffeine are both methylxanthines and have the same pharmacologic actions. One mg of theophylline is equivalent to 2 mg of caffeine (4). Miller used the 'Do-Do' pill manufactured by Ciba-Geigy in the United Kingdom that contains 22 mg of ephedrine, 30 mg of caffeine and 50 mg of theophylline per pill. Each pill therefore contains the equivalent of 22 mg of ephedrine and 130 mg of caffeine (5).

ephedrine with theophylline was the primary treatment for asthma in the 1960s and 1970s and ephedrine is still sold in the United States without a prescription for the treatment of asthma (6). Ephedrine with caffeine is still the most widely sold prescription weight loss medication in Denmark and has held 80% of the market share even, when dexfenfluramine has been available.

This long history using ephedrine in combination with methylxanthines, both for the treatment of asthma and obesity, makes the present concern over the safety of herbal products using lower doses seem somewhat surprising. This review will consider the animal studies and human trials of caffeine, ephedrine and their combinations in treating obesity.

Caffeine

Animal studies

Obesity can be associated with low sympathetic activity (7). Based upon this association, caffeine was evaluated in genetically obese ob/ob mice. Caffeine decreased body fat and improved sympathetic activity in that animal model, suggesting a possible role in the treatment of human obesity (8).

Human studies

Caffeine in an oral dose of 250 mg increased free fatty acids and glucose, but not cortisol levels, in obese and lean humans compared with a water placebo with each subject acting as his own control (9). Oxygen consumption, fat oxidation and serum free fatty acids were increased in six normal subjects given caffeine 8 mg kg^{-1} orally compared with 0.5 gm glucose. Oxygen consumption and fat oxidation were also increased in seven normal and six obese subjects after 4 mg kg^{-1} of caffeinated coffee compared with a decaffeinated control after fasting and after a mixed meal (10).

Six obese, six lean and four post-obese women were evaluated after 4 mg kg^{-1} oral caffeine. Caffeine levels were higher in the lean compared with the obese and post-obese subjects, and the rise in oxygen consumption and free fatty acids was lower in the post-obese compared with the obese and lean subjects. These changes were felt to be due to dif-

ferences in lipolysis (11). Increases in oxygen consumption and fat oxidation suggest a potential role for caffeine in the induction of weight loss.

Since the initial studies evaluating the effect of caffeine on oxygen consumption, further investigations have been undertaken. Caffeine 100 mg was shown to increase resting oxygen consumption 3–4% in nine lean and nine post-obese subjects. Caffeine (100 mg) also improved the defective diet induced thermogenesis over 150 min that was present in the post-obese. Five lean and six post-obese subjects were given 100 mg caffeine every 2 h for 6 h. Daily energy expenditure increased 150 kcal d^{-1} in the lean subjects and 79 kcal d^{-1} in the post-obese subjects (12).

Ten lean and 10 obese women were evaluated for 24 h in a metabolic chamber on two occasions, one with 4 mg kg^{-1} caffeine 5 times a day and the other with placebo. Caffeine increased energy expenditure and lipid oxidation, but less in the obese than in the lean (13). The response of serum catecholamines to 4 mg kg^{-1} caffeine was evaluated in 12 pre-pubertal lean, 15 pre-pubertal obese, 12 pubertal lean and 24 pubertal obese subjects. The rise in serum catecholamines was less in the pubertal obese group (14). Caffeine administration significantly elevated systolic blood pressure 4.5–6.6 mm Hg, but there was no change in diastolic blood pressure or pulse rate. Subjects reported no symptoms or side-effects.

The caffeine-induced increase in thermogenesis is dissipated through an increase in skin temperature (15). The increase in resting metabolic rate induced by 4 mg kg^{-1} of caffeine predicts the amount of weight lost in response to a diet and exercise programme (16).

Pharmacology

The changes in levels of caffeine following an acute dose in the lean compared with the obese subjects prompted more elaborate pharmakinetic studies. The volume of distribution of caffeine was found to be proportional to body weight with caffeine having the same clearance in the obese as in the lean subjects (17). Therefore, for metabolic studies one might justify a loading dose, but for chronic treatment no change in dosage is necessary for the obese (18,19).

Epidemiology studies

Several epidemiologic studies have addressed the safety of caffeine. The positive correlation found between heavy coffee drinking and elevated cholesterol is felt to be due to factors other than caffeine in coffee, since caffeine consumption in the form of tea or cola has no effect on cholesterol (20,21). Heavy caffeine use is associated with resistant hypertension and snoring. Resistant hypertension is defined as high blood pressure not controlled by three blood pressure medications at full doses. Heavy caffeine use is also associated with cigarette smoking. Since cigarette smoking is associated with hypertension and snoring, it may be the smoking that is responsible for the association with these conditions rather than the caffeine (22,23).

On a chronic basis, caffeine consumption has been correlated in epidemiologic studies with a decreased risk of hospitalization for coronary heart disease (24). It has also been associated with lower blood pressure (25,26). Therefore, caffeine consumption on a chronic basis appears to reduce the risk of cardiovascular disease, the opposite suggested by caffeine's acute cardiovascular response. Although the intake of more than 2 cups of coffee per day is associated with osteoporosis, this association has only been demonstrated in women between 50 and 98 years of age and only when they consume less than one glass of milk per day, far below the intake recommended by nutritional guidelines (27). As noted before, coffee contains more than caffeine and any negative effect on bone could as easily be related to one of the other components of coffee.

Clinical trials

A clinical trial with 288 healthy subjects evaluated the effects of a single 200 mg d^{-1} dose of caffeine compared with the placebo. Caffeine gave a 2.2 mm Hg in diastolic blood pressure which was felt to be clinically insignificant. There was no change in pulse rate or systolic blood pressure (28).

caffeine not only has a long history of safe use in food, but has also been used for many medicinal purposes. It is used in headache preparations, to treat fatigue, to treat intracranial hypertension and to treat respiratory distress in the neonate (29,30). The US FDA approves caffeine for sale without a prescription for use as a stimulant by persons 12 years of age or older at a dose up to 200 mg every 3 h (1600 mg d^{-1}) and as an ingredient in pain medications which gives further support to its safety.

Ephedrine

Animal studies

Ephedrine was proposed as a potential treatment for obesity on the basis of a study comparing it to triiodothyronine in six animal models of obesity and lean controls. Triiodothyronine increased both oxygen consumption and food intake, causing death in genetically obese animals. Ephedrine elevated oxygen consumption without increasing food intake while causing weight and fat loss (31). There were no deaths in the ephedrine group. Two other animal models of obesity were treated with ephedrine. Increased energy expenditure, decreased food intake and fat loss were demonstrated (32,33).

In an effort to discover a potential drug to treat obesity, 33 compounds known to stimulate oxygen consumption were screened in several animal models of obesity. In general, these compounds gave selective fat loss without loss of body protein by increasing energy expenditure without increasing food intake. Ephedrine was one of the two most efficient compounds and a case was made for its use in the treatment of obesity (34,35).

Mechanisms

Ephedrine stimulates brown adipose tissue thermogenesis through the activation of β-receptors. It has been estimated that 40% of the acute rise in oxygen consumption to ephedrine is due to activation of the β-3 adrenergic receptor (36). The isomer of ephedrine in pharmaceutical preparations is the most active of the four existing isomers (37). As one would expect for a drug that acts on beta-receptors, the beta blocking drug atenolol prevents the weight loss induced in ob/ob mice by ephedrine (38).

Aspirin has been shown to increase ephedrine-induced thermogenesis. Mice made obese by monosodium glutamate (MSG) and treated with aspirin had no change in their energy expenditure, body fat or body weight. Mice made obese with MSG, and treated with ephedrine increased their energy expenditure by 9%, reduced their body fat by 50% and reduced their body weight by 18%. The combination of aspirin and ephedrine increased energy expenditure by 18%, reduced body fat by 75% and reversed obesity (39).

Ephedrine was proposed as a possible obesity treatment in humans as early as 1974, but was felt to give side-effects in doses adequate to suppress appetite (40). Ephedrine, however, was shown to improve its ability to increase oxygen consumption and enhance peripheral conversion of thyroxine to triiodothyronine with time. Ephedrine 20 mg tid increased oxygen consumption by 1.3 L over 3 h at baseline. This figure rose to 7 L over 3 h at week 4 and 12 of treatment accompanied by weight losses of 2.5 kg and 5.5 kg, respectively (41). Chronic treatment with ephedrine increased metabolic rate by 10% and increased fat oxidation (42).

Human studies

Clinical trials have been conducted with ephedrine for the treatment of obesity. A 3-month trial comparing 25 mg of ephedrine tid (13 subjects) and 50 mg tid (17 subjects) with placebo (16 subjects) showed similar weight losses in all groups with significantly more side-effects (blood pressure elevation, pulse elevation, agitation, insommia, headache, weakness, palpitations, giddiness, euphoria, tremor and diarrhoea) in the ephedrine 50 mg tid group compared with placebo (43). There was more weight loss in the ephedrine groups, however, at the end of the first and second months, a difference that was lost by the end of the third month (44). A second trial compared 50 mg of ephedrine tid with placebo over 8 weeks in 10 low-energy adapted women who had already lost weight. The study used a crossover design. Weight loss was greater during the 2-month period on ephedrine (2.4 kg) than on placebo (0.6 kg). Side-effects were uncommon; agitation (2 subjects), insomnia (3 subjects), giddiness (2 subjects), and palpitations (2 subjects), and none required withdrawal of medication (45).

Ephedrine has also been evaluated in conjunction with a very low calorie diet. Ephedrine decreased urinary nitrogen and blunted the fall in resting metabolic rate (46). The rise in oxygen consumption to ephedrine 1 mg kg^{-1} was increased by 5 weeks of exercise training 1 h per day on a bicycle at a heart rate of 140–160 beats per min. (47).

Mechanisms

Attempts have been made to explore the mechanisms by which ephedrine exerts it effects in humans. Although ephedrine stimulates brown adipose tissue in rodents, ephedrine-induced thermogenesis in humans takes place primarily in skeletal muscle, since humans have little brown adipose tissue (48). Ephedrine has also been shown to decrease gastric emptying which may contribute to its effect on food intake (49). As one might expect from a compound that stimulates β-1, β-2 and β-3 receptors, intravenous ephedrine acutely increases oxygen consumption, serum glucose, insulin and c-peptide (50). β-1 receptors stimulate heart rate, and β-2 receptors increase glucose in addition to stimulating oxygen consumption along with the β-3 receptors.

Post-prandial thermogenesis measured for 160 min following a liquid meal was greater in 10 obese women to an acute dose of ephedrine 30 mg and aspirin 300 mg than to an acute dose of ephedrine 30 mg alone. Aspirin did not have this additional effect on thermogenesis in 10 lean women (51). Ephedrine and aspirin normalized the post-prandial thermogenesis in obese women to levels equal to the lean (52).

Adverse events

Side-effects with ephedrine were agitation, insomnia, headache, weakness, palpitations, giddiness, tremor and constipation, but were only seen with the 50 mg tid dose and dissipated with time. No significant changes were seen in pulse or blood pressure (53). Ephedrine has been reported to cause urinary difficulty in subjects with prostatic hypertrophy and can exacerbate angle-closure glaucoma (54).

Ephedrine with methylxanthines (caffeine, theophylline, and aminophylline)

Animal studies

Caffeine and methylxanthines have been demonstrated to be synergistic in animals. Caffeine or theophylline given alone to mice with MSG-induced obesity caused no change in weight, fat or energy expenditure. Ephedrine decreased weight by 14%, fat by 42% and increased energy expenditure by 10%. When caffeine or theophylline was added to ephedrine, weight decreased by 25%, fat decreased by 75%, energy expenditure increased by 20% and body composition was normalized to that of lean control animals (55).

Caffeine with ephedrine and theophylline also normalized obesity in fa/fa Zucker fatty rats by decreasing food intake by 40% and increasing energy expenditure from 25 to 33% (56). Oxygen consumption was increased by 32% with ephedrine, 48% with caffeine and 47% with caffeine and ephedrine in the LA-corpulent rat, another rodent obesity model. These rats lost three times the weight with the caffeine and ephedrine than with ephedrine alone (57). Not only can rodent obesity be effectively treated with ephedrine and methylxanthines, but caffeine, ephedrine and theophylline also prevent obesity in fa/fa rats by normalizing energetic efficiency to that of lean animals (58).

Although most of the animal studies with caffeine and ephedrine have been done in rodents, the effect of this drug combination was also evaluated in primates. Caffeine and ephedrine gave fat loss in both lean and obese monkeys, but weight loss and decreased food intake was only seen in obese animals. Nocturnal energy expenditure increased by 21% and 24% in the lean and obese monkeys, respectively. There was no change in the glucose tolerance test, but leptin levels decreased (59).

Adipsin

Adipsin is a serine protease with complement factor D activity that is synthesized in fat cells and secreted into the blood stream. Genetically obese mice (ob/ob and db/db) and mice with MSG induced obesity have low adipsin levels that precede the obesity, and the obesity in these animals is associated with low levels of sympathetic activity. Since caffeine and ephedrine correct both the obesity and the adipsin levels, it was postulated that adipsin is under sympathetic control (60). Since it was later demonstrated that BRL 26830 A, a selective beta-3 adrenergic stimulator, depressed adipsin levels, it was suggested that adipsin was inversely related to body fat (61). It now appears that adipsin levels are controlled by food intake, since both ephedrine with caffeine and food restriction increase adipsin levels (62).

Mechanisms

The mechanism by which methylxanthinines potentiate ephedrine-induced thermogenesis was assumed to be inhibition of the adenosine receptor, a known effect of methylxanthines. Using an *in vitro* assay of brown fat cell respiration, it was shown that the adenosine receptor plays only a minor role, and most of the methylxanthine effect is due to phosphodiesterase inhibition (63). Ephedrine and theophylline also increase hepatic lipase activity, the enzyme that degrades atherogenic intermediate density lipoproteins (64). Lower intermediate density lipoproteins should, in turn, protect from atherosclerotic vascular disease.

Herbal caffeine and ephedrine

Herbal forms of caffeine and ephedrine have also been evaluated in rodents. Bofu-tsusho-san containing ephedrine and a phosphodiesterase inhibitor when fed to mice with MSG-induced obesity decreased both fat and body weight by activating brown fat thermogenesis (65). Oolong tea prevented the obesity and fatty liver induced by a high fat diet, stimulated noradrenaline-induced lipolysis, stimulated hormone sensitive lipase and inhibited pancreatic lipase activity in rodents (66). This effect was attributed to caffeine, but more recent studies demonstrate that green tea contains not only caffeine, but also catechin polyphenols that inhibit catechol-O-methyl transferase, the enzyme that breaks down noradrenalineephrine. Just as caffeine and ephedrine are synergistic in their effect on the respiration of brown fat cells *in vitro*, so are the catechins in green tea synergistic with caffeine, ephedrine and the combination of caffeine with ephedrine (67).

Human studies

Initial human studies with caffeine and ephedrine were with the 'Elsinore Pill' which contained 40 mg of ephedrine and 100 mg of caffeine given three times a day. Although this combination increased metabolism, thyroid hormone did not seem to be responsible for this increase. Diet, diethylpropion and the 'Elsinore Pill' all significantly decreased levels of T_3 by a mean of 9% during weight loss (68). Extrapolating from animal studies, the increase in energy expenditure was postulated to come from stimulation of brown adipose tissue. Further studies with ephedrine demonstrated that, at maximum, 15% of the increase in human thermogenesis could come from brown adipose tissue, the majority being due to thermogenesis in muscle (48).

The next published study of ephedrine and methylxanthines used Do-Do pills, a non-prescription asthma medication containing 22 mg of ephedrine, 30 mg of caffeine

and 50 mg of theophylline made by Ciba-Geigy, UK. The ephedrine-methylxanthine combination was twice as effective in raising resting metabolic rate in lean and post-obese subjects than ephedrine alone. Although there was no change in 24-h energy expenditure in lean subjects measured in a metabolic chamber, the post-obese increased their energy expenditure by 8%. The ephedrine-methylxanthine combination normalized the defective thermogenic response to a meal in the post-obese (69).

Since aspirin and methylxanthines both potentiate ephedrine-induced thermogenesis, 100 mg of aspirin with 50 mg of ephedrine and 50 mg of caffeine was given three times a day for 8 weeks in a double blind clinical trial. Weight loss was faster in the aspirin-ephedrine-caffeine group compared to placebo, and there were no significant differences in pulse rate, blood pressure, fasting glucose or symptoms (70).

In an effort to evaluate the best combination of caffeine and ephedrine, single doses of ephedrine (10 mg and 20 mg) and caffeine (100 mg and 200 mg) were compared with three combinations of caffeine with ephedrine (10 mg/200 mg, 20 mg/100 mg, and 20 mg/200 mg). Ephedrine (20 mg) with 200 mg of caffeine gave increases in oxygen consumption that were greater than the sum of the increase seen with 20 mg of ephedrine and 200 mg of caffeine separately. The other two doses of caffeine and ephedrine were equivalent to the additive effect of their component doses of caffeine and ephedrine separately on oxygen consumption. The acute dose of caffeine and ephedrine elevated systolic blood pressure 9 mm Hg and pulse rate 7 beats per minute (bpm). Plasma glucose, insulin and c-peptide were also elevated (71). This acute effect of caffeine and ephedrine in raising blood pressure, pulse, and glucose is lost with chronic treatment (66).

The dose of caffeine with synergism, 20 mg of ephedrine with 200 mg of caffeine given three times a day, was chosen for a clinical trial. One hundred and eighty obese subjects were randomized to 20 mg of ephedrine tid, 200 mg of caffeine tid, 20 mg of ephedrine with 200 mg of caffeine tid or placebo for a 24-week double blind trial. Weight loss with caffeine and ephedrine was greater than placebo from 8 weeks to the end of the trial. Ephedrine alone and caffeine alone were not different than placebo. The caffeine with ephedrine group lost 17.5% of their body weight in the 24-week trial. Side-effects of tremor, insomnia and dizziness reached the levels of placebo by 8 weeks, and blood pressure fell similarly in all four groups. Heart rate rose in a statistically significant manner in the ephedrine group compared with placebo, but fell below the baseline value in the caffeine and ephedrine group (72).

Two weeks after cessation of the 24-week trial, headache and tiredness were more frequent in the group that had taken caffeine with ephedrine. At the end of the 2-week washout period, all subjects were given the opportunity to participate in an additional 24-week open-label trial using caffeine with ephedrine. Those subjects remaining on caffeine with ephedrine maintained their weight loss to the end of trial at week 50 (73). Seventy-five percent of the weight loss was explained by anorexia and 25% was explained by increased thermogenesis (74).

Since acute treatment with 200 mg of caffeine and 20 mg of ephedrine three times a day had cardiovascular and metabolic effects, the chronic effects were evaluated in the 24-week trial. By week 12 the blood pressure had dropped 4–11 mm Hg below baseline and remained similar to the placebo group. The pulse rate dropped 1–2 bpm from baseline during the trial, and reductions in plasma glucose, cholesterol and triglycerides were not different between the groups at the end of the 24-week double-blind trial (75). These findings were confirmed in an 8-week trial using 50 mg of ephedrine, 50 mg of caffeine and aspirin 110 mg given three times a day that was double-blinded and placebo-controlled trial. There was no significant change in heart rate, blood pressure, blood glucose, insulin, cholesterol or side-effects relative to placebo, but weight loss was greater in the ephedrine, caffeine and aspirin group (76).

The effect of 200 mg of caffeine with 20 mg of ephedrine three times a day on body composition has been studied with bio-impedance. At the end of 8 weeks, weight loss was not different, but the group on caffeine and ephedrine lost 4.5 kg more fat and 2.5 kg less lean tissue than the placebo group, a significant difference. As one might expect, the fall in energy expenditure was 13% in the placebo group and only 8% in the group treated with caffeine and ephedrine (77). Treatment with caffeine and ephedrine over 8 weeks also prevented the expected drop in high density lipoprotein (HDL) cholesterol. Since HDL cholesterol protects from atherogenesis, this finding suggests that caffeine and ephedrine may have the potential to reduce atherosclerotic cardiovascular disease. The placebo group experienced the drop in HDL cholesterol routinely reported with diet-induced weight loss (78).

Ephedrine with or without a methylxanthine was evaluated in adolescents. The effect of ephedrine in stimulating thermogenesis was lost after 1 week of treatment, but was restored by combining it with aminophylline for one week (79). This would explain why the trials with ephedrine alone give more weight loss than placebo early in trials that decreases with time unless combined with a methylxanthine.

The same group reported a 20-week, double-blind, placebo controlled and randomized clinical trial of caffeine and ephedrine in 32 adolescents age of 16 ± 1 years and Tanner stage III-V (80). Subjects less than 80 kg were given one tablet containing 100 mg of caffeine and 10 mg of ephedrine three times a day and subjects more than 80 kg were given two pills three times a day. The loss of initial body weight was 14.4% and 2.2% in the caffeine with

ephedrine and placebo groups, respectively ($P < 0.01$). All three dropouts were in the placebo group and adverse events were described as negligible. After the first 4 weeks the adverse events in the caffeine group were not different than placebo.

The most successful weight loss drug combinations have been phentermine with fenfluramine and caffeine with ephedrine. Both combinations give weight losses in the range of 15–20% of initial body weight in 6 months (81). Caffeine (200 mg) with 20 mg of ephedrine given three times a day was compared with dexfenfluramine 15 mg twice a day in a double-blind trial. In subjects with a BMI greater than 30 kg m^{-2}, the weight loss was greater with caffeine and ephedrine treatment. Blood pressure declined significantly in both groups (7.8/4.6 mm Hg in the dexfenfluramine group and 10.6/3.5 mm Hg in the caffeine and ephedrine group) but the differences were not significantly different from each other. Pulse rate declined 1.1–2.7 bpm and was not different between the groups. The subjects treated with dexfenfluramine had more gastrointestinal symptoms (diarrhea, dry mouth, and thirst) and the subjects treated with caffeine and ephedrine had more symptoms of central nervous system stimulation (tremor, insomnia, agitation). Symptoms in both groups declined by the end of the first month of the 15-week trial (82).

Although dexfenfluramine is no longer available due to cardiac valvular toxicity, caffeine and ephedrine are available without prescription. The cardiac valvular problems associated with fenfluramine and dexfenfluramine are felt to be related to serotonin and have not been associated with caffeine and ephedrine which have a noradrenergic mechanism of action. Fenfluramine with phentermine, fenfluramine with mazindol, caffeine with ephedrine and mazindol alone were compared in their ability to reduce weight, cardiovascular risk and low density lipoprotein (LDL) cholesterol. Caffeine with ephedrine was found to be the most cost-effective treatment (83).

Ephedrine (25 mg) and 200 mg of caffeine given three times a day for 10 d had no effect on resting cardiovascular function measured by thoracic bio-impedance, automatic sphygmomanometry or continuous electrocardiographic recording. During cycle ergometer exercise, there was a small increase in the cardiac ejection fraction. Based upon these results, the authors concluded that, in the doses studied, caffeine and ephedrine had no undesirable effects on cardiovascular function in the obese (84).

The efficacy of caffeine and ephedrine in the treatment of human obesity is summarized in Table 1. The safety of caffeine and ephedrine in human obesity studies are summarized in Table 2. Table 2 compiles the incidence of side-effects in the various trials of caffeine and ephedrine, expressing them as a percentage of the total number of subjects studied. Since one trial compared caffeine and ephedrine to diethylpropion and another to dexfenfluramine, some comparison to the safety of these compounds can also be made (see Table 2).

Another way to evaluate the safety of caffeine and ephedrine is to compare the dropouts in caffeine with ephedrine groups to placebo groups or to groups of compounds with which caffeine with ephedrine have been compared in obesity studies (see Table 3). The raw dropout rates, however, do not reflect the reasons for the dropouts.

Table 1 Efficacy of caffeine and ephedrine

Author	Start D/P	End D/P	Dose (E/C)	Length	Kg lost D/P	% wt. lost D/P	Comments
(3)	49/33	42/31	80/300 mg d^{-1}	12 wk	8.1/4.1	8.3/4.5	Diethylpropion & E/C gave equal wt. loss
(69)	16	16	22/130 mg d^{-1}	1 d	0	0	E/C normalized TEF of postobese to lean level
(70)	29	11/13	150/150 mg d^{-1}	8 wk	2.2/0.7	–	E/C with aspirin 330 mg d^{-1}
(71)	6	6	20/200 mg d^{-1}	1 d	0	0	E/C dose synergistic
(72)	45/45	35/35	60/600 mg d^{-1}	24 wk	16.6/13.2	17.5/13.6	E or C alone and placebo gave equal wt. loss. C/E maintained wt. loss for 24 wk on open label C/E
(77)	7/7	6/6	60/600 mg d^{-}	8 wk	10.1/8.4		C/E gave more fat loss & less lean tissue loss than placebo
(78)	20/20	16/16	60/600 mg d^{-1}	8 wk	9.0/7.6	9.6/8.2	C/E gave no drop in HDL
(79)	8	8	75/880 mg d^{-1}	1 d	0	0	Ephedrine loses its effect without methylxanthine in adolescents
(82)	50/53	38/43	60/600 mg d^{-1}	15 wk	9.0/7.0	9.7/7.8	P = dexfenfluramine 30 mg d^{-1} in this study
(89)	20	20	75/600 mg d^{-1}	24 wk	–	8.6	C/E was most cost-effective obesity treatment in the trial
(84)	9/9	9/9	50/400 mg d^{-1}	10 d	0	0	C/E gave no cardiovascular toxicity at 10 d
(80)	16/16	16/13	30/300 & 60/600 mg d^{-}	20 wk	7.9/0.5	14.4/2.2	C/E toxicity negligible and equal to placebo by 4 wk in adolescents
(86)	152/73	27/13	60/600	12 wk	-0.2/–1.5	– 0.3/–2.	Abstinent smokers – C/E gave less weight gain

The table lists the human caffeine (C) and ephedrine (E) studies by number in the reference list. The number of subjects that started and finished the studies in the drug (D) and placebo (P) groups are listed. The study length is given, and the weight lost in kilograms and/or percent initial body weight lost is also given. The comment section lists special aspects of the various studies. –, no data; HDL, high density lipoprotein cholesterol.

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Table 2 Adverse effects

Symptom	C & E	No.	Pl.	No.	DEP	No.	Dex.	No.
Agitation (jitteriness, anxiety)	3.9%	(15/388)	0%	(0/216)	8%	(4/50)	0%	(0/53)
Dizziness	16.7%	(65/388)	8.3%	(18/216)	0%	(0/50)	7.5%	(4/53)
Headache	1.0%	(4/388)	0%	(0/216)	0%	(0/50)	5.7%	(3/53)
Tremor	6.2%	(24/388)	2.8%	(6/216)	4%	(2/50)	0%	(0/53)
Depression (fatigue)	0.5%	(2/388)	0%	(0/216)	0%	(0/50)	5.7%	(3/53)
Insomnia	8.2%	(32/388)	4.2%	(9/216)	10%	(5/50)	1.9%	(1/53)
Postual hypotension	0.5%	(2/388)	0.5%	(1/216)	0%	(0/50)	0%	(0/53)
Nausea	16.5%	(64/388)	8.3%	(18/216)	0%	(0/50)	11.3%	(6/53)
Thirst	0.3%	(1/388)	0%	(0/216)	0%	(0/50)	9.4%	(5/53)
Paresthesias	0%	(0/388)	0%	(0/216)	0%	(0/50)	5.7%	(3/53)
Diarrhoea	0%	(0/388)	0%	(0/216)	0%	(0/50)	11.3%	(6/53)
Dysrhythmia	21.6%	(84/388)	6.5%	(14/216)	0%	(0/50)	1.9%	(1/53)
Constipation	1.2%	(3/256)	0.9%	(2/216)	2%	(1/50)	3.8%	(2/53)
Urinary problems	0.3%	(1/388)	0.5%	(1/216)	2%	(1/50)	0%	(0/53)
Dry mouth	1.0%	(4/388)	0%	(0/216)	0%	(0/50)	1.9%	(1/53)
Heart rate	0.5%	(2/388)	0%	(0/216)	0%	(0/50)	0%	(0/53)
BP elevated	0.3%	(1/388)	0.5%	(1/216)	0%	(0/50)	0%	(0/53)
Glucose	0%	(0/388)	0%	(0/216)	0%	(0/50)	0%	(0/53)
Sweating	19.1%	(74/388)	8.3%	(18/216)	0%	(0/50)	0%	(0/53)
Other	2.6%	(10/388)	4.2%	(9/216)	0%	(0/50)	0%	(0/53)

Adverse events reported in trials of caffeine and ephedrine are listed as a percent incidence with the number of subjects experiencing the symptoms and the total number of subjects in the trials in parentheses. One trial compared caffeine (C) and ephedrine (E) to Diethylpropion (DEP) 25 mg tid in 50 subjects and another trial compared caffeine and ephedrine to dexfenfluramine (Dex) 15 mg bid in 53 subjects. No., number, Pl, placebo.

Table 3 Subjects withdrawn from the caffeine and ephedrine trials

Author	C & E	Placebo	DEP	Dexfen
(3)	0	4	4	–
(72)	10	10	–	–
(77)	1	1	–	–
(78)	4	4	–	–
(82)	10	–	–	7
(80)	0	3	–	–
(86)	15	7	–	–
	11.3% (44/388)	10.6% (23/216)	8% (4/50)	13.2% (7/53)

All subjects that withdrew from the studies of caffeine (C) and ephedrine (E) are listed. Each study is identified by reference list number. The bottom row on the table expresses the dropout incidence in percent followed by the number of subjects who dropped and the total number of subjects in the trials. There was one trial in which caffeine and ephedrine were compared with 50 subjects on Diethylpropion (DEP) 25 mg tid and one trial in which caffeine and ephedrine were compared with 53 subjects on dexfenfluramine (Dexfen) 15 mg.

Table 4 Adverse events responsible for withdrawal listed for subjects participating in caffeine and ephedrine trials

Adverse event	C & E	Placebo	Dexfen
HTN	1	2	0
Dysrhythmia	2	0	0
Agitation	1	0	0
Vomiting	2	0	0
Insomnia	3	0	0
Headache	0	0	1
Diarrhea	0	0	1
Totals	3.3% (8/241)	1.6% (2/127)	3.8% (2/53)

This table lists the reasons given for study withdrawal in subjects dropping for adverse events during the caffeine (C) and ephedrine (E) trials. The bottom row lists the incidence of dropouts for adverse events described in the trials followed by the number withdrawing and the number in the trials. Dexfen, dexfenfluramine.

Safety can also be evaluated by comparing the dropouts for adverse events in the caffeine with ephedrine groups to the dropouts for adverse event in the placebo groups or other compounds with which caffeine with ephedrine have been compared (see Table 4).

Caffeine and ephedrine are unique in that the side-effects return to placebo levels by 8 weeks and remain at placebo levels at least to 24 weeks despite subjects remaining on the compounds (72) (Fig. 1). Therefore, the incidence of adverse events may over-estimate their true clinical significance in obesity studies, since obesity is a chronic disease and one for which chronic treatment is appropriate.

Catechins in green tea are synergistic with caffeine in stimulating thermogenesis in man. No adverse effects were detectable, even with acute dosing of caffeine with catechins in a study performed in a metabolic chamber (85).

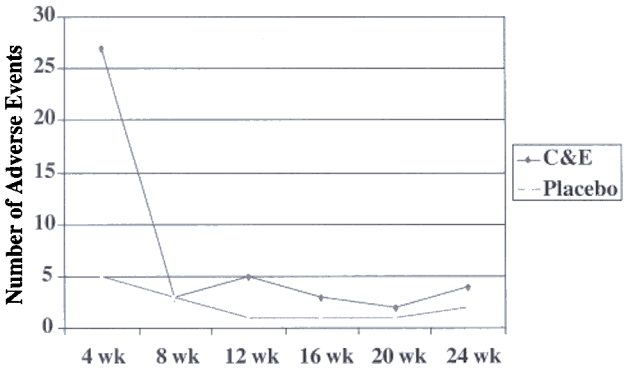

Figure 1 Incidence of adverse events with caffeine and ephedrine compared with placebo at monthly intervals during a 6-month trial (68). The incidence of adverse events (dizziness, tremor, headache, depressed mood, anxiety, euphoria, insomnia, postural hypotension, palpitation and tachycardia) were mild, transient and reached the placebo level at 8 weeks where they remained for the rest of the trial.

Additional literature

Caffeine (200 mg) and 20 mg of ephedrine tid have been tested for the prevention of weight gain after smoking cessation. Two thirds of 225 subjects were randomized to receive caffeine and ephedrine for 12 weeks and the rest were randomized to placebo. All subjects were off medication by week 39, and at 1-year weight loss and the percent not smoking were similar in both groups. At 12 weeks, however, weight gain was less in the caffeine and ephedrine group (86).

Concerns have been raised regarding the safety of caffeine and ephedrine use in subjects with controlled hypertension. One hundred and thirty-six overweight normotensive or drug-controlled hypertensive subjects were randomized to five groups. After 6-weeks of treatment systolic blood pressure was reduced 5.5 mm Hg more in controlled hypertensive subjects treated with 200 mg of caffeine and 20 mg of ephedrine three times a day than placebo in subjects treated with medication other than β-blockers. The antihypertensive effect of β-blocker medication was not reduced by caffeine and ephedrine. Normotensive patients treated with caffeine and ephedrine had a 4.4/3.9 mm Hg greater drop in blood pressure than those treated with placebo. The mean loss of weight of 4 kg was significant for all groups (87).

Caffeine was combined with phenylpropanolamine in the past to treat obesity (88). Since caffeine is not synergistic or even additive to phenylpropanolamine in stimulating weight loss, and can give central nervous system stimulation, it was removed from phenylpropanolamine products sold for weight loss (89). This is in contradistinction to caffeine and ephedrine that do give more weight loss when combined than either compound induces alone. The addition of caffeine to ephedrine in a 6-month trial blocked the rise in pulse rate seen with ephedrine alone (72). Energy expenditure with mention of caffeine has been reviewed (90), and nonprescription appetite suppressants including caffeine have also been reviewed (91).

Ephedrine has been proposed as an adjunct to cognitive restructuring (92). Ephedrine has been considered in reviews relative to nonprescription weight loss supplements (93), obesity management (94), energy balance (95) and obesity treatment (96).

Caffeine and ephedrine have been included in recent reviews of obesity medication (97–102). Thermogenic approaches to treat obesity have been reviewed (103). More specifically, caffeine and ephedrine relative to obesity treatment have also been reviewed (104–107). In a letter to the editor of the journal in which the clinical trial was published, the authors reported that ephedrine alone, on reanalysis, actually gave more weight loss than placebo, but less than ephedrine and caffeine, in the 24-week trial of caffeine, ephedrine, caffeine with ephedrine and placebo (108). Caffeine and ephedrine have also been used to induce weight loss prior to comparing different weight maintenance diets (109).

Discussion

Caffeine is a component of foods. Ephedrine has been used in oriental medicine for centuries. Ephedrine combined with methylxanthines including caffeine was a standard treatment for asthma in the 1960s and 1970s, and was sold for many years without prescription. In fact, it was the serendipitous finding of involuntary weight loss by a general practitioner in Denmark treating his patients with asthma using a caffeine and ephedrine product that initiated the use of this combination for the treatment of obesity.

Ephedrine products are sold without a prescription for the treatment of asthma and have a recommended dosage of up to 150 mg per day. Caffeine sold without a prescription has a recommended dose of up to 1600 mg per day. The popular herbal products containing caffeine and ephedrine and taken for weight loss have dosage recommendations up to 100 mg of ephedrine equivalent per day as ephedrine. The caffeine content of these herbal products containing caffeine and ephedrine varies, but is less than 600 mg a day. The most popular and widely sold herbal product containing caffeine and ephedrine has only 240 mg of caffeine per day, less than 3 cups of coffee. Pharmaceutical grade products have greater potency than the herbal products containing caffeine and ephedrine in equivalent doses because the herbal products contain some of the less active isomers of ephedrine.

The peer-reviewed literature documents central nervous system stimulation, an increase in pulse rate, an increase in blood pressure and an increase in glucose when caffeine

and ephedrine are given acutely either separately or together. These side-effects disappear with chronic treatment, and are no longer present after 4–12 weeks, depending on the trial. A 24-week trial of caffeine and ephedrine found a decrease in pulse rate and blood pressure. The pulse rate in that trial was no different than placebo in the caffeine and ephedrine group, but was significantly higher than placebo in the ephedrine group. There were no differences between the caffeine with ephedrine group and the placebo group relative to serum glucose, serum cholesterol or symptoms of stimulation.

Ephedrine and caffeine have each been sold for years without a prescription for the treatment of asthma and to combat drowsiness, respectively. Toxicity has not been a concern, even with recommended doses higher than that used in herbal products containing caffeine and ephedrine for weight loss. Overweight and obesity are common problems affecting more than half of the population, yet obesity is stigmatized by society. Therefore, it is not surprising that an effective weight loss product containing compounds with a long history of safe non-prescription use would be embraced enthusiastically by the public. When large numbers of the public are using any product, adverse events will inevitably occur, but the cause and effect relationship of these adverse events to the product use are usually unclear.

Obesity is a disease that predisposes to diabetes, hypertension and cardiovascular disease. These increased risks are reversed with weight loss. Although there may be small risks to the use of caffeine and ephedrine as a treatment for obesity, based upon the literature and the Danish experience, the risks appear to be outweighed by the potential benefits of weight loss.

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 caffeine with ephedrine suggest that the risks (elevation of blood pressure, elevation of pulse rate, agitation, dizziness, headache, tremor, fatigue, insomnia, nausea, thirst, dysrhythmia and dry mouth) are usually mild and transient, existing primarily during the first few days to weeks of treatment. The cardiovascular, stimulatory and other potential adverse effects of caffeine and ephedrine are at placebo levels in a few weeks while the benefits of weight loss persist for at least a year. Since asthma is usually an acute intermittent disease, those who take ephedrine and methylxanthines to treat asthma are disproportionately exposed to its risks relative to those taking caffeine and ephedrine on a more chronic basis for weight loss.

There have been a relatively small number of serious adverse events reported to a surveillance system in response to government requests to do so, compared with the widespread use of herbal products containing caffeine and ephedrine. These reports are not an objective method upon which to restrict the use of these herbal products containing caffeine and ephedrine. This statement is based upon several observations. First is the safety and efficacy of caffeine with ephedrine documented in the scientific literature for the treatment of obesity. Second is the history of safety using higher doses of caffeine and ephedrine as non-prescription medications for other uses. Thirdly, the side-effects seen with the acute use of caffeine and ephedrine reach placebo levels in a few weeks of continued treatment. This suggests that the safety of caffeine and ephedrine used chronically for weight loss is at least as great, if not greater, than the safety of ephedrine and methylxanthines in the acute treatment of asthma. Lastly, the levels of caffeine and ephedrine contained in herbal products for weight loss are less than the amounts of caffeine and ephedrine recommended for sale without a prescription for other purposes.

There remains a caveat to these conclusions. Most of the herbal products containing caffeine and ephedrine also contain many other compounds such as minerals and herbs that might alter or interact with caffeine or ephedrine. Therefore, these herbal products containing caffeine and ephedrine should be tested in controlled clinical trials to confirm their presumed safety and efficacy which cannot truly be extrapolated from the peer-reviewed scientific literature using pharmaceutical grade caffeine and ephedrine in isolation.

Obesity is epidemic, and the incidence is increasing in all segments of the population. Being overweight or obese are health risks that have few effective treatments. Herbal products containing caffeine and ephedrine should remain an option for weight loss and to reduce the associated health risks of being overweight and obese while controlled clinical trials of these products are simultaneously encouraged. Voluntary case reports having no denominator with which to calculate incidence and no control group with which to compare – they do not represent persuasive arguments to restrict the use of herbal products containing caffeine and ephedrine (1). The peer-reviewed scientific literature suggests that the risks of caffeine and ephedrine are outweighed by the benefits of achieving and maintaining a healthy weight. Confirmation of that conclusion for herbal products containing caffeine and ephedrine awaits controlled clinical trials.

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