Arrhythmogenicity of weight-loss supplements marketed on the Internet

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BACKGROUND We examined nonprescription weight-loss supplements marketed on the Internet for ingredients with potential arrhythmogenic and life-threatening cardiac adverse effects.

OBJECTIVE We aimed to define the risks of life-threatening cardiac adverse effects that are associated with weight-loss supplements marketed on the Internet.

METHODS We entered the key words “weight-loss supplements” and “diet pills” into three popular Internet search engines. The top four nonoverlapping hits from each search engine were purchased. After receipt, the products and their ingredient lists were inspected, and Medline and the Natural Medicines Comprehensive Database were searched for reports of significant associations between each ingredient and various key words for life-threatening cardiac adverse effects.

RESULTS All supplements had the list of ingredients on the label. We identified 60 different ingredients (7.25 ± 4.66 per supplement; range 1–21). Eleven ingredients representing eight different substances (because multiple names were used for some substances) were each associated with two or more reports of life-threatening cardiac complications or death. Eight of the 12 products contained one or more such ingredients, but none of these eight products had warnings about life-threatening cardiac adverse effects on the Web pages, on the labels, or in the package inserts. One product contained ma huang (Chinese ephedra), even though the marketing of ephedra-containing products is banned in the United States.

CONCLUSIONS The Internet provides easy access to weight-loss supplements, several of which contain ingredients with potentially life-threatening adverse effects. There is a need for increased public education and awareness regarding such weight-loss products.

KEYWORDS Weight loss; Tachyarrhythmias; Cardiac side effects; Supplements; Obesity; Death

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Introduction

Obesity is rapidly becoming a health problem of epidemic proportions. Since the mid-1970s, the prevalence of overweight and obesity has increased sharply in both adults and children. Data from two National Health and Nutrition Examination Surveys show that among adults aged 20–74 the prevalence of obesity increased from 15% in 1976–1980 to 33% in 2003–2004.¹

Use of over-the-counter weight-loss supplements has become more common in the United States.²³ Retail sales of weight-loss supplements were estimated to be more than $1.3 billion in 2001. Possible reasons for the popularity of these supplements include the social stigma of obesity, desire for a “magic bullet” for weight loss, the supplements’ rapid availability without prescription or consultation with a health care professional, the perception that “natural equals safe,” and inflated advertising claims.³

The Internet is a growing resource for finding health information and purchasing health products, including weight-loss supplements.⁴ To our knowledge, the U.S. Food and Drug Administration (FDA) does not strictly regulate the sale and marketing of these supplements on the Internet; unlike prescription drugs, dietary supplements are not required to pass safety studies before being sold to consumers, and the companies that make these supplements are not required to obtain FDA approval to sell them. Furthermore, as Jordan et al⁶ have shown, Internet Web sites selling weight-loss supplements do not accurately describe (or do not describe at all) the potential health hazards these products may pose.

The cardiovascular adverse effects of various herbal supplements have been reported previously. With this background, we aimed to define the risks of arrhythmogenic and life-threatening cardiac adverse effects that are associated with weight-loss supplements readily found and purchased on the Internet.

Methods

During the winter of 2007, we used three search engines—www.yahoo.com (Yahoo), www.google.com (Google), and
www.msn.com (MSN)—with the goal of purchasing four nonoverlapping products from each search engine for a total of 12 products. Our search procedure (see Figure 1) was as follows: We first searched the term “weight-loss supplements” on each search engine—Yahoo first, then Google, then MSN. If any search produced overlapping results (i.e., if one or more of the top four hits from a given search engine matched a hit from a previously used search engine), we then searched for the term “diet pills.” If there was still overlap, we returned to the list of hits from the “weight-loss supplements” search, starting with the fifth hit and continuing down the list until four products were purchased via that search engine.

The Web pages and all packages and inserts were inspected for warnings about cardiovascular adverse effects. We identified the ingredients exactly as they were listed on the package labels, and we performed a comprehensive search of Medline and of the Natural Medicines Comprehensive Database for any reported association between each ingredient and cardiac arrhythmias or other life-threatening cardiac adverse effects. The key words “cardiac arrhythmias,” “ventricular tachycardia,” “ventricular fibrillation,” “myocardial infarction,” “cardiac arrest,” and “death” were used in each database search.

**Results**

Each of the 12 products was purchased online and delivered to us at a designated U.S. address without any restrictions. All products had a list of ingredients on the label. From these lists, we identified 60 different ingredients (7.25 ± 4.66 per supplement; range 1–21) exactly as they were listed on the labels. Of these ingredients, 42 were herbal extracts, five were synthetic compounds, four were minerals, and nine were vitamins or other organic substances. Eleven of the listed ingredients—which corresponded to eight different substances, because some ingredients were listed by various names—were associated with at least one report of life-threatening cardiac events or death; in fact, all eight ingredients were associated with two or more such reports. Eight of the 12 products included at least one of these ingredients. Warnings about potential adverse effects did not appear on any of the Web pages from which we purchased these eight products or on the labels and other materials shipped with these products. One product’s list of ingredients included *ma huang* (Chinese ephedra), even though the marketing of ephedra-containing products is banned in the United States.

The other potentially hazardous ingredients were bitter orange (also listed as *Citrus aurantium* and synephrine HCl), green tea (also listed as *Camellia sinensis*), buckwheat, guarana, ginseng (listed as Korean ginseng), licorice root, caffeine anhydrous, and *ma huang* root. Eight of the 12 products contained one or more of these ingredients (see Table 1).

**Discussion**

In this study, we examined 12 weight-loss supplements and identified eight ingredients with reported life-threatening cardiac adverse effects. We briefly review these ingredients and discuss the risks that they may pose to consumers.

*Ma huang*, or Chinese ephedra, is also known as ephedra, *Ephedra distachya*, and *Ephedra vulgaris*. Its principal alkaloid constituents are ephedrine and pseudoephedrine, both of which are nonselective α- and β-receptor agonists. Ephedra is taken orally for weight loss and to enhance athletic performance. In 2001, ephedra accounted for less

**Table 1** The distribution of ingredients with reported serious cardiac adverse effects among the 12 weight-loss products

<table>
<thead>
<tr>
<th>Product</th>
<th>Ingredient(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bitter orange&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Bitter orange, buckwheat</td>
</tr>
<tr>
<td>4</td>
<td>Bitter orange, ginseng</td>
</tr>
<tr>
<td>5</td>
<td>Bitter orange, green tea, guarana</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>Caffeine anhydrous, green tea&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>Green tea</td>
</tr>
<tr>
<td>9</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>Bitter orange, caffeine anhydrous, green tea, licorice root</td>
</tr>
<tr>
<td>12</td>
<td><em>Ma huang</em> root (ephedra)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Labeled “synephrine HCl.”

<sup>b</sup>Labeled “Citrus aurantium.”

<sup>c</sup>Labeled “Camellia sinensis.”
than 1% of herbal product sales but caused 64% of herbal adverse reactions reported to poison control centers. Ephe dra is associated with life-threatening cardiac adverse effects, including cardiomyopathy, hypersensitivity myocarditis, chest tightness, myocardial infarction, cardiac arrest, cardiac arrhythmias, and sudden cardiac death. In healthy volunteers, ephedra causes electrophysiologic changes; prolonged QT interval and premature atrial contractions can both occur after ingestion of ephedra. The FDA banned the sale and marketing of ephedra-containing products in the United States in 2004.

Bitter orange is also known as green orange, Citrus aurantium, synephrine HCl, and synephrine. Bitter orange fruit and peel, which are taken orally for weight loss, contain the adrenergic agonists synephrine and octopamine. Structurally, synephrine is similar to epinephrine, and octopamine is similar to norepinephrine. Several case reports have associated bitter orange with significant adverse cardiovascular effects. Between 1998 and 2004, Health Canada received 16 reports of serious adverse cardiovascular reactions to bitter orange. The reported cardiac side effects we identified included tachycardia, tachyarrhythmias, QT prolongation, variant angina, myocardial infarction, cardiac arrest, ventricular fibrillation, syncope, and death. Most of these side effects occurred when bitter orange was taken with caffeine or ephedrine. Because bitter orange can inhibit the metabolism of drugs by cytochrome P450 3A4 (CYP3A4), taking bitter orange with CYP3A4-metabolized drugs can increase blood levels of those drugs and thus increase the risk of adverse effects. The extent of this interaction effect is not yet known.

Green tea is also known as Camellia sinensis and Camellia thea. It is taken orally and can be used for weight loss. Green tea contains polyphenols, catechins, and Camellia thea. It is taken orally and can be used for weight loss. Ginseng can increase the QT interval in healthy adults on the first day of use. Ginseng’s effects have not been studied in individuals with cardiovascular disease. Ginseng can diminish the effects of warfarin.

Licorice is also known as Glycyrrhiza glabra, Gan Cao, glycyrrhizinic acid, and isoflavone. The applicable part of licorice is the root. There is conflicting information about the effectiveness of licorice for weight loss. Licorice has antispasmodic, anti-inflammatory, laxative, and soothing properties. The mineralocorticoid effects of licorice can induce fluid retention and worsen congestive heart failure. Licorice can also cause severe hypokalemia, increasing the risk of arrhythmias. There are multiple case reports of patients with life-threatening ventricular tachyarrhythmias and torsades de pointes due to licorice-induced hypokalemia, presumably caused by a mineralocorticoid excess syndrome associated with licorice consumption. Overusing licorice or combining it with cardiac glycoside therapy may increase the risk of cardiac toxicity due to potassium loss. Patients with heart disease should avoid licorice. In addition, licorice can reduce the effects of antihypertensive drugs, and it may have adverse interactions with other drugs, including but not limited to warfarin, digoxin, and furosemide.

Caffeine anhydrous, scientifically known as 1,3,7-trimethylxanthine, is commonly called caffeine. Its uses include weight loss and treating type 2 diabetes. Caffeine is a methylxanthine compound and is structurally related to theophylline, theobromine, and uric acid. It is 100% bioavailable after oral administration. Its possible mechanisms of action include adenosine receptor blockade and phosphodiesterase inhibition. Caffeine is thought to act on adenosine receptors to increase the release of dopamine and other neurotransmitters. In large doses, caffeine can stimulate massive catecholamine release, causing sinus tachycardia, metabolic acidosis, hyperglycemia, and ketosis. In rare cases, caffeine overdose can result in death from ventricular fibrillation. Using caffeine in combination with bitter orange or caffeine-containing herbs, such as green tea, black tea, oolong tea, guarana, mate, kola nut, and ephedra, increases the risk of serious life-threatening or debilitating adverse effects such as hypertension, myocardial infarction, stroke, seizure, and death. It must be emphasized that caffeine’s deleterious effects occur almost exclusively when caffeine is combined with other stimulants or taken in massive doses.

Guarana is also known as Paullinia cupana and Brazilian cocoa. Taken orally, guarana is used for weight loss and enhancing athletic performance. Oral guarana may promote weight loss when used in combination with mate and damiana. Guarana contains 3.6%–5.8% caffeine (compared with 1%–2% in coffee), which is responsible for guarana’s pharmacologic effects. When taken in combination with other caffeine-containing herbs or with bitter orange, guarana can increase blood pressure and heart rate in...
otherwise healthy, normotensive adults, potentially increasing their risk of serious cardiovascular adverse effects.\textsuperscript{9,35} Some reports have associated the use of a product containing both ephedra and guarana with jitters, hypertension, seizures, temporary loss of consciousness, and hospitalization requiring life support. Also, like other caffeine-containing supplements, guarana may have adverse interactions with a variety of drugs.\textsuperscript{7}

Buckwheat is also known as buchweizen, grano turco, and sarrasin. The active constituents of buckwheat include tocopherols, phenolic acids, and flavonoids. Buckwheat is taken orally to treat diabetes, improve vascular tone, and prevent hardening of the arteries.\textsuperscript{36–38} Noma et al\textsuperscript{39} reported a case in which buckwheat had caused fatal food-dependent exercise-induced anaphylaxis and cardiopulmonary arrest; additionally, the authors found specific IgE bands that were associated with the patient’s reaction to buckwheat. Kashima et al\textsuperscript{40} reported a case of sudden death in a patient who had eaten nyan-mien, or Korean buckwheat noodles.

The use of weight-loss supplements is common. In a study performed by Blanck et al\textsuperscript{2} to assess the prevalence of nonprescription weight-loss supplement use in the United States, an estimated 15.2% of adults (20.6% of women and 9.7% of men) had used a weight-loss supplement. The greatest use was among women aged 18–34 years (16.7%), and 73.8% of the supplements used by these women contained one or more stimulants, including ephedra, caffeine, and bitter orange. Of 3500 U.S. adults surveyed at random by Pillitteri et al\textsuperscript{1} in 2005, 41.2% had made serious weight-loss attempts during their lifetimes, and 33.9% of this group reported using a weight-loss supplement at least once in the case reports. Also, most of the reported effects were induced by substances taken in large doses or in combination with other substances. There is a lack of strong evidence from clinical trials on the safety of weight-loss supplements.

**Conclusion**

The Internet provides easy access to weight-loss supplements, including those with potentially life-threatening effects. Consumers are vulnerable to them because there is inadequate information or no information on the marketing Web sites about the life-threatening cardiac adverse effects of these products. The general public, health care professionals, and especially weight-loss consultants need to be educated about these products. We recommend more strict regulation of the sale and marketing of weight-loss supplements on the Internet.

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8. E.L.S., contributed to the editing of this manuscript.