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ORIGINAL ARTICLE

Multinutrient supplement containing ephedra and caffeine causes weight loss and improves metabolic risk factors in obese women: a randomized controlled trial

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Objective: To determine the safety and efficacy of a dietary supplement with a low dose of ephedra and caffeine in overweight/obese premenopausal female subjects.
Design: A 9-month, double-blind, randomized control study compared the efficacy and safety of a dietary supplement with ephedra and caffeine to a control supplement.
Subjects: Sixty-one healthy, premenopausal women with body mass index (BMI) from 27 to 39 kg/m^2 were randomly assigned and received a dietary supplement (40 mg/day ephedra alkaloids, 100 mg/day caffeine, high potency mixture of vitamins, minerals, omega-3 fatty acids) or a control supplement for 9 months.
Measurements: *Efficacy*: changes in body weight, body composition, lipids, insulin, leptin, adiponectin, ghrelin, and self-reports of physical activity, diet and quality of life indices. *Safety*: blood pressure, heart rate, electrocardiograms, urinalysis, blood histology, serum chemistry measures and self-reported symptoms.
Results: Forty-one women completed the study. The treatment group lost significantly more body weight (−7.18 kg) and body fat (−5.33 kg) than the control group (−2.25 and −0.99 kg, respectively), and showed significant declines in heart rate, serum cholesterol, triglycerides, cholesterol to high-density lipoprotein ratio, glucose, fasting insulin, and leptin. Blood pressure, electrocardiograms, other clinical chemistry measures, blood histology, urinalysis, and self-reported physical activity were similar in the groups. Minor symptoms included dry mouth, insomnia, nervousness and palpitations. The treatment group reported more energy and decreased appetite compared to controls and scored higher on a quality of life domain assessing vitality.
Conclusion: A dietary supplement containing a low potency ephedra/caffeine mixture appeared safe and effective in causing loss of weight and body fat, and improving several metabolic parameters, including insulin sensitivity and lipid profiles when tested under physician supervision. Such supplements could be a useful tool to assist with weight loss.
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Keywords: (MeSH) ephedra; weight loss; dietary supplement; lipids; insulin; leptin

Introduction

An estimated 64% of American adults are overweight or obese (body mass index (BMI) in kg/m$^2 \geqslant 25.0$).[1] Obesity is associated with a number of chronic health problems, contributes to at least 300 000 deaths per year,[2] and conservatively costs an estimated $75 billion annually in health care and related costs in the US.[3]

Physicians tend to underreport obesity, and less than half of obese persons are advised to lose weight or offered a supervised diet or exercise program by their doctor.[4,5] These trends may encourage people seeking weight loss to respond to heavily marketed products such as nutrition supplements, many of which have limited evidence of safety or efficacy.

Studies in the early 1990s found that a combination of ephedrine and caffeine significantly reduced body weight and fat in humans over a 6-month period.[6] Subsequent

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2- and 6-month studies using combinations of ephedra (Ma Huang) and caffeine reported similar weight loss findings.[7,8] The US Food and Drug Administration (FDA) banned the sale of dietary supplements containing ephedrine alkaloids in 2004, citing concerns such as consumption of high, unregulated dosages, and use by at-risk populations with comorbid conditions.[9] However, in 2005, a US District Court found insufficient evidence of adverse events related to the sale of a dietary supplement containing 10 mg/day ephedra alkaloids, and ordered the FDA to rewrite its ephedra rule with consideration for dose–response relationships (Nutraceutical Corp. and Solaray, Inc. vs Lester Crawford, Acting Commissioner, US FDA *et al*.).

Intake of vitamins, minerals, and omega-3 fatty acids may be compromised in overweight and obese individuals due to improper dietary choices, and a multinutrient supplement may be valuable in providing basic micronutrient support. We tested the hypothesis that a high-potency multivitamin and mineral formula, plus additional omega-3 fatty acids and botanical extracts including a low level of ephedra alkaloids and caffeine would have a greater effect in reducing body weight and body fat than a control formula containing a lower potency multivitamin and mineral formula devoid of omega-3 fatty acids, botanical extracts, ephedra alkaloids, and caffeine over a 9-month period. We further evaluated the effects of these two types of supplements on cardiovascular and metabolic indices, serum chemistry, self-reported symptoms, and behavioral and psychosocial measures.

Methods

Subjects

Sixty-one healthy pre-menopausal women, aged 25–47 years old, with BMI from 27 to 39 kg/m^2 were enrolled in the study (Table 1). During an enrollment period from February to August 2002, 216 prospective volunteers responded to recruitment. Ninety-four passed a telephone-based health screening and were further evaluated by a health interview, physical exam, and clinical chemistry. Exclusion criteria included resting systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg, history of, or existence of, any medical condition, use of prescription medications (except birth control pills), use of antihistamines or other medications used for mild asthma, coughs, colds, and allergies for 30 days prior to randomization and for the duration of the study, caffeine intake greater than 150 mg/day, smoking presently or at least 6 months prior to the study, involvement in any weight loss program or diet presently or at least 6 months prior to the study, and women who were pregnant, lactating or planning a pregnancy during the study period. All subjects provided written informed consent, and the University of California, Davis Institutional Review Board approved the study protocol.

Table 1 Baseline characteristics of the subjects[a]

Characteristic	*Control (N = 32)*	*Treatment (N = 29)*
Race or ethnic group		
African American	1	2
Filipino American	2	0
Latino American	2	6
Mexican American	0	1
Asian	1	1
Polynesian	1	0
Caucasian	24	19
Did not reply	1	0
Age (year)	35.5 ± 0.9	38.4 ± 1.1
Body mass index[b]	31.6 ± 0.5	32.4 ± 0.6
Weight (kg)	84.3 ± 1.7	88.6 ± 2.4[c]
Systolic blood pressure (mm Hg)	105 ± 1.4	107 ± 1.7
Diastolic blood pressure (mm Hg)	68 ± 1.2	70 ± 1.3
Heart rate	69.5 ± 1.5	67.1 ± 1.4
Cholesterol (mg/dl)		
Total	197.4 ± 6.4	182.4 ± 5.8
Low-density lipoprotein	124.9 ± 5.7	113.7 ± 5.1
High-density lipoprotein	48.5 ± 1.9	47.2 ± 2.1
Triglycerides (mg/dl)	105.8 ± 11.7	107.8 ± 11.0

[a]Plus-minus values are means ± s.e.m. [b]Body mass index is the weight in kilograms divided by the square of the height in meters. [c]A significant difference ($P < 0.05$) in body weight existed between the two groups after randomization at baseline.

Study design

Randomization of an equal proportion of subjects to one of two groups was conducted with a random number generator in multiples of 20.[10] Subjects and research staff were blinded to group assignment throughout the intervention. A sealed copy of the code was available to the study physicians for emergency purposes. The statistician was the only person with access to the code until completion of the study and data verification.

The control group received a supplement containing vitamins and minerals at 100% Daily Value, a small amount of lutein, a corn oil capsule, and a cellulose tablet (Table 2). The treatment group received a high-potency multivitamin and mineral formula, an omega-3 fatty acid capsule and a botanical supplement containing *Garcinia cambogia* extract, green tea extract, ephedra (*Ephedra sinica*) extract, guarana (*Paullinia cupana*) extract (a source of caffeine), and other botanical extracts (Table 2). The treatment group received a total of 40 mg of ephedra alkaloids per day, provided as 20 mg prior to breakfast and 20 mg prior to lunch, and 100 mg of caffeine per day, provided as 50 mg prior to breakfast and 50 mg prior to lunch. Independent analysis conducted at the Department of Pharmacy Science, Creighton University, confirmed the ephedrine and caffeine content. Study supplements were provided in daily strip packs and were of similar size, shape and color. Subjects were instructed to take the botanical caplets or placebo 30–45 min prior to breakfast and again prior to lunch, and to take the multivitamin-mineral caplets and omega-3 fatty acid or corn

Table 2 Composition of supplements for control and treatment groups

Ingredient	*U/day*	*DRI*	*Amount*	
			Control	*Treatment*
Vitamin A (palmitate)[a]	μg	700	1200	750
Vitamin A (beta-carotene)[a]	μg	700	300	3750
Vitamin C	mg	75	60	1200
Vitamin D[b]	μg	5	10	10
Vitamin E[c]	mg	15	13.5	70.5
Vitamin K	μg	90	25	0
Thiamin	mg	1.1	1.5	9
Riboflavin	mg	1.1	1.7	10.2
Niacin[d]	mg	14	20	160
Vitamin B_6	mg	1.3	2	16
Folate[e]	μg	400	400	800
Vitamin B_{12}	μg	2.4	6	36
Biotin	μg	30	30	100
Pantothenic Acid	mg	5	10	40
Calcium	mg	1000	162	150
Iron	mg	18	18	0
Phosphorus	mg	700	109	100
Iodine	μg	150	150	0
Magnesium	mg	320	100	200
Zinc	mg	8	15	15
Selenium	μg	55	20	80
Copper	μg	900	2000	2000
Manganese	mg	1.8	2	4
Chromium	μg	25	120	200
Molybdenum	μg	45	75	50
Chloride	mg	[f]	72	0
Potassium	mg	[f]	80	300
Boron	μg	[f]	150	300
Nickel	μg	[f]	5	0
Silicon	mg	[f]	2	500
Tin	μg	[f]	10	0
Vanadium	μg	[f]	10	50
Lutein	μg	[f]	250	0
Eicosapentaenoic acid	mg	0	0	180
Docosahexaenoic acid	mg	0	0	120
Choline	mg	0	0	60
Coenzyme Q-10	μg	0	0	150
Garlic extract	mg	0	0	50
L-Glutathione	mg	0	0	5
L-Methionine	mg	0	0	100
Bioflavonoids	mg	0	0	100
L-Carnitine	mg	0	0	25
Taurine	mg	[f]	0	50
Beta-sitosterol	mg	[f]	0	25
Gingko biloba extract	mg	[f]	0	10
Silymarin extract	mg	[f]	0	5
Red wine polyphenols	mg	[f]	0	5
Garcinia cambogia extract	mg	[f]	0	2000
Tulsi extract	mg	[f]	0	50
Gymnema sylvestre extract	mg	[f]	0	10
Green tea extract	mg	[f]	0	20
Oolong tea extract	mg	[f]	0	200
Eleutherococcus senticosis extract	mg	[f]	0	50
Guarana extract	mg	[f]	0	550[g]
Ephedra extract	mg	[f]	0	500[h]

[a]As retinol activity equivalents. [b]As cholecalciferol. [c]As alpha-tocopherol. [d]As niacin equivalents. [e]As dietary folate equivalents. [f]No DRI established. [g]Contains 100 mg caffeine. [h]Contains 40 mg ephedrine group alkaloids.

oil capsule with either lunch or dinner. Compliance was assessed at each clinic visit and by scheduled telephone interviews weekly, then monthly.

Women were instructed to refrain from eating or drinking beverages containing caffeine or alcohol for at least 12 h, and to refrain from heavy physical activity for 3 h, prior to the clinic visits. Normal hydration was maintained during the testing. Body weight was measured to the nearest 0.1 kg while wearing light clothing and without shoes using an electronic scale (Scale-Tronix 6002). Height was measured to the nearest 0.5 cm without shoes using a wall-mounted stadiometer (Ayrton S100). Body composition was assessed with a Xitron Hydra 4200 bioelectrical impedance spectrometer (Xitron Technologies, San Diego, CA, USA) in a supine position 30 min after voiding.[11] The manufacturer's software was used to calculate body composition. Body weight and body composition were measured at baseline and at months 1.5, 3, 6, and 9 after beginning the supplement regimens. With the subject remaining supine after measurement of body composition, a 12-lead resting electrocardiograph (ECG) (Welch Allyn) was recorded and subsequently read by a board-certified cardiologist (JCR). Electrocardiograph's were recorded at baseline, weeks 1, 2, and 4, and at months 1.5, 3, 6, and 9.

Blood pressure was measured three times in a resting, seated position with an aneroid sphygmomanometer (Welch Allyn), according to standardized methods.[12] A 1-min rest period was observed between each measurement. The last two readings were averaged for the final measurement. Heart rate was measured in beats per minute after the second blood pressure reading. Blood pressure and heart rates were recorded at baseline, weeks 1, 2, and 4, and monthly thereafter. Accepted values for normal blood pressure at the time of the study (130/85 mm Hg) were used.[13]

Blood collected from the antecubital vein and urine samples were obtained at baseline and at months 1.5, 3, 6, and 9. Serum levels of sodium, potassium, bicarbonate, chloride, magnesium, carbon dioxide, urea nitrogen, creatinine, glucose, phosphorus, calcium, protein, albumin, alkaline phosphatase, aspartate transaminase (AST/SGOT), total bilirubin, alanine transaminase (ALT/SGPT), creatinine kinase, lactate dehydrogenase, ketone bodies, cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were determined by chemistry analyzers (Beckman LXI and LX20 Pro). Low-density lipoprotein (LDL) cholesterol was calculated (TChol–HDL–TG/5 = Calculated LDL). Insulin, thyroxine, and thyroid stimulating hormone were assessed by chemiluminescent immunoassay (Bayer Advia Centaur). The above tests, as well as blood histology, were performed by the Department of Pathology at the University of California Davis Medical Center. Urinalyses by dipstick and urine pregnancy tests were performed at our clinic.

Plasma glucose concentrations were measured with a YSI Glucose Analyzer Model STAT 2300 (Yellow Springs Instruments, Yellow Springs, OH, USA). Free fatty acids were assayed with an enzymatic colorimetric assay (Wako

Chemicals USA, Richmond, VA, USA) adapted to a microtiter plate reader. Intra- and interassay coefficients of variation in our laboratory are 4.7 and 7.5%, respectively. Insulin was assayed as described elsewhere,[14] using human insulin standards (Linco Research, St Charles, MO, USA), (3-^{125}I) insulin (human recombinant) (Amersham Biosciences, Piscataway, NJ, USA) and antiinsulin antisera (Radioassay Systems Laboratories, Carson, CA, USA). Intra- and interassay variations are 5.5 and 8.9%, respectively. Leptin was measured with a radioimmunoassay kit using an I-125-iodinated human leptin tracer and human leptin standards (Linco Research, St Charles, MO, USA). Intra- and interassay variations are 5.8 and 5.7%, respectively. Adiponectin was determined with a radioimmunoassay kit using an I-125-iodinated murine adiponectin tracer, a multispecies adiponectin rabbit antiserum, and human adiponectin standards (Linco Research, St Charles, MO, USA). Intra- and interassay variations are 5.1 and 8.6%, respectively. Ghrelin was measured with a radioimmunoassay kit using rabbit antiserum specific for the synthetic peptide (Phoenix Pharmaceuticals, Belmont, CA, USA). Intra- and interassay variations are 5.9 and 13.3%, respectively. The homeostasis assessment model (HOMA-IR) was used to calculate an index of insulin resistance/sensitivity.[15]

Self-reported symptoms were assessed in person at baseline, weeks 1, 2, and 4 and monthly hereafter, as well as by regularly scheduled telephone calls. Events were self-rated for intensity (mild, moderate, severe, or serious), reviewed by the study physicians and classified according to the FDA coding system and thesaurus for adverse events terminology.[16]

Food intake was assessed by a standardized self-administered food frequency questionnaire (Block Food Frequency Questionnaire[17]) at baseline and month 9. Physical activity was assessed by an interview-administered standardized instrument (Seven-Day Physical Activity Recall[18]) at baseline and at months 1.5, 3, 6, and 9. Psychosocial indices were determined at baseline and months 1.5, 3, 6, and 9 using a self-administered, standardized survey (Medical Outcomes Study 36-item Health Survey [SF-36 version 2][19]) to assess domains of general health status, limitations in physical activities due to health problems, limitations in usual role activities due to physical or emotional problems, bodily pain, energy and fatigue levels, social functioning, general mental health and general health perception.

Statistical analysis

Outcome measures were analyzed using mixed model analysis of variance. Least squares means comparisons were performed to determine significant differences between groups overall and between the groups at specific time points. When model assumptions were not met, transformations were used prior to analysis.[20] Missing values were not imputed; they were left as missing.[21,22] Fisher's exact test was used to determine differences between groups for categorical response terms (e.g. blood pressure above normal values). Reported *P*-values were two-sided and a *P*-value of 0.05 or less was considered statistically significant. Analyses were performed with SAS software (version 9.1).[23]

Results

Attrition

Of the 61 subjects enrolled, 41 (67%) completed the 9-month study. Figure 1 depicts the randomization flow and reasons for attrition. The study code never needed to be broken for emergency purposes. No subjects were removed from the study due to clinically abnormal changes in serum chemistry, hematology, urinalysis, pregnancy, or ECG readings. No subjects were removed by the study physicians due to severe or serious symptoms. Of the nine subjects in the treatment group who withdrew, two started a medication that was exclusionary for the study, two reported headaches, one was lost to follow-up, one was noncompliant and one each reported insomnia, nervousness, and dizziness. Of the nine subjects in the control group who withdrew, four were lost to follow-up, three reported personal conflicts, one refused to participate, and one started a medication that was contraindicated for study participation.

Body weight and composition

The treatment group had a slightly higher average body weight (89.0 kg) than the control group (84.0 kg) at baseline. Body weights were rank transformed prior to statistical analysis, and all values from subjects completing 3 months of the intervention were included in the model. Significant differences between groups for weight loss occurred at months 1.5, 3, 6, and 9 ($P<0.0001$ between groups at each time; Figure 2), with the treatment group losing significantly more body weight than the control group (overall change between groups, $P=0.0022$). Changes in BMI were similar to those found for changes in body weight, with the treatment group showing a significant reduction in BMI at months 1.5, 3, 6, and 9 compared to controls ($P<0.0001$ between groups at each time; $P=0.0002$ overall). The amount of body fat did not differ between groups at baseline ($P=0.71$). Significant reductions in body fat were noted for the treatment group at months 1.5, 3, 6, and 9 compared to controls at each time, and was significant overall ($P=0.0017$; Figure 2). No differences in fat-free mass were found between the two groups at specific visits ($P=0.60$).

Blood pressure, heart rate, and electrocardiograph

Mean systolic and diastolic blood pressure values remained fairly constant throughout the intervention and were within the normal range at all measurement periods. At the time of the study, normal blood pressure was defined as systolic <140 mm Hg and diastolic <90 mm Hg. Using these criteria,

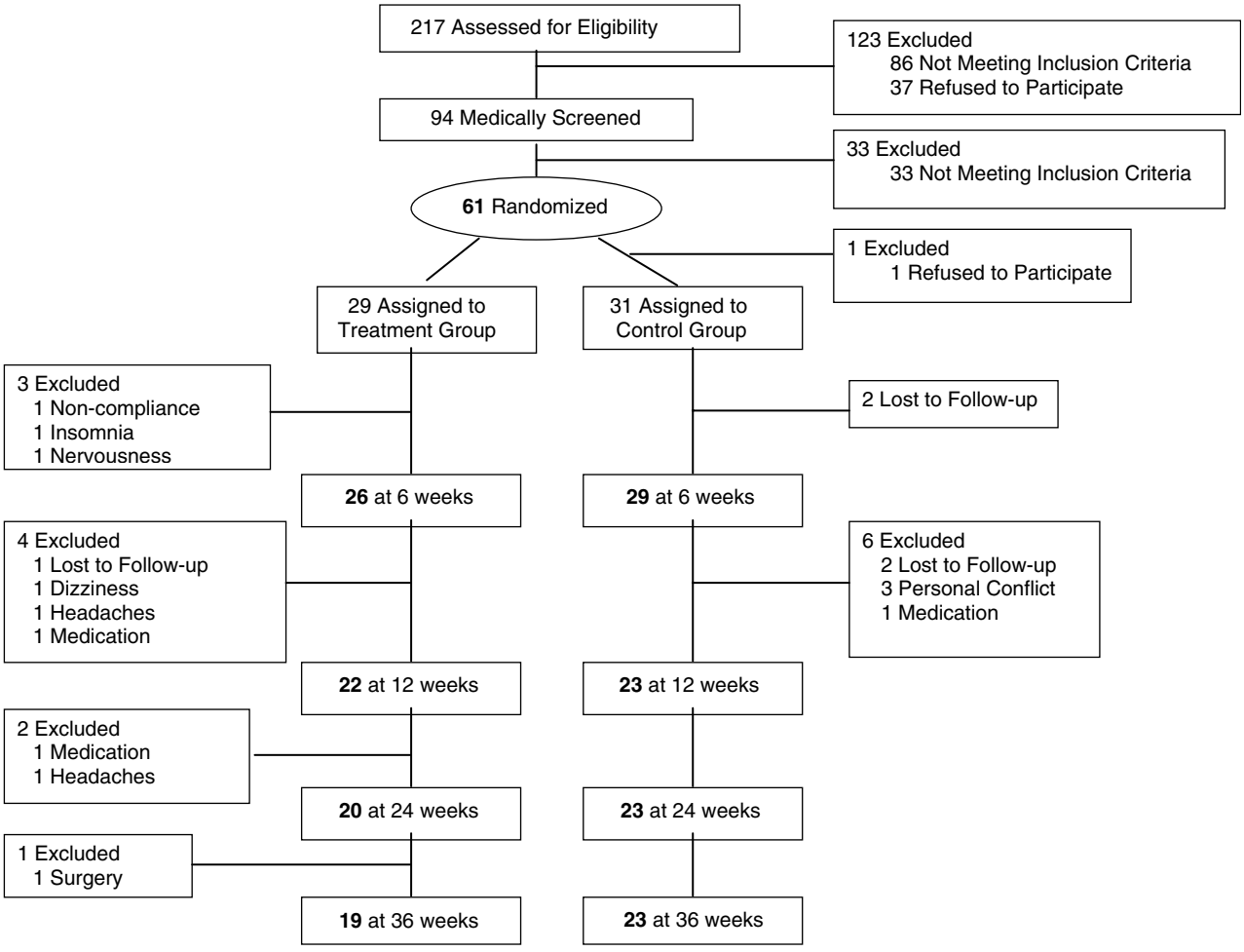


Figure 1 Randomization flow.

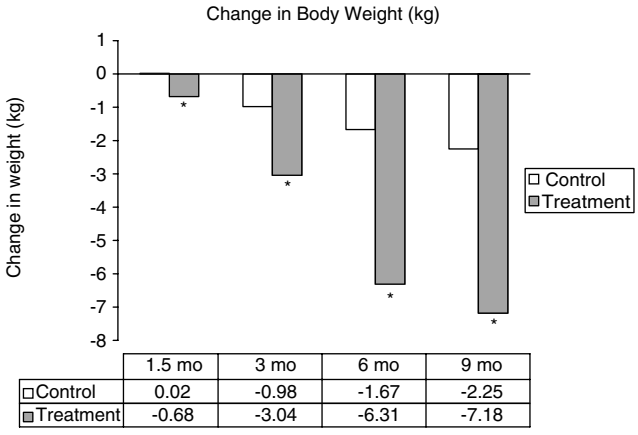
no differences in the number of high values for systolic or diastolic blood pressure were found between groups. By the completion of the study, new standards had been adopted to define normal blood pressure as systolic <120 mm Hg and diastolic <80 mm Hg. Using these newer criteria, no differences in systolic blood pressure were observed between groups except at month 3. No differences in diastolic values were found (Table 3).

Heart rates were similar between groups at baseline and were log transformed for analysis. Following ANOVA, mean values and 95% confidence intervals were calculated[24] and are shown in Table 3. Heart rates in the control group were significantly higher at week 1, month 3, and month 9 compared to the treatment group. Heart rates for the treatment group were significantly higher at week 2 than the control group. Overall, the treatment group showed a significant decline in heart rate compared to the control group ($P=0.0003$).

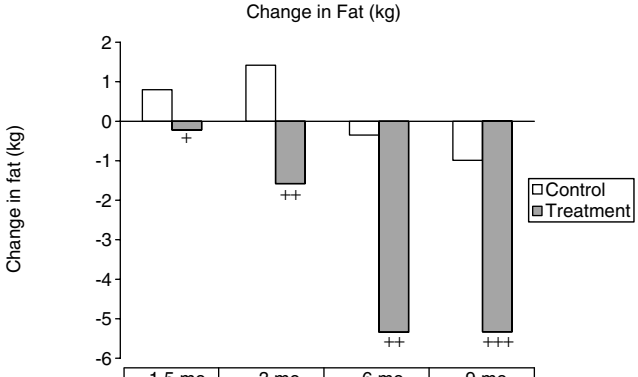
Most electrocardiograms (ECGs) were considered within the normal range. Clinically insignificant deviations in ECGs were noted for a small number of subjects in each group at various times, but in no case were the readings sufficiently alarming to warrant discontinuation of any subject. One subject in the treatment group was found to have a heart murmur, confirmed by an echocardiogram, which was diagnosed by the study cardiologist during the blinded phase of the intervention. The murmur most likely was due to a congenital anomaly and was not considered to be clinically significant.

Serum lipids, chemistry, urinalysis, and histology

Total serum cholesterol levels were significantly higher in the control group at baseline than in the treatment group ($P=0.002$). Both groups showed a similar decline in cholesterol over the course of the study ($P=0.78$; Table 4). High-density lipoprotein cholesterol was similar at baseline for the two groups ($P=0.49$) and was log transformed for analysis.[24] Levels did not differ between groups at any time except month 6, when the treatment group had significantly



	1.5 mo	3 mo	6 mo	9 mo
Control	0.02	-0.98	-1.67	-2.25
Treatment	-0.68	-3.04	-6.31	-7.18



	1.5 mo	3 mo	6 mo	9 mo
Control	0.8	1.42	-0.35	-0.99
Treatment	-0.22	-1.58	-5.34	-5.33

Figure 2 Changes in body weight and body fat in control and treatment groups.

higher HDL than the control group ($P<0.0001$). The ratio of total cholesterol to HDL cholesterol was significantly lower at months 1.5, 3, 6, and 9 for the treatment group compared to the control group, as was the trend over time ($P=0.004$). Low-density lipoprotein cholesterol was significantly higher at baseline in the control group compared to the treatment group, and both groups showed a decline over the course of the intervention. Triglyceride values were log transformed for analysis. Values for the treatment group consistently declined over the study, while values in the control group increased from baseline to 6 months and then declined at 9 months. Differences between groups were significant over time ($P=0.050$).

Among all other clinical chemistry, blood histology and urinalysis values monitored, no clinically significant changes were found.

Endocrine parameters

Fasting glucose levels were unchanged in the control group over time, while values in the treatment group declined significantly ($P=0.001$) (Table 5). Fasting plasma insulin concentrations were not different after 9 months in control subjects but decreased by nearly 18% ($P=0.017$) after 9 months in the treatment group. Insulin sensitivity as assessed by the HOMA index was unchanged in the control group, but improved by 23% ($P=0.004$) in the group consuming the dietary supplement with ephedra and caffeine. The absolute and proportional (percent) changes of plasma glucose, insulin, and insulin sensitivity in the treatment group were not related to either the absolute or the percent change of body fat mass by simple regression analysis. Baseline plasma leptin concentrations averaged approximately 20–22 ng/ml in both groups. Leptin was unchanged in the control group, but decreased by $25.8\pm5.2\%$ ($P=0.0004$) after 9 months in the supplement-treated subjects (Table 5). The absolute and proportional changes of leptin were significantly correlated with the absolute and percent changes of BMI ($P=0.0005$ and 0.001, respectively). Circulating adiponectin levels at baseline were similar in the control and treatment groups and remained unchanged after 9 months. Initial concentrations of total plasma ghrelin averaged approximately 700 pg/ml in both the control and supplement-treated groups, and were unchanged after 9 months in both groups.

Diet, physical activity, and quality of life

At the beginning of the study, reported daily energy intake for the treatment group was 8079 kJ (1930 kcal) compared to 6614 kJ (1580 kcal) for the control group ($P=0.005$). After 9 months, the reported mean daily energy intake in the treatment group decreased to 6367 kJ (1521 kcal) ($P<0.006$ compared to baseline value), while the mean daily caloric intake in the control group was 6455 kJ (1542 kcal). Two subjects reported energy intake <2512 kJ/day (<600 kcal/day) at both the beginning and end of the study, and six additional subjects reported energy intakes of <4186 kJ/day ($<1{,}000$ kcal/day).

The two groups reported similar levels of physical activity at the beginning and end of the study, and no differences were found between groups. Six of the seven quality of life domains assessed did not differ between groups. Subjects in the treatment group reported a significantly lower vitality index at baseline compared to those in the control group, and the vitality scores rose significantly for the treatment group while no change was found in the control group.

Self-reported symptoms

The treatment group reported significantly more dry mouth, nervousness, and palpitations than the control group (Table 6). None of the symptoms were severe and no subject was dropped from the study due to such self-reports. The treatment group also reported significantly more increased energy and decreased appetite than the control group.

Table 3 Blood pressure and heart rate in control and treatment groups

Blood pressure (mm Hg)		*Control*			*Treatment*			
		n	*mean*	*±s.e.m.*	n	*mean*	*±s.e.m.*	P
Systolic								
	Baseline	30	105	1.5	29	107	1.7	0.226
	Week 1	31	108	1.4	29	108	1.3	0.767
	Week 2	30	106	1.5	28	108	1.3	0.252
	Week 4	30	108	1.5	28	110	1.5	0.112
	Week 6	29	106	3.5	26	107	2.0	0.589
	Month 2	26	108	1.4	24	111	2.0	0.113
	Month 3	23	107	2.1	22	111	2.1	0.035
	Month 4	23	110	1.7	21	111	2.4	0.645
	Month 5	23	109	2.7	20	112	2.7	0.350
	Month 6	23	110	2.3	19	110	1.6	0.774
	Month 7	23	110	1.3	19	112	2.8	0.770
	Month 8	23	111	1.9	18	111	2.8	0.814
	Month 9	23	112	2.1	17	109	2.2	.075
Overall: Group $P=0.609$ Group × Visit $P=0.381$								
Diastolic	Baseline	30	68	1.3	29	70	1.3	0.079
	Week 1	31	68	1.3	29	69	1.3	0.309
	Week 2	30	68	0.9	28	68	1.1	0.978
	Week 4	30	68	1.5	28	68	1.3	0.845
	Week 6	29	68	1.5	26	69	1.4	0.322
	Month 2	26	68	1.4	24	70	1.4	0.195
	Month 3	23	68	1.5	22	70	1.7	0.139
	Month 4	23	69	1.3	21	71	1.3	0.375
	Month 5	23	68	1.5	20	72	1.8	0.065
	Month 6	23	69	1.5	19	69	1.4	0.510
	Month 7	23	68	1.3	19	71	1.6	0.074
	Month 8	23	70	1.0	18	69	1.7	0.408
	Month 9	23	70	1.5	17	71	1.9	0.689
Overall: Group $P=0.518$ Overall: Group × Visit $P=0.471$								

Heart rate[a] *(beats/min)*		*Control*				*Treatment*				
		n	*Mean*	*Lower 95% CI*	*Upper 95% CI*	n	*Mean*	*Lower 95% CI*	*Upper 95% CI*	P
	Baseline	30	68.9	66.7	71.3	29	66.7	64.5	69.0	0.174
	Week 1	31	76.9	74.5	79.5	29	72.7	70.3	75.2	0.018
	Week 2	30	74.2	71.7	76.7	29	78.6	76.0	81.3	0.016
	Week 4	30	75.3	72.8	77.8	28	76.5	73.9	79.2	0.490
	Week 6	29	72.3	69.9	74.8	26	70.7	68.2	73.3	0.351
	Month 2	26	76.0	73.3	78.8	24	75.6	72.8	78.5	0.818
	Month 3	23	72.2	69.5	75.1	22	66.3	63.7	69.0	0.002
	Month 4	23	73.9	71.0	76.8	21	74.2	71.3	77.3	0.914
	Month 5	23	74.7	71.8	77.6	19	73.7	70.6	76.9	0.600
	Month 6	23	71.4	68.6	74.2	19	70.4	67.4	73.5	0.585
	Month 7	23	75.3	72.4	78.3	19	77.9	74.6	81.3	0.275
	Month 8	23	74.3	71.5	77.3	18	76.3	73.1	79.6	0.402
	Month 9	23	75.0	72.2	78.0	17	68.0	65.2	70.9	<.001
Overall: Group $P=0.552$ Overall: Group × Visit $P<0.001$.										

[a]Measurements were log transformed for ANOVA; s.e.m. is not accurate. Means and 95% confidence intervals (CI) were back-transformed.

Discussion

Concerns have been appropriately raised about negative side effects that might be associated with the inappropriate use of ephedra and caffeine.[25–28] While the level of ephedra alkaloids (40 mg/day) used in the current study was appreciably less than that in other ephedra–caffeine trials of 3- to 6-month duration, the extent of weight loss and change in body composition in the present study is similar to outcomes at higher doses.[7,8,29,30]

A limitation of the study is that the two supplements differed in concentration of vitamins, minerals, omega-3

Table 4 Mean serum lipid and glucose levels in control and treatment groups

Cholesterol (mg/dl)

	Control			*Treatment*			
	n	*mean*	±*s.e.m.*	n	*mean*	±*s.e.m.*	P
Baseline	30	197	6.6	29	182	5.8	0.002
Month 1.5	28	185	6.8	25	177	5.6	0.009
Month 3	23	190	8.1	22	175	6.8	<0.001
Month 6	23	185	7.1	18	175	5.9	0.017
Month 9	21	184	7.9	19	174	7.1	0.003
Overall: Group $P=0.051$							
Group × Visit $P=0.782$							

HDL cholesterol[a] *(mg/dl)*

	Control				*Treatment*				
	n	*mean*	*Lower 95% CI*	*Upper 95% CI*	n	*mean*	*Lower 95% CI*	*Upper 95% CI*	P
Baseline	30	46.9	45.0	48.9	29	46.0	44.1	47.9	0.491
Month 1.5	28	44.8	42.9	46.8	25	47.5	45.3	49.9	0.070
Month 3	23	43.3	41.2	45.6	22	44.4	42.1	46.7	0.520
Month 6	23	42.3	40.2	44.5	18	50.7	47.8	53.7	<0.001
Month 9	21	44.7	42.4	47.2	19	47.0	44.5	49.8	0.191
Overall: Group $P=0.311$									
Group × Visit $P=0.002$									

LDL cholesterol (mg/dl)

	Control			*Treatment*			
	n	*mean*	±*s.e.m.*	n	*mean*	±*s.e.m.*	P
Baseline	30	124.9	5.9	27	113.7	5.3	0.015
Month 1.5	28	118.2	5.2	25	106.7	5.2	0.001
Month 3	23	123.8	6.5	22	108.0	5.6	<0.001
Month 6	23	119.0	6.3	18	104.1	4.4	0.005
Month 9	21	118.0	6.7	19	107.3	5.9	0.004
Overall: Group $P=0.032$							
Group × Visit $P=0.787$							

Triglycerides[a] *(mg/dl)*

	Control				*Treatment*				
	n	*Mean*	*Lower 95% CI**	*Upper 95% CI**	n	*mean*	*Lower 95% CI**	*Upper 95% CI**	P
Baseline	30	91.7	83.5	100.7	29	93.3	84.9	102.6	0.791
Month 1.5	28	92.6	83.8	102.4	25	93.6	84.0	104.2	0.890
Month 3	23	101.1	90.1	113.3	22	83.3	74.1	93.7	0.020
Month 6	23	100.4	89.6	112.6	18	77.3	67.8	88.1	0.003
Month 9	21	82.9	73.5	93.5	19	74.1	65.3	84.3	0.205
Overall: Group $P=0.351$									
Group × Visit $P=0.050$									

Cholesterol to HDL ratio

	Control			*Treatment*			
	n	*mean*	±*s.e.m.*	n	*mean*	±*s.e.m.*	P
Baseline	30	4.17	0.14	29	4.07	0.23	0.368
Month 1.5	28	4.19	0.16	25	3.77	0.22	0.001
Month 3	23	4.40	0.18	22	3.80	0.22	0.001
Month 6	23	4.40	0.17	18	3.23	0.14	<0.001
Month 9	20	4.26	0.19	19	3.57	0.22	<0.001
Overall: Group $P=0.018$							
Group × Visit $P=0.001$							

[a]Measurements were log transformed for ANOVA; *s.e.m.* is not accurate. Means and 95% confidence intervals (CI) were back-transformed.

Table 5 Endocrine parameters in control and treatment groups

	Control		*Treatment*		P-*value vs control*
	Mean±*s.e.m.*	P-*value vs baseline*	*Mean*±*s.e.m.*	P-*value vs baseline*	
Fasting glucose (mg/dl)					
Baseline	85.5±1.4		86.3±1.3		
9 Month	83.6±1.7		79.5±1.6		
Δ9 Month	−2.2±1.5	0.149	−6.8±1.7	0.001	0.033
Fasting insulin (μU/ml)					
Baseline	12.3±0.9		14.5±1.3		
9 Month	13.3±1.9		12.0±1.6		
Δ9 Month	0.9±1.2	0.960**	−2.6±1.0	0.017	0.023*
HOMA-IR					
Baseline	47.1±3.9		55.5±4.8		
9 Month	51.0±8.1		42.6±5.7		
Δ9 Month	3.2±5.1	0.687**	−13.0±4.0	0.004*	0.011*
Leptin (ng/ml)					
Baseline	20.7±1.7		22.6±1.5		
9 Month	19.6±2.4		17.0±1.8		
Δ9 Month	−1.4±1.5	0.362	−5.6±1.3	0.0004	0.027
Adiponectin (μg/ml)					
Baseline	8.7±0.7		9.5±0.9		
9 Month	9.4±0.9		9.9±1.0		
Δ9 Month	0.8±0.4	0.091	0.5±0.5	0.376	0.672
Ghrelin (pg/ml)					
Baseline	752.1±48.1		694.9±52.6		
9 Month	758.0±49.8		744.4±71.0		
Δ9 Month	5.9±20.4	0.774	49.5±31.8	0.137	0.243

*The overall ANOVA model was not significant but the pre-post changes were significant. **Uses sign-rank test.

Table 6 Number of most commonly self-reported symptoms in control and treatment groups

Condition	*Control*	*Treatment*
Appetite decreased	1	22
Dizziness	3	5
Dry mouth	4	14
Energy increased	3	19
Fatigue	4	7
Headache	13	16
Insomnia	2	7
Nausea	3	7
Nervousness	1	13
Palpitations	1	13

fatty acids, and some botanical extracts. The multicomponent dietary supplement with ephedra and caffeine does not enable assessment of the efficacy or safety of individual ingredients. Mixed ingredient formulas containing ephedra and caffeine are typically studied in clinical trials.[7,8,27–30] A broad based multinutrient supplement mixture containing vitamins and minerals may be useful for weight loss for a number of reasons. Insufficient intake of numerous vitamins and minerals has been linked to a number of chronic diseases.[31] Low levels of plasma vitamins C and E and serum levels of zinc and magnesium have been associated with a higher percent body fat,[32] and low plasma zinc levels have been associated with higher leptin production in obese humans.[33] Botanical extracts in addition to ephedra may be useful for weight loss. Extracts of *Garcinia cambogia* contain (−)-hydroxycitric acid (HCA), which have been reported to decrease energy intake by 15–30% in overweight human male and female subjects consuming 900 mg/day HCA.[34] Hydroxycitric acid has also been shown to promote fat oxidation and reduce the rate of weight gain in male and female rats.[35]

Self-reported symptoms were minor and transitory among the subjects who completed the study, and none were terminated from participation due to any clinically significant measurement. The higher incidence of dry mouth and insomnia reported here are consistent with other studies.[6,8] The treatment group reported more nervousness and palpitations than the control group. The incidence of dizziness and headache were approximately similar between groups. Reports of decreased appetite and increased energy found here have not been noted in other studies.

The present study found no differences in blood pressure or ECG between treatment and control groups. Mean blood pressure values were within the normal range at each measurement period for both groups. Although subjects in the treatment group lost weight, blood pressures remained unchanged, a finding consistent with other ephedra–caffeine studies that enrolled overweight and obese subjects with normal blood pressure.[7,30] In contrast, acute hemodynamic and ECG studies with a single dose of Metabolife 356, a dietary supplement with ephedra and caffeine (12 mg ephedra alkaloids, 40 mg caffeine, and 16 other ingredients), reported increases in systolic blood pressure and the mean maximal QTc interval.[27] Differences in ECG results between the two studies may be due to a number of reasons, including different ingredients in the supplements that were tested, different ECG measurement techniques, differences in the physiology or metabolism of subjects tested, or random chance. Differences in experimental design (single dose vs multiple dosing with possible adaptation effects) may also be important to consider.

The decreases in total and LDL cholesterol and triglyceride levels indicate that these risk factors for atherosclerosis and other cardiovascular morbidity/mortality are improved in conjunction with the weight loss induced by the treatment. Similarly, the decreases in fasting glucose, insulin, and the HOMA-IR index observed after weight loss in the treatment group indicate that insulin sensitivity was improved, an effect that would be expected to decrease the risks of impaired glucose intolerance, metabolic syndrome, and type-2 diabetes associated with obesity.

The decrease in plasma leptin (~25%) at 9 months that accompanied the decrease of total body fat (~18%) has been observed during both acute energy restriction and in

response to weight/body fat loss.[36] A reduction in leptin after weight loss has been associated with increased appetite[37] and decreased energy expenditure,[38] and may be a predisposing factor to weight regain when weight loss treatment is discontinued.[39] However, results from the present study showed maintenance of weight loss between 6 and 9 months.

Circulating levels of the orexigenic gastric hormone ghrelin did not increase after weight loss in the treatment group, in contrast to increases of ghrelin reported in other studies when subjects lose weight following energy-restricted diets.[40] The lack of an increase of ghrelin after weight loss in the supplement-treated group could contribute to decreased appetite and maintenance of weight loss with the supplement combination. Further studies are needed to determine the mechanism underlying the failure of ghrelin to increase during weight loss induced by this regimen. Circulating adiponectin concentrations did not increase after the moderate degree of weight loss induced by the supplement treatment. Increases of adiponectin are observed after greater degrees of weight loss, such as after gastric bypass surgery and are associated with improved insulin sensitivity.[41] Levels of adiponectin in the treated subjects were not associated with the decreases of fasting insulin levels or HOMA-IR indicating that changes of adiponectin are unlikely to have a role in the observed improvement of insulin sensitivity.

Subjects were instructed to follow their normal dietary intakes and did not receive standardized dietary advice. The significant decrease in reported energy intake in the treatment group, but not in the control group, may account in part for the differences in weight loss, particularly since reported levels of physical activity did not change in either group. However, indirect methods of assessing food intake have limitations and accuracy is difficult to verify. It is likely that both a reduction in food intake and an increase in thermogenesis are responsible for the significant weight and fat loss found in the treatment group.

Improved vitality found in the treatment group has also been associated with weight loss among women in the Nurses' Health Study.[42] In addition to weight loss, the improved vitality reported here might be associated with an increased perception of energy, which may be due to the intake of ephedrine and caffeine, and/or supplementation with vitamins, minerals or omega-3 fatty acids.

Adaptation effects from the long-term intake of ephedra and caffeine in combination with vitamins, minerals, and omega-3 fatty acids may also explain the differences in metabolic and hemodynamic effects noted here compared with results from acute studies. Tachyphylaxis and physiological adaptation, resulting in decreased side effects over time, have been reported in studies using a combination of ephedrine, caffeine and aspirin.[43,44] In the present study, no differences were found in blood pressure or ECG measurements between the two groups, in contrast to abnormalities in ECG and blood pressure noted after a single dose of Metabolife.[27] Further, a study of 16 healthy adults taking two doses, 5 h apart, of an ephedra–caffeine mixture (total intake 23 mg ephedra alkaloids, and 167 mg caffeine) or of a commercial product, Xenadrine RFA (25 and 185 mg, respectively) found increases in blood pressure and heart rate compared to a placebo treatment when measured over a 17-h period.[45] The study also reported significant increases in blood glucose and insulin levels over a 10-h period when ephedra–caffeine or the commercial product was taken, compared to levels when taking a placebo. In contrast, our study did not find changes in blood pressure, but did find significant decreases in heart rate, blood glucose, fasting insulin, and insulin sensitivity in the treatment group compared to controls. Another possibility to explain these differences is the presentation of ephedra alkaloids and caffeine as part of a multinutrient system, compared to isolated herbal extracts or herbal combinations devoid of vitamins, minerals, and omega-3 fatty acids.

Toxicity studies in mice fed up to 10 times the same dietary supplement used in the present study found no significant changes in normal serum chemistry, including cardiosensitive enzymes (creatine kinase, lactate dehydrogenase, and aspartate aminotransferase) and normal cardiac histopathological architecture.[46] The normal serum chemistry results in mice over a wide range of intake are consistent with the clinical findings reported here.

While lifestyle choices are necessary for weight loss, a variety of treatment interventions must be available to physicians as part of a comprehensive approach. Mean weight loss in the group of women taking the dietary supplement with ephedra and caffeine in this study is similar to mean weight loss found in a meta-analysis of obese patients treated with orlistat in addition to a hypocaloric diet.[47] Under the conditions tested (carefully selected, healthy overweight and obese population; physician prescription and monitoring; regular checks of blood pressure, heart rate, ECG, and self-reported symptoms), a low-dose of ephedra alkaloids and caffeine combined with a broad-spectrum multinutrient supplement and other botanical extracts may be a useful option to help physicians and patients with safe and effective weight loss. Results from the present study cannot be generalized to other population groups that may be at elevated risk, such as those with high blood pressure, diabetes, or a family history of heart disease. Patients with contraindicated conditions may not be appropriate for this regimen. Given the limited number of clinical options available for obesity treatment, further studies of low-dose ephedra and caffeine mixtures in conjunction with dietary supplements under regulated conditions may provide physicians with additional safe and effective therapies.

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LETTER TO THE EDITOR

Response to Dr Inchiosa

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Our opportunity to respond to the letter by Inchiosa allows us to expand upon and update a number of important points that were not fully addressed in our paper 'Multinutrient supplement containing ephedra and caffeine causes weight loss and improves metabolic risk factors in obese women: a randomized controlled trial'.[1] Inchiosa correctly points out that our study tested the effect of a high-potency mixture of vitamins, minerals, omega-3 fatty acids and botanical extracts including ephedra and caffeine, against a control formula containing 100% of the Daily Value of vitamins and minerals. This is indeed a controlled study design that has been used in numerous other studies assessing ephedra and caffeine, and our title, introduction and conclusions very carefully note the multinutrient formula that was tested, rather than drawing conclusions regarding only the effects of ephedra and caffeine.

We believe that it is unlikely that a *Garcinia cambogia* extract containing (−)-hydroxycitric acid (HCA) could have accounted for approximately 60% of the weight loss noted in our results. While a few studies suggest that HCA can reduce food intake or promote weight loss,[2] a number of other studies have produced negative results.[3–5] One of us (PJH) has recently completed a double-blind, placebo-controlled study in overweight/obese men and women, administering HCA (2700 mg/day) plus chromium polynicotinate (400 μg/day) for 12 weeks. No differences were measured in appetite, energy intake, body weight or body composition (personal communication), suggesting a minimal contribution of HCA, if any, to the body weight and body fat loss reported in the current study.

It is correctly noted that the treatment group had a significantly higher baseline body weight than the control group, although all participants were randomly assigned at the inception of the study in a double-blind manner. We do not think this initial difference accounts for the substantial differences in body weight and body fat loss noted at the end of the study. While differences in the reported daily energy intake at baseline between the two groups are duly noted, one must be skeptical of self-reported diet records, which give at best a rough estimate of a person's true energy intake. Indeed, we note that numerous self reports from our participants showed an unusually low estimation of energy intake (two <2512 kJ/day (<600 kcal/day) and six <4186 kJ/day (<1000 kcal/day)), which raises doubt regarding the accuracy of the baseline energy intake measurements.

The issue of palpitations was considered very carefully by the study physicians and authors. Self-reported symptoms from all participants were noted and graded by one of us (HJS) as mild, moderate or severe. All reports of palpitations were minor, and none of them persisted more than a few days. At no point was any participant removed from the study as a result of these symptoms. Electrocardiograms were obtained regularly on all participants, read (blindly) by one of us (JCR; a board-certified cardiologist) and none of the readings showed any patterns that caused concern. Palpitations are a well-known side effect of ephedra and caffeine, but at the doses used in our study, they seemed to subside and disappear after a brief period. Our observation is consistent with tachyphylaxis of this effect and with other studies on ephedrine/ephedra and caffeine previously published in this journal.[6,7]

Statements about the legal and regulatory status of dietary supplements containing ephedra and caffeine contained in our paper were accurate in March 2006, at the time of its online publication. Subsequent to the online publication, on 17 August 2006, the Tenth US Circuit Court of Appeals upheld the FDA's position that unregulated sale of supplements containing ephedra and caffeine posed a public health risk. Most recently, a petition was filed asking the US Supreme Court to review the Tenth Circuit Court of Appeals ruling on 3 January 2007,[8] thus this is still an evolving issue. Regardless of the next legal decision, it is important to note that the FDA's decision was based on unregulated use that enabled anyone to freely obtain ephedra and caffeine even if its use was contraindicated by existing medical conditions, and to consume these supplements in uncontrolled amounts. A viable alternative to unrestricted use would be the regulated use of ephedra and caffeine by prescription with proper physician monitoring, which in our opinion remains a viable option to debate.

Table 1 Summary of meta-analysis of weight loss drugs

Agent	*Duration (months)*	*Number of studies*	*Mean weight loss (kg) from meta-analysis*	*95% CI range (kg)*
Sibutramine	12	5	−4.45	−3.6 to −5.3
Orlistat	12	22	−2.89	−2.3 to −3.5
Phentermine	6	6	−3.60	−0.6 to −6.0
Bupropion	12	3	−2.77	−1.1 to −4.5

Abbreviation: CI, confidence interval.
Adapted from Li *et al.*[9]

Lastly, we disagree with Inchiosa's assertion that 'it would appear difficult to conclude that this prescription represents a useful option for the treatment of obesity.' Table 1 summarizes a recent meta-analysis of the currently approved medications used for the treatment of obesity and the range of weight loss associated with each.[9] Many of these studies included a low-calorie diet in addition to the medication. In our 9-month study, participants were asked not to alter their normal dietary patterns or to change their physical activity levels. The mean weight loss in the treatment group (7.61 kg; 95% confidence interval: 5.3–9.7 kg) is greater than the means noted for any of the drugs. While it is inappropriate to compare a single study to a larger number of studies investigating the effects of pharmaceutical agents, our results suggest that further studies of dietary supplements containing ephedra and caffeine are warranted. Rather than dismiss a modest level of ephedra and caffeine, combined with vitamins, minerals and omega-3 fatty acids, as not useful for the treatment of obesity, additional studies are needed to determine if such an approach, prescribed and monitored by a physician, can safely and effectively be employed as one aspect of addressing the current obesity epidemic.

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