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Subcommittee on Oversight of Government Management, Restructuring, and the District of Columbia

When Diets Turn Deadly: Consumer Safety and Weight Loss Supplements

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What is a Dietary Supplement?

There exist three categories of chemical agents available for weight loss treatment. The first two categories are prescription drugs and over-the-counter drugs. The Federal Drug Administration (FDA) regulates these agents under carefully controlled guidelines for safety and efficacy. The process is particularly rigorous for weight loss agents as over 60% of Americans are now overweight or obese, excess adiposity effects increasing numbers of vulnerable children and adolescents, and drug treatments for weight loss have a notorious past history of both abuse and damaging physical and behavioral effects extending back over a century. Prescription and over-the-counter drugs are rigorously tested using modern scientific guidelines and procedures to ensure public and individual safety.

In 1994 a third category of agents emerged referred to as "dietary supplements". The term dietary supplements is a legal one as stated by the FDA:

"FDA regulates dietary supplements under a different set of regulations than those covering "conventional" foods and drug products (prescription and Over-the-Counter). Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), the dietary supplement manufacturer is responsible for ensuring that a dietary supplement is safe before it is marketed. FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market. Generally, manufacturers do not need to register with FDA nor get FDA approval before producing or selling dietary supplements. Manufacturers must make sure that product label information is truthful and not misleading.

FDA's post-marketing responsibilities include monitoring safety, e.g. voluntary dietary supplement adverse event reporting, and product information, such as labeling, claims, package inserts, and accompanying literature. The Federal Trade Commission regulates dietary supplement advertising."

Dietary supplements for weight loss, unlike traditional drugs, often include multiple ingredients; the word "supplement" is misleading as most agents do not "add" to the natural body stores of the compound nor does the agent usually prevent or correct a deficiency state.

What Are Some of the Most Popular Weight Loss Products?

Weight loss can be produced when ingestion or absorption of calories or energy is less than energy released from the body as heat. Dietary supplements purportedly produce weight loss by suppressing appetite, reducing absorption, increasing heat production or metabolic rate, and changing the proportion of calories stored as fat and muscle.

The ephedra alkaloids, discussed below, are thought to suppress appetite and increase energy expenditure, by two different mechanisms. These actions are enhanced with herbal sources of caffeine and aspirin are added to the ephedra-containing product.

Some agents are reported to reduce fat and thus energy absorption from the gastrointestinal tract, notably chitosan. Chitin is a substance derived from the exoskeletons (shells) of arthropods such as crabs, shrimps, and lobster.

Some dietary supplements reportedly increase the storage of ingested nutrient as muscle and decrease the proportion stored as fat. These include the herbal ingredient garcinia cambogia and the widely used group of compounds referred to as chromium picolinate and other chromium salts.

My colleagues and I have reviewed these agents in a recent report (1).

I would now like to focus some specific comments on dietary supplements that include MaHuang as the main active ingredient. I select MaHuang because consumers are exposed with these products to a potentially dangerous family of ingredients, the ephedra alkaloids, that not only produce weight loss but that may lead to strokes and heart attacks with associated disability and death in selected susceptible patients.

A key concern is that overweight and obese patients are particularly vulnerable to taking purported dietary supplement weight loss products because they are often desperate, want to lose weight quickly, find evaluations by their physicians time consuming and costly, and have often tried dietary and medical therapies of limited current effectiveness.

By avoiding medical oversight, overweight and obese consumers purchasing dietary supplements make the false assumption that dietary supplements and herbal preparations are inordinately safe and may pose no or very little risk. Moreover, many overweight and obese consumers harbor "silent" diseases such as high blood pressure and narrowing of the coronary arteries that manifest under the biological conditions produced with ingestion of the purported weight loss agent. The overweight consumer of dietary supplements who harbors a potentially silent killer may be bypassing the critical medical

oversight needed to detect, prevent, or treat a serious underlying medical condition. A large percentage of overweight and obese Americans have undiagnosed and untreated medical conditions (2).

What is MaHuang?

Ma-Huang, now defined as a dietary supplement in the US, is primarily used today as an ingredient in herbal weight loss products and acts to lower appetite and potentially increases energy expenditure through stimulant mechanisms (3-12).

Ma-Huang is the Chinese name of Ephedra sinica, an acrid tasting stimulant herb (1). Other Ephedra species include Ephedra equisentina and Ephedra intermedia.

What are the Active Ingredients in MaHuang?

The ephedra alkaloids represent a family of compounds that vary in proportion depending on plant species, harvest season, weather conditions, geographic location, and other factors. The ephedra content of dietary may vary substantially from label claims (13).

The ephedra alkaloids include the major component, up to 90%, (-)-ephedrine, up to 30% pseudoephedrine, and lesser amounts of (+/-)-norephedrine or phenylpropanolamine, and (+)-norpseudoephedrine or cathine. The +/- refers to the three dimensional positioning of atoms within the molecule and this feature of a molecule may influence its biological activity.

Ephedrine, an ephedra extract, was synthesized in 1927 and is also widely used today in weight loss and other pharmaceutical preparations, particularly in Europe. Although studies are limited, the pharmacokinetics of synthetic and botanical forms of ephedrine appear similar (14; **Appendix 1**) although some questions on drug disposition remain and more studies are needed (15). Pharmacokinetic properties of a drug describe its absorption, distribution, and elimination from the body.

Phenylpropanolamine (PPA) has biological properties similar to ephedrine and for many years was the main ingredient used in over the counter weight loss products and cough/cold preparations. A recent report supports earlier observations of increased hemorrhagic stroke risk in subjects taking PPA (**Appendix II**). The Food and Drug Administration (FDA) is taking steps to remove PPA from all drug products and has requested that drug companies discontinue marketing products containing PPA. In addition, FDA has issued a public health advisory concerning PPA. (http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3647b1_tab19.doc).

The chemical structures of ephedrine and other ephedra alkaloids are very similar to the hormones epinephrine or adrenaline and nor-epinephrine. These are the “flight and fight” hormones that have many important biological effects including increasing blood pressure, respiration, heart rate, and arousal. Ephedra alkaloids are also very similar in

structure to the banned group of chemical compounds referred to as amphetamines (**Appendix III**). Widely used five decades ago for weight loss and other stimulant effects, amphetamines were addicting and had many serious other side effects.

How Does MaHuang Produce Weight Loss?

Ephedrine alkaloids appear to exert their main weight loss effects by suppressing appetite and thus food intake via central "sympathomimetic" (beta-agonist) actions. Ephedrine alkaloids also appear to have a small effect on increasing energy expenditure (16). Taken collectively, the ephedra family of compounds promotes negative energy balance and weight loss by lowering both energy intake and increasing energy expenditure.
Ephedrine and other Ephedra alkaloids have variable stimulant effects

Ephedrine and ephedra alkaloids alone have modest weight loss effects and their efficacy appears to be enhanced by addition of caffeine and aspirin either as the pharmaceutical grade ingredients or as their natural counterparts such as Guarana and Willow-bark, respectively (17-21).

Addition of caffeine (i.e., "Guarana") and aspirin (i.e., Willow-bark) to Ma-Huang purportedly potentiates the actions of ephedrine. Caffeine competitively antagonizes adenosine receptors and may be an adrenaline antagonist; adenosine is a hormone produced by endothelial cells that dilates blood vessels. Many commercial weight loss preparations include varying proportions of these three components. Caffeine per se has a small thermogenic (i.e., heat-producing) effect in humans (17). Aspirin has actions that also potentiate ephedrine actions.

Is MaHuang Effective as a Weight Loss Agent?

There are many studies that have examined the effectiveness of ephedrine alone or in combination with other ingredients; fewer studies examine the weight loss effects of ephedra alkaloids in combination with other natural sources of caffeine and aspirin.

The collective studies strongly support the premise that ephedrine, particularly in combination with caffeine and also aspirin, promote significant short-term (~3-6 months) weight loss when ingested as part of an intervention program including dietary and lifestyle management. Long-term (>6 months) controlled trials with large and diverse subject populations are lacking.

The efficacy of Ma-Huang, separate from that of chemically synthesized ephedrine, is supported by fewer published abstracts and papers, although conceptually, there is no reason to expect a "large" difference between "natural" ephedra and chemically-synthesized ephedrine. As noted earlier, the pharmacokinetics of chemically synthesized and botanical sources of ephedrine appear similar (**Appendix I**).

A major limitation of reviewed research is that most studies administered ephedrine or Ma-Huang in forms that mimic commercially available preparations and thus: the

efficacy of ephedrine as a sole weight loss agent is not entirely clear and is questionable; the efficacy of ephedrine with varying amounts of caffeine and aspirin is difficult to ascertain as studies failed to include varying amounts of these other agents independent of ephedrine or as separate experimental limbs in controlled trials.

Ephedrine is used in association with caffeine and aspirin, or their herbal equivalents guarana and willow bark, to produce the "fat-burning stack (18)." The stack has some evidence to support its efficacy and is used in Europe. The three compounds, when taken in the following ratio, 200 mg caffeine/60mg epihedrine/300mg aspirin, produces a significant thermogenic effect. Very limited published information is available on the safety and efficacy of the "stack" or related products.

A concern is that the concentration of ephedrine in the plant and method of preparation vary widely among products (13). Product labels may therefore not reflect actual ingredient content or bioavailability.

Are Ephedra-Containing Products Safe?

Why do we know that ephedra alkaloids may be unsafe in some consumers? Scientists know that ephedra alkaloids, particular when used in combination with potentiating agents that include caffeine and aspirin, produce variable increases in blood pressure, heart rate, cardiac output, and respiration (**Table 1**). These effects in susceptible individuals can trigger heart attacks and strokes.

The molecular basis of the stimulant effect for the class of compounds, "sympathomimetic agents", is well known. While the effects of ephedra alkaloids alone or in combination are often small in magnitude and transient, given the large and potentially medically vulnerable obese population taking these agents we can predict that some individuals with have a relatively large drug-induced biological effect. Others may have only a small effect but be medically vulnerable due to silent underlying heart or cerebrovascular diseases. Many of the patients taking these agents do so in the complete absence of medical supervision or evaluation. They may inadvertently take a large dose due to product variation or consciously in the hope of boosting their weight loss. Unsupervised, they may unduly exercise or take excessive amounts of caffeinated beverages or aspirin. The predictable result, given the millions of Americans taking these products, is serious medical events including heart attacks and strokes.

Given the well-recognized risks of this group of dietary supplements and the appropriate lack of interest in the area by pharmaceutical companies, there exist very few careful safety and efficacy trials that meet the current standards set forth for evaluation of pharmaceutical weight loss agents.

In the studies carried out by my colleagues and I using a commercial weight loss product containing ephedra and caffeine as active ingredients, some patients in the "active" treatment group experienced untoward effects at "usual" doses such as palpitations, blood pressure elevations, and other typical stimulant effects that led to their discontinuation in

the study (21). I have observed similar effects in other unpublished ephedra studies carried out at our institution. These effects are the well characterized sympathomimetic effects that I mentioned earlier and that support our projection that some medically unscreened patients with underlying disease may suffer heart attacks and strokes following ingestion of this or similar dietary supplements. This projection is supported by the study of Haller and Benowitz (23)(**Appendix IV**).

Another concern with the few well controlled trials is that subjects were appropriately medically screened prior to entry into the trial so as to reduce the medical risks of those exposed. One such trial was carried out at our institution (22) and only those subjects deemed medically acceptable were entered into treatment. Rigorous testing of blood pressure and heart rhythm was used to detect and eliminate those subjects who may have suffered a serious adverse event during the trial. The lack of serious injuries and side effects in trials such as these cannot be interpreted as a safety endorsement as the actual consumer population still includes the medically vulnerable and unscreened individual who may harbor a potentially lethal silent disease manifest by ingestion of ephedra alkaloids.

Specifically, concerns have been raised about the safety of products containing Ma-Huang/ephedra. Several serious case-reports of adverse effects and fatalities have appeared in the literature. Strokes, myocardial infarction, and cardiac arrhythmias are reported in association with ephedra ingestion. Benowitz and Haller (23; **Appendix IV**) provided the FDA with an independent review of adverse events related to ephedra alkaloid containing supplements. The authors concluded that ephedra alkaloids may pose a health risk for selected individuals. Some of the reported side effects in patients occurred within the commonly used therapeutic ranges.

Ephedrine alone or combination with other ingredients may raise heart rate and blood pressure (e.g., systolic BP increase ~3-7 mmHg) in some subjects (1-23), although the magnitude and length of time for which these adverse effects remain evident is not well established. Restlessness, headache, and insomnia have been reported by subjects ingesting some commercial dietary supplements and with ephedrine-caffeine combinations. Subjects with bleeding tendencies may be at risk when taking aspirin-like compounds.

Taken collectively, Ma-Huang taken alone or combination with other agents may place certain subjects at risk of adverse and potentially fatal effects. More long-term safety data, beyond six months, is needed, particularly in selected populations such as the elderly.

Finally, there exists particularly vulnerable populations such as pregnant or lactating women, the elderly, and subjects with eating disorders in whom particular concern exists for their use of weight loss dietary supplements.

Should the Regulations for Dietary Supplements be Changed?

Although my review here has been brief and focused, we can envision two types of dietary supplement for weight loss: one that is safe and ineffective and the other that is effective but unsafe.

The first type of product provides false hope to the unwitting highly vulnerable overweight or obese consumer and delays their entry into an appropriate medical or nutritional care system.

The second type of product is more dangerous and actual product efficacy will lure consumers into trying the product while erroneously assuming dietary supplements, because of their herbal or natural ingredients are unduly safe compared to their pharmaceutical counterparts.

Improved product safety testing, quality control, labeling, and nomenclature are all needed in order to forestall or eliminate the problems now inherent with the dietary supplement category of weight loss products.

Table 1. Patterns of Signs and Symptoms Associated With Dietary Supplements Containing Ephedrine Alkaloids.[1]

ORGAN/SYSTEM INVOLVED	CLINICAL SIGNIFICANCE	SIGNS AND SYMPTOMS
Cardiovascular system	Serious	Dysrhythmias, severe hypertension, cardiac arrest, angina, myocardial, infarction, and stroke[2]
	Less clinically significant	Tachycardia, mild hypertension, palpitations.
Nervous system	Serious.	Psychosis, suicidal, altered or loss of consciousness (including disorientation or confusion), and seizures.
	Less clinically significant	Anxiety, nervousness, tremor, hyperactivity, insomnia, altered behavior, memory changes.
Gastrointestinal (GI)	Serious	Altered serum enzymes, hepatitis.
	Less clinically significant	GI distress (nausea, vomiting, diarrhea, constipation).
Dermatologic	Serious	Exfoliative dermatitis
	Less clinically significant	Less clinically significant Nonspecific rashes.
General manifestations		Numbness, tingling, dizziness, fatigue, lethargy, weakness.

[1] Reproduced from Federal Register: June 4, 1997 (Volume 62, Number 107), Dietary Supplements Containing Ephedrine Alkaloids.

[2] For the purposes of this document, strokes (i.e., cerebrovascular accidents) are considered to be related to the cardiovascular system, because predisposing or inciting factors include hypertension, dysrhythmias and ischemia, although it is recognized that the consequences affect the central nervous system.

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Appendix I

Pharmacology of ephedra alkaloids and caffeine after single-dose dietary supplement use.

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OBJECTIVE: Serious cardiovascular toxicity has been reported in people taking dietary supplements that contain ma huang (Ephedra) and guarana (caffeine). We assessed the pharmacokinetics and pharmacodynamics of a dietary supplement that contains these herbal stimulants. METHODS: Eight healthy adults received a single oral dose of a thermogenic dietary supplement labeled to contain 20 mg ephedrine alkaloids and 200 mg caffeine after an overnight fast. Serial plasma and urine samples were analyzed by use of liquid chromatography-tandem mass spectrometry for ephedrine alkaloid and caffeine concentrations, and heart rate and blood pressure were monitored for 14 hours. RESULTS: Plasma clearance and elimination half-lives for ephedrine, pseudoephedrine, and caffeine were comparable to published values reported for drug formulations. A prolonged half-life of ephedrine and pseudoephedrine was observed in 1 subject with the highest urine pH. Mean systolic blood pressure increased significantly to a maximum of 14 mm Hg above baseline at 90 minutes after ingestion ($P < .001$). There was a lag in the mean heart rate response that reached a maximum change of 15 beats/min above baseline at 6 hours after ingestion ($P < .001$). Diastolic blood pressure changes were insignificant. Two subjects who were taking oral contraceptives had longer caffeine half-lives (15.5 +/- 0.3 hours versus 5.6 +/- 1.7 hours) and lower values for oral clearance (0.34 +/- 0.01 mL/min. kg versus 0.99 +/- 0.41 mL/min. kg) than subjects who were not taking oral contraceptives. CONCLUSIONS: Botanical stimulants have disposition characteristics similar to their pharmaceutical counterparts, and they can produce significant cardiovascular responses after a single dose.

Appendix II

PHENYLPROPANOLAMINE & RISK OF HEMORRHAGIC STROKE:
Final Report of The Hemorrhagic Stroke Project

May 10, 2000

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EXECUTIVE SUMMARY

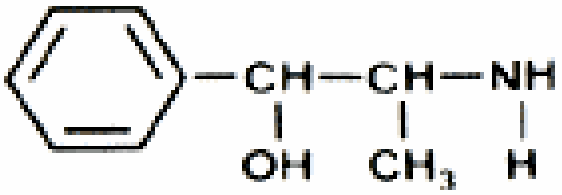
Case reports have linked exposure to phenylpropanolamine (PPA) to the occurrence of hemorrhagic stroke. Many of the affected patients have been young women using PPA as an appetite suppressant, often after a first dose. To further examine the association between PPA and c, we designed a case-control study involving men and women ages 18 to 49 years who were hospitalized with a subarachnoid hemorrhage (SAH) or intracerebral hemorrhage (ICH). Eligible case subjects had no prior history of stroke and were able to participate in an interview within 30 days of their event. Case subjects were recruited from hospitals in four geographic regions of the United States. For each case subject, random digit dialing was used to identify two control subjects who were matched on age, gender, race, and telephone exchange. Cases and control subjects were interviewed to ascertain their medical history, health behaviors, and medication usage. A subject was classified as exposed to PPA if they reported use within 3 days of the stroke event for case subjects or a corresponding date for control subjects, and the exposure was verified.

The final study cohort comprised 702 case subjects and 1376 control subjects. All control subjects were matched to their case subjects on gender and telephone exchange. Age matching was successful for 1367 controls (99%) and ethnicity matching was achieved for 1321 controls (96%). For the association between hemorrhagic stroke and any use of PPA within three days, the adjusted odds ratio was 1.49 (lower limit of the one-sided 95% confidence interval (LCL)=0.93, p=0.084). For the association between hemorrhagic stroke and PPA use in cough-cold remedies within the three-day exposure window, the adjusted odds ratio was 1.23 (LCL=0.75, p=0.245). For the association between hemorrhagic stroke and PPA use in appetite suppressants within the three-day exposure window, the adjusted odds ratio was 15.92 (LCL=2.04, p=0.013). For the association between PPA in appetite suppressants and risk for hemorrhagic stroke among women, the adjusted odds ratio was 16.58 (LCL=2.22, p=0.011). For first dose PPA uses among women, the adjusted odds ratio was 3.13 (LCL= 1.05, p = 0.042). All first dose PPA use involved cough-cold remedies.

In conclusion, the results of the HSP suggest that PPA increases the risk for hemorrhagic stroke. For both individuals considering use of PPA and for policy makers, the HSP provides important data for a contemporary assessment of risks associated with the use of PPA.

Appendix III

PHENYLPROPANOLAMINE



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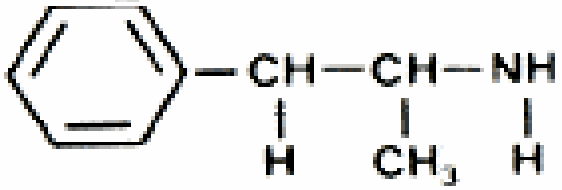

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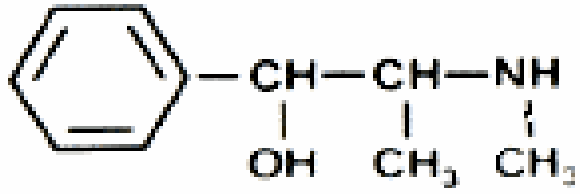

Appendix IV

Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids.

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BACKGROUND: Dietary supplements that contain ephedra alkaloids (sometimes called ma huang) are widely promoted and used in the United States as a means of losing weight and increasing energy. In the light of recently reported adverse events related to use of these products, the Food and Drug Administration (FDA) has proposed limits on the dose and duration of use of such supplements. The FDA requested an independent review of reports of adverse events related to the use of supplements that contained ephedra alkaloids to assess causation and to estimate the level of risk the use of these supplements poses to consumers. METHODS: We reviewed 140 reports of adverse events related to the use of dietary supplements containing ephedra alkaloids that were submitted to the FDA between June 1, 1997, and March 31, 1999. A standardized rating system for assessing causation was applied to each adverse event. RESULTS: Thirty-one percent of cases were considered to be definitely or probably related to the use of supplements containing ephedra alkaloids, and 31 percent were deemed to be possibly related. Among the adverse events that were deemed definitely, probably, or possibly related to the use of supplements containing ephedra alkaloids, 47 percent involved cardiovascular symptoms and 18 percent involved the central nervous system. Hypertension was the single most frequent adverse effect (17 reports), followed by palpitations, tachycardia, or both (13); stroke (10); and seizures (7). Ten events resulted in death, and 13 events produced permanent disability, representing 26 percent of the definite, probable, and possible cases. CONCLUSIONS: The use of dietary supplements that contain ephedra alkaloids may pose a health risk to some persons. These findings indicate the need for a better understanding of individual susceptibility to the adverse effects of such dietary supplements.