Dietary Supplement Adverse Events: Report of a One-Year Poison Center Surveillance Project

Christine A. Haller, MD^a, Tom Kearney, PharmD^b, Stephen Bent, MD^c, Richard Ko, PharmD, PhD^d, Neal L. Benowitz, MD^e, Kent Olson, MD^b

^aAmgen, Inc. Department of Global Regulatory Affairs and Safety, South San Francisco, CA

^bCalifornia Poison Control System, San Francisco Division, University of California, San Francisco, CA

^cSan Francisco Veterans Administration Medical Center, San Francisco, CA

^dCalifornia Department of Health Services, Food and Drug Branch, Sacramento, CA

^eDepartment of Medicine, Division of Clinical Pharmacology, University of California, San Francisco, San Francisco, CA

ABSTRACT

Background: The safety and efficacy of dietary supplements is of growing concern to regulators, health-care providers and consumers. Few scientific data exist on clinical effects and potential toxicities of marketed products. Harmful supplements may not be identified for months or years with existing adverse event monitoring mechanisms. Retrospective review of poison center statistics to capture supplement-associated toxicity also has limitations.

Methods: We collaborated with the FDA Center for Food Safety and Nutrition (CFSAN) to conduct a 1-year prospective surveillance study of dietary supplement-related poison control center calls in 2006. Prompt follow-up of symptomatic cases, laboratory analysis of implicated dietary supplements, and causality assessment by a case review expert panel were performed.

Results: Of 275 dietary supplements calls, 41% involved symptomatic exposures; and two-thirds were rated as probably or possibly related to supplement use. Eight adverse events required hospital admission. Sympathomimetic toxicity was most common, with caffeine products accounting for 47%, and yohimbe products accounting for 18% of supplement-related symptomatic cases. Suspected drug-herb interactions occurred in 6 cases, including yohimbe co-ingested with bupropion (1) and methamphetamine (3), and additive anticoagulant/antiplatelet effects of NSAIDs taken with fish oils (1) and ginkgo (1). Laboratory analysis identified a pharmacologically active substance in 4 cases; supplement toxicity was ruled unlikely when analytical testing was negative in 5 cases.

Conclusion: Most supplement-related adverse events were minor. Clinically significant toxic effects were most frequently reported with caffeine and yohimbe-containing products. Active surveillance of poison control center reports of dietary supplement adverse events enables rapid detection of potentially harmful products, which may facilitate regulatory oversight.

INTRODUCTION

Dietary supplements including vitamins, minerals, botanicals, glandular extracts, amino acids, and proteins are regulated as food products by the U.S. Food and Drug Administration (FDA), thus

are not subject to strict pre- and post-marketing standards applicable to drugs. In recent years, there has been growing concern about the effectiveness and safety of dietary supplements, with newly published clinical trials showing lack of therapeutic benefit of products such as saw palmetto [1], echinacea [2], black

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Corresponding Author: Christine A. Haller, MD, Amgen, Inc. 1120 Veterans Blvd, ASF3-3, South San Francisco, CA 94080. Email: challer@amgen.com

cohosh [3], and glucosamine [4], and increasing reports of adverse effects of dietary supplements leading to product warnings, withdrawals, and bans, as in the cases of kava [5], Lipokinetix [6], and ephedra [7], respectively. It is difficult to properly ascertain the safety of dietary supplements without a standard and systematic approach to monitoring reports of adverse events. The FDA adverse event monitoring system for dietary supplements has improved surveillance, but the system is still hindered by passive reporting and limited capabilities to investigate adverse events through retrospective data collection. Because of these limitations, it could take months or years for an association between a harmful supplement and a new health risk to be recognized.

Increasing reports of adverse events associated with dietary supplements raise concern among consumers, health-care providers, regulators, and lawmakers about the safety of these products. Although media and medical journal reports of adverse health effects of dietary supplements are increasingly common, many reports are neither well documented nor substantiated by scientific evidence. In many of the reported cases, a clear association between use of the product and the suspected adverse reaction is not evident. Episodic case reports of adverse effects have been interpreted by some as evidence of the dangers of dietary supplements, but by others as confirmation that such cases are rare given their widespread use. With passage of the Dietary Supplement and Nonprescription Drug Consumer Protection Act in 2006, manufacturers of dietary supplements will be mandated to report all complaints of serious adverse events to the FDA within 15 business days.

In 2004, the Institute of Medicine Committee on the Framework for Evaluating the Safety of Dietary Supplements recommended to the FDA that a prospective systematic monitoring and tracking mechanism for dietary supplement ingredients should be maintained and refined, and that the FDA should work with the nation's poison control centers as a source of adverse event reports [8]. American Association of Poison Control Centers (AAPCC) annual reports of poisoning exposures provide summary data on adverse events related to a variety of substances, including drugs, chemicals, animals, plants, and dietary supplements. However, reliance on retrospective reports of poison center statistics to evaluate dietary supplement safety has a number of limitations including inaccurate coding of cases, misattributing co-ingestant-related symptoms to dietary supplements, incomplete product information, lack of confirmatory laboratory testing, and inadequate follow-up.

In this report, we describe the results of a 1-year prospective surveillance study of dietary supplement-related calls made to one regional poison control center. Key elements of the surveillance project included prompt follow-up of symptomatic cases, laboratory analysis of implicated dietary supplements and patient specimens, causality assessment by a case review panel, and quarterly summary reports made to the FDA for regulatory oversight.

METHODS

In collaboration with the FDA Center for Food Safety and Nutrition (CFSAN) we designed and conducted a 1-year surveillance study of

dietary supplement-related calls made to the California Poison Control System, San Francisco Division (CPCS-SF) from January 1 through December 31, 2006. All calls involving products regulated as dietary supplements were included. Excluded were traditional remedies such as Chinese herbal and Ayurvedic medicines, homeopathic products, and traditional food supplements such as beverages and energy bars because these products fall under different regulatory jurisdiction than dietary supplements.

The overall goal of this project was to apply a consistent, objective approach in collection and evaluation of reported adverse events to be able to determine whether the event was related to the exposure (i.e., causation) and also to monitor trends in dietary supplement adverse event reporting.

All calls made to the CPCS-SF that involved dietary supplements were collected by poison center staff and medical toxicology fellows. Cases that did not involve symptoms were tallied but not further investigated. Cases that involved symptoms were promptly investigated. Follow-up calls were made to health-care providers, and in some cases patients and family members, for additional information and to request shipment of patient urine and plasma specimens and dietary supplement product samples to our laboratories for analysis, when appropriate.

Symptomatic cases were redacted and summarized for causality assessment by a multidisciplinary case review panel comprised of 5 individuals with expertise in dietary supplements. Each panel member reviewed and scored case summaries for causation, relying on individual expertise, published literature, and other personal resources. Uniform guidelines were utilized for causality assessment based on the World Health Organization (WHO) Classification for Adverse Drug Reactions. A description of the WHO causality categories is listed in Table 1. Face-to-face meetings of the principal investigator (CH) and panel members (co-authors) were held quarterly to determine causality scores for each case by consensus of the panel.

Table 1: World Health Organization (WHO) Causality Classification for Adverse Drug Reactions

Very Likely/Certain: A clinical event with a plausible time relationship to exposure, which cannot be explained by concurrent disease or other drugs or chemicals.
Probable: A clinical event with a reasonable time relationship to exposure, which is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Possible: A clinical event with a reasonable time relationship to exposure, but which could also be explained by concurrent disease or other drugs or chemicals.
Unlikely: A clinical event whose time relationship to exposure makes a causal connection improbable, but which could be plausibly explained by underlying disease or other drugs or chemicals.
Unrelated: A clinical event with an incompatible time relationship, which could be explained by underlying disease or other drugs or chemicals.
Unclassifiable: A clinical event with insufficient information to permit assessment and identification of the cause.

A symptom severity score was assigned for adverse events that were rated on causality assessment as possible, probable, or very likely/certain. Severity scores were based on AAPCC definitions using criteria for symptom severity and required treatment and include no effect, minor, moderate, severe, and death.

Quarterly reports were submitted to FDA CFSAN, which included a list of asymptomatic calls, case summaries of calls involving symptoms, causality and severity ratings for adverse events, results of laboratory testing, and reports of observed trends in dietary supplement adverse events.

This study was approved by the University of California, San Francisco Committee on Human Research with a waiver of patient informed consent.

RESULTS

During the 1-year period from January 1 to December 31, 2006, a total of 275 calls about dietary supplements were received by the CPCS-SF, which comprised approximately 0.4% of the 75,390 calls made to the poison center division during the year. Of these calls, 112 (40.7%) concerned persons who were symptomatic and 163 (59.3%) involved dietary supplement exposures in individuals who had no symptoms or consisted of information requests about supplements. The types of dietary supplements most commonly involved in asymptomatic calls included

melatonin (29%); caffeine-containing multicomponent products (12%); glucosamine (11%); omega-3/fish oils (6%); echinacea (5%); amino acids (4%); and 5-hydroxytryptophan (5-HTP), saw palmetto, yohimbe, and black cohosh (2% each). Unintentional or accidental exposures comprised 87% of asymptomatic dietary supplement calls; children under age 5 years accounted for most of these.

Among the 112 calls that involved individuals experiencing signs or symptoms of toxicity, 20 cases (18%) involved intentional misuse or overdose, while the remaining 82% of adverse events occurred with apparently appropriate use of the dietary supplement. The consensus on causality likelihood of symptomatic cases by the case review panel concluded that 2% were very likely or certain; 30% were probable; 34% were possible; and 20% were unlikely to be attributed to the use of the dietary supplement. Cases judged to be likely, probably, or possibly related to supplement use will be described as "related" in the remainder of this report. In 14% of cases there was insufficient information to adequately assess causation; these cases were rated as unclassifiable.

Eight adverse events related to dietary supplements required hospital admission, including 3 patients admitted to intensive care units. There was one death due to stroke possibly associated with concomitant use of several caffeine- and yohimbe-containing dietary supplements (inset, *Figure 1*). The types of related adverse events grouped by body system along with the suspected causative

Case Summary: Death Possibly Related to Stimulant Supplement Use

- A 39-year-old male body builder was using **RedLine Fat Incinerator**, **Shrink Wrap**, **Xenadrine 8-hour release**, **Twin Lab Blood Pressure Control**, and **Relacore** for fat burning/weight loss.
- He was observed to "black out" with a possible seizure.
- Upon presentation to a hospital emergency department, he was minimally responsive with right-sided paralysis and a left gaze preference. Vital signs included: Blood pressure, 125/61 mm Hg; heart rate, 62/min, Serum potassium was 3.2 mEq/L, and other laboratory values were normal.
- Computed topography (CT) of the head showed infarction of the left middle cerebral artery. He had a possible history of hypertension but was not taking any medications. A small atrial-septal defect was seen on echocardiogram.
- His mental status continued to decline. On Day 2, he was declared brain dead based on a brain blood flow study. No autopsy was performed, and his death was ruled due to embolic stroke.
- Supplement Ingredients:
 - **Shrink Wrap** contains dandelion root (500 mg), uva ursi (250 mg), juniper berry (200 mg), buchu leaf (150 mg).
 - **Blood Pressure Control** contains C-12 peptide (100 mg).
 - **Relacore** contains Relacortin (266 mg), magnolia bark, passion flower, scutellaria, niacinamind, DHEA, panax ginseng, pinellia, poria, jujuba, perilla, phosphotidylserine (quantities not listed).
 - **Xenadrine NRG 8 hour** contains Norambolide (sclareolide extract), thermoxanthin (proprietary blend of L-tyrosine, coffee bean, green tea, cocoa seed, yerba mate and caffeine (quantities not listed).
 - **RedLine Fat Incinerator** contains caffeine, evodiamine, N-acetyl-L-tyrosine, guggulsterone, yerba mate, green tea 5-hydroxy- L-tryptophan, cAMP, vinpocetine, yohimbine HCl (quantities not listed).
- Samples of RedLine Fat Incinerator were analyzed by gas chromatography/mass spectrometry (GC-MS), which confirmed the presence of yohimbine, and liquid chromatography-tandem mass spectrometry (LC-MS/MS), which found 85 mg caffeine per capsule (255 mg per serving ~ equivalent to 3 cups coffee).
- This death case was determined to be possibly related to dietary supplement use.

Figure 1. Synopsis of Death Case Possibly Related to Dietary Supplement Use

Table 2: Reported Signs and Symptoms of Related Adverse Events grouped by Body System and Suspected Causative Ingredient

Body/Organ System Effect	Associated Signs and Symptoms	Suspected Causative Supplement Ingredient
Sympathetic nervous system stimulation	Anxiety, tremulousness, diaphoresis, hypertension, palpitations, headache, chest pain, tachycardia, shortness of breath, stroke, dizziness, agitation, mydriasis	Caffeine Yohimbine Citrus aurantium Gentian (Berberine)
Peripheral neuropathy or myopathy	Paresthesias, muscle pain, muscle cramping, rhabdomyolysis	Creatine St. John's wort
Hypersensitivity reaction	Rash, urticaria, diaphoresis, bronchospasm	Grape seed extract Echinacea Glutamic acid Spirulina
Gastrointestinal disturbance	Nausea, vomiting, diarrhea	Caffeine Yohimbe Creatine Arginine
Blood Coagulation Abnormalities	Epistaxis, post-operative hemorrhage, menorrhagia	Vitamin E Fish Oil Ginkgo biloba
Central nervous system depression	Drowsiness, sleepiness	Tryptophan Melatonin

dietary supplement ingredient are shown in *Table 2*. Sympathomimetic toxicity was the most common type of adverse event reported among related cases.

The supplement type, severity of reported adverse events, and number of related dietary supplement cases are summarized in *Table 3*. Multicomponent dietary supplements are listed by the ingredient believed to be responsible for the reported symptoms. Supplements that contained both caffeine and yohimbe are listed as yohimbe multicomponent products. Caffeine single- and multicomponent dietary supplements accounted for 47%, and yohimbe single- and multicomponent products accounted for 18% of supplement-related symptomatic cases. The multicomponent caffeine and yohimbe products involved in related cases are listed by brand name, listed ingredients, and frequency of calls in *Table 4*. Suspected drug-herb interactions occurred in 6 cases, including yohimbe co-ingested with bupropion ($n = 1$) and methamphetamine ($n = 3$), and additive anticoagulant/antiplatelet effects of non-steroidal anti-inflammatory drugs taken with fish oils ($n = 1$) and ginkgo ($n = 1$).

Laboratory analysis of dietary supplements and patient urine or plasma was performed in 9 symptomatic cases. In 5 cases, supplement toxicity was ruled unlikely when analytical testing was negative for suspected causative supplement ingredients or chemical adulterants. In 4 cases, a substance with known pharmacological activity that could plausibly be linked to the adverse event was identified, including the cardiovascular stimulants berberine, yohimbine, and caffeine, and high concentrations of Vitamin E, which has anticoagulant effects [9].

DISCUSSION

In this paper, we have described a systematic approach for surveillance of poison control center calls as a method for monitoring and tracking dietary supplement adverse events that is consistent with Institute of Medicine recommendations for evaluating the safety of dietary supplements. Poison control centers historically have played an important role in rapid detection of new health risks related to consumer products with prompt dissemination of information to health-care professionals, regulatory officials, and the public. Active surveillance and follow-up of poison center reports of adverse dietary supplement events allows for detection of new signals of potentially harmful products that may be missed by other spontaneous reporting systems.

Although the majority of supplement-related adverse events were minor, clinically significant toxic effects were more frequently reported with caffeine-containing multicomponent supplements than with any other type of supplement. Moderate and severe adverse events most often involved sympathomimetic symptoms attributed to the stimulant actions of caffeine- and yohimbe-containing products. There was one death due to stroke that was possibly attributed to use of multiple caffeine- and yohimbe-containing supplements in the setting of strenuous physical exertion. Detection of several similar adverse events raises concern about these stimulant products that warrants further investigation.

As illustrated in *Table 4*, adverse events attributed to stimulant-containing supplements involved a large number of different

Table 3: Supplement Type, Frequency, and Severity of Related Adverse Events

Supplement	Minor	Moderate	Severe	Death	Total
Caffeine, multicomponent	27	2		1	30
Yohimbe, multicomponent	6	3	1		10
Herbal caffeine, alone	5				5
Yohimbe, alone	2	1			3
Grape seed extract	3				3
Creatine	2				2
Melatonin	2				2
Gentian, multi-component	2				2
Amino acids	2				2
Morinda citrifolia (Noni)		1			1
Bilberry/Eyebright combination		1			1
Fish oils		1			1
Echinacea	1				1
Saw palmetto (topical)	1				1
St. John's wort, multicomponent	1				1
Conjugated linolenic acid	1				1
Methylsulfonyl methane	1				1
Vitamin E, multicomponent	1				1
Ginkgo biloba	1				1
Oxymatrine	1				1
Glandular extract, multicomponent	1				1
Spirulina, multicomponent	1				1
Cayenne pepper	1				1
Tryptophan	1				1

brands with a wide variety of ingredients. For the majority of products, the concentrations of active stimulants, particularly caffeine, are not provided in the ingredient list on the label. Although the dose equivalent of yohimbine is listed frequently on the label, the quantity of other stimulant alkaloids such as synephrine, tyramine, and phenethylamine is rarely provided. Listings of so-called "proprietary" botanical blends of amino acids, bioamines, and methylxanthines in total gram quantities fail to provide adequate information for consumers and health-care providers about dose amounts of potentially potent stimulants.

Although few scientific studies have been conducted on the clinical effects and interactions of multicomponent stimulant dietary supplements, preliminary human data indicates that combinations of caffeine with other herbal stimulants intensify cardiovascular and central nervous system effects [10]. These products are marketed for weight loss and athletic performance enhancement and thus are likely to be used under conditions of cardiovascular stress (strenuous exercise) and by individuals with

possible underlying cardiovascular risks (hypertension, coronary artery disease, diabetes). Further investigation is needed to determine if the sympathomimetic adverse effects of stimulant-containing dietary supplements observed in this study signal a potentially significant risk of toxicity for consumers.

The largest number of calls related to specific products involved Zantrex 3 (n = 7), and Trim Spa (n = 5), however, we could not determine whether this observation suggests greater risk of toxicity or higher prevalence of use of these products relative to other brands. Product sales information and epidemiological data on consumer use rates are needed to ascertain relative risk of individual products as well as to compare adverse-event incidence between types of supplements.

Possible drug-supplement interactions were observed in several cases, including 3 cases of yohimbe use in the context of recent or concurrent use of methamphetamine, and one case of combined use of yohimbe with the antidepressant drug, bupropion. Sympathomimetic stimulants such as cocaine and

Table 4: Multicomponent caffeine and yohimbine product formulations associated with adverse dietary supplement events

Product Name	Listed Ingredients	Caffeine and Yohimbine Dose Quantity	Adverse Events
Acutrim	Thiamine, riboflavin, niacin, Vitamin B6, folate, Vitamin B12, Biotin, Iodine, chromium, energy blend (EGCG and caffeine)	50 mg caffeine	1
Cortislim	Magnolia bark extract (40% honokiol), beta-sitosterol, L-theanine, green tea extract, ginseng, banaba leaf, vanadium (5 µg), and bitter orange extract	Caffeine not quantitated	1
Dexatrim Green Tea	Green tea extract, Asian ginseng, caffeine, maltodextrin, and niacinamide	Caffeine not quantitated	1
Dieter's Secret	Guarana, yerba mate, white willow bark, ginger root, green tea, cellulase, garcinia cambogia root, taurine, yucca root extract, bladderwrack extract, <i>Crataegus laeviata</i> berry extract, fo ti, ginkgo biloba, curcuma root extract, saw palmetto, <i>Gymnema sylvestre</i> leaf	Caffeine not quantitated	1
Endorush	Caffeine, taurine, L-arginine, L-citrulline, L-histidine, L-tyrosine, B vitamins, magnesium, calcium, vinpocetine	Caffeine not quantitated	1
Fahrenheit	<i>Salvia sclarea</i> , guggulsterone, and caffeine	Caffeine not quantitated	1
Fast Twitch	Creatine, caffeine, Vitamins C, E, B6, B12, folate, magnesium, sodium, potassium, calcium, arginine, L-citrulline, L-serine, glycine, taurine, L-tyrosine, glutamine, potassium citrate, and sodium citrate	Caffeine not quantitated	1
Hot Rox	Thiamine, niacin, Vitamin B12, N-acetyl-L-tyrosine, salvia sclarea, guggulsterone Z and E, caffeine, and 5-hydroxy-L-tryptophan	Caffeine not quantitated	1
Hydroxycut	Hydroxycitric acid, L-carnitine, green tea extract, guarana, willow bark	Caffeine not quantitated	3
Hydroxycut Hardcore	Green tea, caffeine, white willow bark, <i>Aspidosperma quebracho-blanco</i> , <i>Cnidium monnieri</i> , Troxerutin, black pepper, <i>Codonopsis pilosula</i> , <i>Inula racemosa</i> , <i>Evodia rutaecarpa</i> , xanthinol nicotinate, deanol acetamidobenzoate hydrogentartrate, yohimbine	4.5 mg yohimbine 280 mg caffeine	2
Max Size	500 mg yohimbe extract (3% alkaloids) Vitamin B3, zinc, other unlisted herbs	15 mg yohimbine	2
Metabolife	Caffeine, exact formulation unknown	Caffeine not quantitated	1
Metabolift	Guarana, <i>Citrus aurantium</i> , St. John's wort, L-phenylalanine, green tea extract, quercetin, citrus bioflavonoid, ginger root, cayenne fruit	176 mg caffeine	2
Metabolink	<i>C. aurantium</i> , rhodiola, green tea, chitosan, bee pollen, Siberian ginseng, lecithin, bovine cartilage, damiana, sarsaparilla, goldenseal, nettles, gotu kola, spirulina, and royal jelly, and Vitamins E, B6, B12, thiamine, riboflavin, niacin, magnesium, zinc	Caffeine and synephrine not quantitated	1

Table 4: (Continued)

Product Name	Listed Ingredients	Caffeine and Yohimbine Dose Quantity	Adverse Events
Natrol Hoodia	Hoodia, green tea extract, <i>C. aurantium</i> , and chromium picolinate.	Caffeine and synephrine not quantitated	1
Nature's Bounty V-Power	Niacin 45 mg, yohimbe extract 250 mg, guarana extract 300 mg, ginkgo biloba extract 40 mg, saw palmetto extract 100 mg, taurine 20 mg, raw testicular extract 50 mg, oats extract 150 mg, and eleuthero 30 mg.	Caffeine and yohimbine not quantitated	1
NV Weight Loss	Green tea, hoodia gordonii, Panax ginseng, and <i>Rhodeola rosea</i>	Caffeine not quantitated	2
Power Flush	beta carotene, water, yerba mate, guarana, Vitamins A and E, folic acid, creatine, citrus bioflavonoid complex, rutin, and Vitamins B6 and B12	Caffeine not quantitated	1
Redline Fat Incinerator	Caffeine, evodiamine, N-acetyl-L-tyrosine, guggulsterone, yerba mate, green tea 5-hydroxy-L-tryptophan, cAMP, vinpocetine, yohimbine HCl	255 mg caffeine (by analysis)	2
Stacker 2	Yohimbine alkaloids, yerba mate, guarana, kola nut, capsaicin and caffeine anhydrous	Caffeine and Yohimbine not quantitated	1
Stacker 3	Caffeine, ephedra(?), exact formulation unknown	Caffeine, ephedrine not quantitated	1
Sta-Max	yohimbe extract (8%), "L-argine," γ -aminobutyric acid, and horny goat weed (<i>Epimedium</i>)	Yohimbine not quantitated	1
Stamina RX	L-arginine, yohimbe extract, GABA, <i>Epimedium</i> extract, <i>Cnidium</i> extract	4 mg yohimbine	2
Trim Spa	<i>Hoodia gordonii</i> , glucosamine, green tea extract, cocoa extract, Citrus naringin, chromium, vanadium, Glucomannan	Caffeine not quantitated	5
Xenadrine EFX	L-tyrosine, acetyl-L-tyrosine, green tea, cocoa extract containing phenylethylamine, tyramine, and theobromine, yerba mate, D-methionine, ginger root, 3,3',4',5-7-pentahydroxyflavone, 3,3',4',7-tetrahydroxyflavone, bitter orange (synephrine, N-methyltyramine, hordenine, octopamine, tyramine), DMAE (2-dimethylaminoethanol), grape seed	Caffeine not quantitated	1
Xenadrine NRG 8 hour	Norambolide (sclareolide extract), thermoxanthin (proprietary blend of L-tyrosine, green coffee bean, green tea, cocoa seed, yerba mate and caffeine	Caffeine not quantitated	1
Yellow Jacket	Ephedra, capsicum, <i>C. aurantium</i> , <i>sida cordifolia</i> , and kola nut	Caffeine, synephrine, ephedrine not quantitated	1
Zantrex 3	Yerba mate, caffeine, guarana, damiana, schizonepeta, green tea, <i>Piper nigrum</i> , ginseng, maca root, cocoa nut, kola nut, and <i>Thea sinensis</i>	Caffeine not quantitated	7

methamphetamine induce short-term erectile dysfunction due to vasoconstriction, and self-treatment with sildenafil and similar drugs has been reported [11]. It may be that use of yohimbe as a sexual enhancer is popularly promoted among illicit stimulant users, and represents a potentially risky drug-supplement combination.

In addition to sympathomimetic stimulant effects of supplements, several other trends in supplement-related symptoms were observed (Table 2), including some potentially novel associations. A number of reports of muscle pain and cramping with elevated creatine kinase and, in some cases, rhabdomyolysis were reported with several different supplements, frequently taken in combination with other supplements and medications. Complaints of muscle pain and cramping were reported with various multi-component dietary supplements containing creatine, amino acids (taurine, L-carnitine, glutamine, L-tyrosine, and L-arginine), *Morinda Citrifolia* (Noni), yohimbe, saw palmetto, caffeine, and *Citrus aurantium*. Creatine has been reported to cause muscle cramping and, rarely, rhabdomyolysis [12,13]; however, some recent clinical studies do not support this association [14,15]. Although definitive causality could not be established in our cases because of a lack of substantiating scientific evidence, the frequency of similar reports raises questions about possible muscle toxicity of some dietary supplements.

Two cases of bleeding were reported with combined use of a nonsteroidal anti-inflammatory drug with ginkgo biloba and fish oils, two dietary supplements that are known to have anticoagulant effects [16]. In one case, bleeding was spontaneous and minor (epistaxis), but the second case (post-spinal surgical hemorrhage) was more serious and required hemostatic therapy. Other case reports of impaired coagulation due to dietary supplement use have raised concerns among physicians about increased risk of perioperative hemorrhage [9,17]. Some clinicians now advise patients to stop all herbal medicines and supplements for at least 1 week prior to scheduled surgery [18].

The approach used in this study—including active surveillance of poison center calls with prompt case follow-up, committee review for causation analysis, and substantiation of exposures through product and specimen analysis—is a first step towards implementation of the IOM recommendations for dietary supplement safety. This approach could be implemented at other poison control centers, and could also serve as a model for systematic tracking of poison center reports of adverse drug events, medication errors, and drug interactions.

A notable limitation of this study was incomplete case follow-up, which prevented causality assessment in 14% of cases. This frequently occurred when the poison center staff didn't identify a case of dietary supplement toxicity and failed to obtain adequate information or request samples of dietary supplement products. Other limitations included possible under- and over-reporting due to inaccurate case coding or inclusion of alternative medicine products that were not dietary supplements. These limitations lessened over the course of the project period with staff training and standardization of inclusion criteria. Objective

assessment of causality by expert clinical toxicologists using a standardized rating system and analytical testing of dietary supplement products strengthened the quality of information derived from poison center adverse event reports.

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