Safety by the Numbers: Making Sense of Dietary Supplement Adverse Event Data

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Rick Kingston, PharmD.

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Dietary Supplements, Safety and Adverse Events by the Numbers

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- Academically affiliated with the University of Minnesota
- Core practice areas include clinical toxicology, product safety and regulatory reporting support for corporate entities including a 24/7 Human and Animal Adverse Event Medical Call Center

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REVIEW ARTICLE

Benefits, Adverse Effects and Drug Interactions of Herbal Therapies With Cardiovascular Effects

Georgianne Valli, MD, Elsa-Grace V. Giardina, MD, FACC
New York, New York

Because the use of herbal therapies in the U.S. is escalating, it is essential to be aware of clinical and adverse effects, doses and potential drug-herb interactions. A consumer poll in

Table 3. Important Cardiovascular Drug Interactions

Drug	Herb	Evidence for Interaction
Warfarin	Dong quai	Case reports of elevation of PT and INR in patient stable on warfarin (157). Demonstration of pharmacological interaction in rabbits (158).
	Danshen	Decreases warfarin clearance and increases bioavailability (45). Case reports of hemorrhage in subjects on warfarin (43,44).
	Garlic	Rare reports of elevation in INR in subjects previously stable on warfarin (62). No other supporting data (63).
	Ginkgo	Case report of CNS hemorrhage in patient previously stable of warfarin (97). No other supporting data (63).
	Ginseng	Case report of decreased INR in patient stable on warfarin (131). No other supporting data (63).
Antiplatelet drugs (NSAIDs, ticlopidine, others)	Dong quai	In vitro evidence of platelet antagonism (157).
	Feverfew	Potential antiplatelet effects (50). No case reports of hemorrhage.
	Garlic	Case reports of platelet dysfunction with increased bleeding time (61,77). Conflicting evidence from clinical trials of antiplatelet effects (74,78–82).
	Ginger	In vitro evidence of antiplatelet activity, but no effects seen in clinical trials and no case reports of adverse events (162–165).
	Ginkgo	Case reports of hemorrhage (94–96). In vitro evidence of antiplatelet activity but no confirmatory evidence in human trials (115–119).
	Kava	In vitro evidence of platelet antagonism (174).
Digitalis	Hawthorn	Claims of interaction but no case reports and no pharmacologic data (145).
	Herbal laxatives	Herbal laxatives such as buckthorn, cascara sagrada and senna can cause loss of potassium leading to digitalis toxicity (200).
	Oleander	Contains active cardiac glycosides (197).
	St. John's wort	Reduces serum digoxin levels (199).
	Siberian ginseng	May interfere with assay, does not cause elevated digoxin levels (132,133).
Clonidine	Yohimbine	Competitive α_2-antagonist (186).
Tricyclic antidepressants	Yohimbine	Antidepressants potentiate pressor effects (190).
Methysergide, pizotifen, other serotonin antagonists	Feverfew	Antagonizes serotonin release, may potentiate the effect of other serotonin antagonists (56).

CNS = central nervous system; INR = international normalized ratio; NSAID = nonsteroidal anti-inflammatory drug; PT = prothrombin time.

Interactions of Warfarin with Garlic, Ginger, Ginkgo, or Ginseng: Nature of the Evidence

Leon PJ Vaes and Peter A Chyka

OBJECTIVE: To review and characterize the evidence describing potential interactions between warfarin and garlic, ginger, ginkgo, or ginseng.

DATA SOURCES: Searches of MEDLINE (1966–1999), other bibliographic databases, several abstracting services, and tertiary references were conducted.

STUDY SELECTION AND DATA EXTRACTION: Articles were examined by each author, and additional citations were obtained from the references of these articles. Preference was given to English-language articles of human studies.

DATA SYNTHESIS: Evidence is lacking for an interaction of warfarin with garlic or ginger. One case report associates ginseng use with decreased warfarin-maintained anticoagulation effect. Another case report links concomitant use of ginkgo and warfarin with the development of intracerebral hemorrhage. Hemorrhage and bleeding tendencies were noted in four cases with ginkgo use and in three cases with garlic; in none of these cases were patients receiving warfarin.

CONCLUSIONS: The true risks of these interactions and effects are difficult to characterize due to the limited number and nature of existing reports.

KEY WORDS: drug interactions, warfarin, garlic, ginger, ginkgo, ginseng, dietary supplements.

Ann Pharmacother 2000;34:1478-82.

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STATE-OF-THE-ART PAPER

Use of Herbal Products and Potential Interactions in Patients With Cardiovascular Diseases

Ara Tachjian, MD,* Viqar Maria, MBBS,* Arshad Jahangir, MD†
Rochester, Minnesota; and Scottsdale, Arizona

Table 1 Herbal Products to Avoid in Patients With Cardiovascular Diseases*

Herb	Purported Use	Cardiac Adverse Effect of Interaction
Alfalfa	Arthritis, asthma, dyspepsia, hyperlipidemia, diabetes	Increases bleeding risk with warfarin
Aloe vera	Wounds (topical), diabetes (oral)	Hypokalemia causing digitalis toxicity and arrhythmia
Angelica (dong quai)	Appetite loss, dyspepsia, infection	Increases bleeding risk with warfarin
Bilberry	Circulatory disorders, local inflammation, skin conditions, diarrhea, arthritis	Increases bleeding risk with warfarin
Butcher's broom	Circulatory disorders, inflammation, leg cramps	Decreases effects of alpha-blockers
Capsicum	Shingles, trigeminal and diabetic neuralgia	Increases blood pressure (with MAOI)
Fenugreek	High cholesterol	Increases bleeding risk with warfarin, hypoglycemia
Fumitory	Infection, edema, hypertension, constipation	Increases effects of beta-blockers, calcium-channel blockers, cardiac glycosides
Garlic	High cholesterol, hypertension, heart disease	Increases bleeding risk with warfarin
Ginger	High cholesterol, motion sickness, indigestion, antioxidant	Increases bleeding risk with warfarin
Ginkgo	Poor circulation, cognitive disorder	Increases bleeding risk with warfarin, aspirin, or COX-2 inhibitors Potential risk of seizures
Ginseng	Aging, diminished immunity, improves mental and physical capacity and stress tolerance	Increases blood pressure Decreases effects of warfarin Hypoglycemia

Interaction Between Warfarin and *Panax ginseng* in Ischemic Stroke Patients

Sang-Hun Lee, K.M.D., M.A., Young-Min Ahn, K.M.D., Ph.D., Se-Young Ahn, K.M.D., Ph.D., Ho-Kyung Doo, K.M.D., Ph.D., and Byung-Cheol Lee, K.M.D., Ph.D.

Abstract

Background: Today, the combined use of Oriental herbal medicines and Western biomedical medicines has been a prevalent yet controversial practice. Case reports and healthy volunteer trials have had conflicting results on the effect *Panax ginseng* has on warfarin's pharmacologic action, some reporting a reductive and others a potentiating influence.

Objective: This study investigated the interaction between warfarin and *P. ginseng* by observing the prothrombin time (PT) and the international normalized ratio (INR) in ischemic stroke patients who did not have a history of taking warfarin.

Design: Randomized, open-label, controlled study.

Subjects: Twenty-five (25) patients newly diagnosed with ischemic stroke by brain computed tomography or magnetic resonance imaging in the Korean Medical Hospital, Kyung Hee University (Seoul, Republic of Korea).

Intervention: Ischemic stroke patients were randomized into 2 groups: the ginseng group (n = 12), given both *P. ginseng* and warfarin, and the control group (n = 13), given only warfarin, both for 2 weeks. The warfarin dose was restricted to 2 mg in the first week and 5 mg in the second week.

Results: The peak values and the international normalized ratio (INR) and prothrombin time (PT) areas under the curve (AUC) in both groups significantly increased compared to those at baseline. However, there was no statistically significant difference in peak values and INR and PT AUC between groups in both the first and second weeks.

Conclusions: This study suggests that coadministration of *P. ginseng* and warfarin in ischemic stroke patients does not influence the pharmacologic action of warfarin.

THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 14, Number 6, 2008, pp. 715–721

Table 4 Herbal Products That May Interfere With Digoxin Level and Assays

Herb	Extent of Interference	Comments
Chan su	High	Active components (e.g., bufalin) cross-react with digoxin assay Monitoring free digoxin eliminates interference
Danshen	Moderate	Falsely increases (FPIA) or falsely decreases low levels (MEIA) of digoxin Monitoring free digoxin eliminates interference
Asian ginseng	Moderate	Falsely increases elevated (FPIA) or falsely decreases low (MEIA) digoxin level Monitoring free digoxin does not eliminate interference
Siberian ginseng	Moderate	Falsely increases elevated (FPIA) or falsely decreases low (MEIA) digoxin Monitoring free digoxin does not eliminate interference
Uzara root (diuretic)	NA	Increases effect with digoxin Interferes with digoxin assay

Adapted and reprinted, with permission, from Dasgupta A. Review of abnormal laboratory test results and toxic effects due to use of herbal medicines. Am J Clin Pathol 2003;120:127–37.

FPIA = fluorescence polarization immunoassay; MEIA = microparticle enzyme immunoassay; NA = not available.

Chan su – dried venom from a Chinese toad (*Bufo bufo gargarizans*)
http://www.ifrog.us/wp-content/gallery/bufonidae-true-toads/bufo-gargarizans.jpg

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STATE-OF-THE-ART PAPER

Use of Herbal Products and Potential Interactions in Patients With Cardiovascular Diseases

Ara Tachjian, MD,* Viqar Maria, MBBS,* Arshad Jahangir, MD†
Rochester, Minnesota; and Scottsdale, Arizona

that of testosterone, estrogen, and glucocorticoids (26). Ginseng should not be used by women who are pregnant or receiving hormone replacement therapy. Neonatal death has been related to maternal use (27). Increased levels of digoxin are associated with Siberian ginseng, which interferes with the digoxin assay (Table 4).

27. Awang DV. Maternal use of ginseng and neonatal androgenization. JAMA 1991;266:363.

JAMA The Journal of the American Medical Association

ARTICLE | December 12, 1990

Maternal Ginseng Use Associated With Neonatal Androgenization

Gideon Koren, MD, ABMT, FRCPC; Samuel Randor, MD, ND; Sheelagh Martin, RN; Denis Danneman, MB, BCh, FRCPC

[+] Author Affiliations

JAMA. 1990;264(22):2866. doi:10.1001/jama.1990.03450220028007.

ABSTRACT

To the Editor.— The term *ginseng* refers to any of 22 different plants, usually of the genus *Panax*, used as a tonic and restorative. It is estimated that 5 million people in North America consume ginseng regularly[1] because of its purported antifatigue, immunologic, and hormonal qualities. No reproductive studies are available to address its safety during pregnancy. We report apparent androgenic effects in a male infant whose mother consumed large amounts of pure ginseng throughout pregnancy and early lactation.

Report of a Case.— A 30-year-old white nurse, gravida 3, para 2 (one miscarriage), contacted the Motherisk Program in Toronto, Ontario, to inquire whether her self-medication with pure Siberian ginseng (650-mg tablets twice daily, Jamieson Natural Sources, Toronto) was safe while breast-feeding her 2-week-old neonate. She had been taking the ginseng, purchased from a health store, for irritability and mood swings for 1 1/2 years, including the 9 months of

Part of complete coverage on
Matters of the Heart

Herbal remedies, heart drugs a dangerous combo

"Stay away from the four G's: garlic, ginkgo, ginseng, and ginger," says Dr. [redacted], a cardiologist at Columbia University, in New York, who has studied herbal remedies and heart drugs but did not participate in the current report. "They all have effects on bleeding. "Frankly, I would just avoid them all," she says. "Go into your medicine cabinet and get rid of anything you bought in an herbal store that you take in a pill form. Save your money and go buy a pair of shoes."

cation, you may want to avoid some of the most popular over-the-counter herbal supplements on the market, including ginseng, saw palmetto, and echinacea. These herbal remedies -- and many others -- can cause potentially serious problems in people taking heart medications, a new report warns.

Am J Med. 2008 Mar;121(3):207-11. doi: 10.1016/j.amjmed.2007.11.014.

Potential for interactions between dietary supplements and prescription medications.

Sood A[1], Sood R, Brinker FJ, Mann R, Loehrer LL, Wahner-Roedler DL.

Author information

Abstract

PURPOSE: The objective of this study was to assess the frequency of clinically significant interactions caused by concurrent use of dietary supplements and prescription medication.

METHODS: We conducted a cross-sectional, point-of-care survey and combined the findings with a review of patient medical records. Patients treated at Mayo Clinic (Rochester, Minn) in 6 different specialty clinics were surveyed for their use of dietary supplements. Concurrent use of prescription medications was obtained from patients' medical records. We used the Lexi-Interact online medication and dietary supplement interaction analysis program to assess the potential clinical significance of each interaction.

RESULTS: We surveyed 1818 patients; 1795 responded (overall response rate of 98.7%) and 710 (39.6%) reported use of dietary supplements. In total, 107 interactions with potential clinical significance were identified. The 5 most common natural products with a potential for interaction (garlic, valerian, kava, ginkgo, and St John's wort) accounted for 68% of the potential clinically significant interactions. The 4 most common classes of prescription medications with a potential for interaction (antithrombotic medications, sedatives, antidepressant agents, and antidiabetic agents) accounted for 94% of the potential clinically significant interactions. No patient was harmed seriously from any interaction.

CONCLUSIONS: A small number of prescription medications and dietary supplements accounted for most of the interactions. The actual potential for harm was low.

Review and Assessment of Medicinal Safety Data of Orally Used *Echinacea* Preparations

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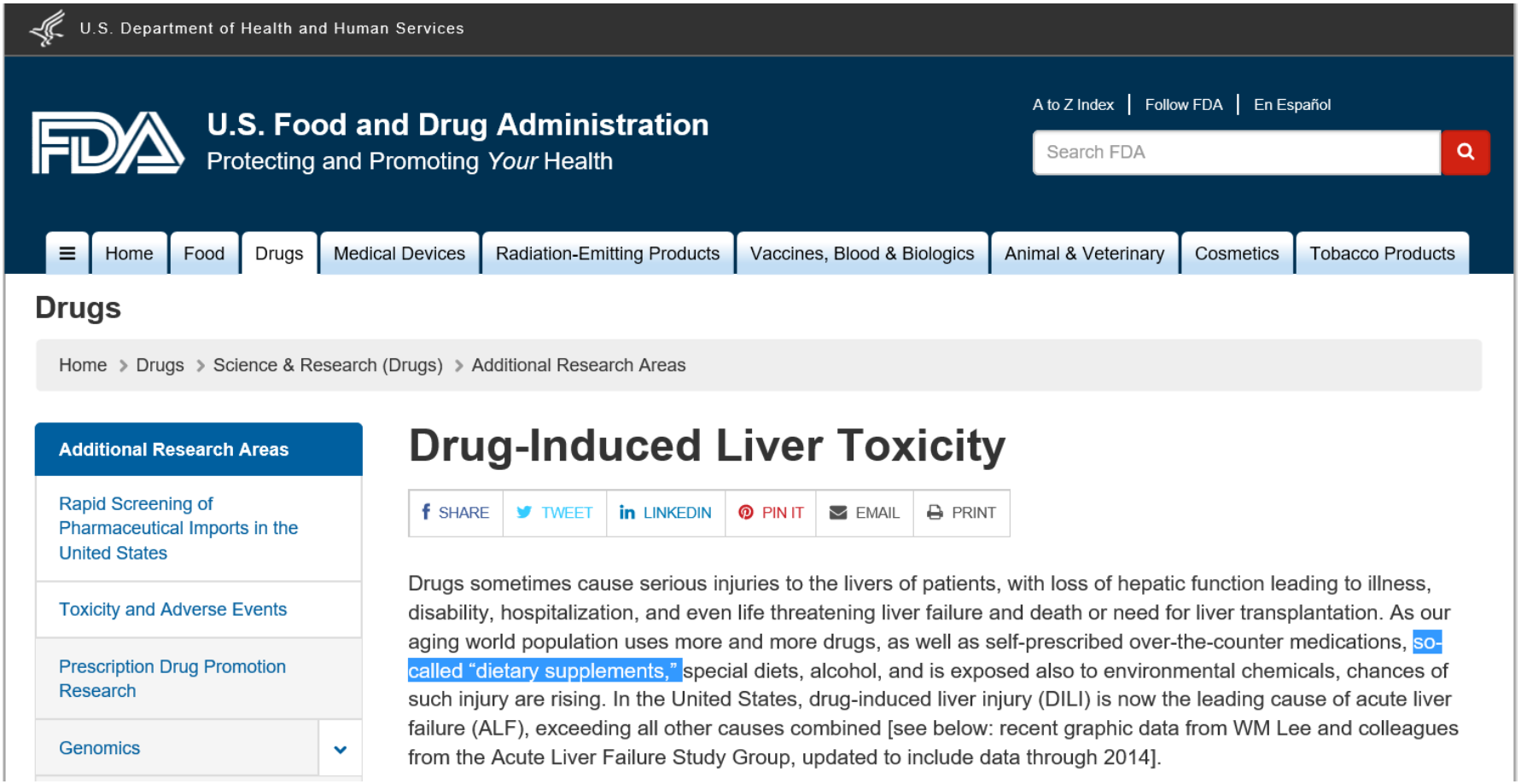
Abstract

Echinacea purpurea, *Echinacea angustifoli* and *Echinacea pallida* are frequently used as medicinal plants. Besides asking for evidence on their efficacy, there is an increasing interest for safety data. This review systematically presents the available literature on drug interactions, contraindications, adverse events, duration of use, and safety of use in pregnant and nursing women, and assesses the safety profile of corresponding *Echinacea* preparations. It is noteworthy that all safety data reported are as product specific as the pharmacological or efficacy data are. In pharmacokinetic herb-drug interaction studies performed *in vivo*, no significant inhibitions of human CYP2D6 and CYP3A4 isoforms have been found after the administration of standardized *E. purpurea* preparations. However, contradictory results exist in studies using liver microsomes. Adverse events reported during clinical trials following administration of *Echinacea* spp. mono-preparations were generally mild and mostly without causality. Due to published long term studies with continuous ingestion of different *Echinacea* preparations up to 6 month with no reported toxicological concerns, *Echinacea* can be recommended also for long-term use. Moreover, the contraindications in cases of autoimmune diseases and immune-suppression are questionable, since lipophilic *Echinacea* preparations containing alkamides suppress cellular immune responses, and beneficial effects in autoimmunity were reported. The same applies for the use during pregnancy. Although there has been some impact reported on embryonic angiogenesis in mice, no association with an increased risk for major or minor malformations during organogenesis was found in a literature review. Altogether, the different evaluated *Echinacea* preparations are well-tolerated herbal medicines in the management in children and adults alike.



http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ucm071471.htm

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Journal of Hepatology 47 (2007) 444–446

Journal of Hepatology

www.elsevier.com/locate/jhep

Editorial

Slimming at all costs: Herbalife®-induced liver injury ☆

Felix Stickel*

Institute of Clinical Pharmacology, University of Berne, Murtenstrasse 35, CH-3010 Berne, Switzerland

See Articles, pages 514–520 and 521–526

What if the title read????

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Journal of Hepatology 47 (2007) 444–446

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Editorial

Slimming at all costs: Eli Lilly© induced liver injury ☆

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See Articles, pages 514–520 and 521–526

PUBLIC RELEASE: 4-SEP-2014

Liver injury caused by herbals, dietary supplements rises in study population

Supplements more likely than medications to lead to death or liver transplantation

WILEY

New research shows that liver injury caused by herbals and dietary supplements increased from 7% to 20% in a U.S. study group over a ten-year period. According to the study published in *Hepatology*, a journal of the American Association for the Study of Liver Diseases, liver injury caused by non-bodybuilding supplements is most severe, occurring more often in middle-aged women and more frequently resulting in death or the need for transplantation than liver injury from bodybuilding supplements or conventional medications."

IMAGE: THIS IS THE STUDY AUTHOR: DR. NAVARRO, EINSTEIN MEDICAL CENTER PHILADELPHIA. view more ›

CREDIT: DR. NAVARRO

Nearly half of all adult Americans consume herbal and dietary supplements with prior reports suggesting that is on the rise.

Top 10 therapeutic classes and individual agents to cause DILI in the USA (N=899)

	Therapeutic Class	n
1	Antimicrobials	408
2	Herbal and dietary	145
3	CVS agent	88
4	CNS agents	82
5	Anti-neoplastics	49
6	Analgesics	33
7	Immunomodulatory	27
8	Endocrine	20
9	Rheumatologic	13
10	Gastrointestinal	12

	Individual agent	n
1	Amox-Clavulanate	91
2	INH	48
3	**Nitrofurantoin**	42
4	TMP/SMX (Bactrim)	31
5	**Minocycline**	28
6	Cefazolin	20
7	Azithromycin	18
8	Ciprofloxacin	16
9	Levofloxacin	13
10	Diclofenac	12

Catechins in Dietary Supplements and Hepatotoxicity

Victor J. Navarro · Herbert L. Bonkovsky · Sun-Il Hwang · Maricruz Vega · Huiman Barnhart · Jose Serrano

Dig Dis Sci (2013) 58:2682–2690

	Catechin as labeled ingredient	No Catechin as labeled ingredient	Total
Catechin Concentration/g product			
Less than lower limit of detection	2/18 (11.1%)	49/82 (59.8%)	51/100 (51.0%)
0 - <10 mcg/g	3/18 (16.7%)	4/82 (4.9%)	7/100 (7.0%)
10 - 500 mcg/g	1/18 (5.6%)	25/82 (30.5%)	26/100 (26.0%)
> 500 mcg/g	12/18 (66.7%)	4/82 (4.9%)	16/100 (16.0%)

~ 40% of products implicated in liver injury had unlabeled Catechin

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HEALTHY LIVING

Dietary, Herbal Supplements Lead To Liver Damage 20% Of The Time

Sep 5, 2014 01:12 PM By Stephanie Castillo

Dietary and herbal supplements increase risk for liver damage by 20 percent. *Photo courtesy of Shutterstock*

So much for health: A new study published in the *Journal of Hepatology* found dietary and herbal supplements lead to liver damage 20 percent of the time.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Emergency Department Visits for Adverse Events Related to Dietary Supplements

Andrew I. Geller, M.D., Nadine Shehab, Pharm.D., M.P.H.,
Nina J. Weidle, Pharm.D., Maribeth C. Lovegrove, M.P.H.,
Beverly J. Wolpert, Ph.D., Babgaleh B. Timbo, M.D., Dr.P.H.,
Robert P. Mozersky, D.O., and Daniel S. Budnitz, M.D., M.P.H.

ABSTRACT

BACKGROUND

Dietary supplements, such as herbal or complementary nutritional products and micronutrients (vitamins and minerals), are commonly used in the United States, yet national data on adverse effects are limited.

METHODS

We used nationally representative surveillance data from 63 emergency departments obtained from 2004 through 2013 to describe visits to U.S. emergency departments because of adverse events related to dietary supplements.

RESULTS

On the basis of 3667 cases, we estimated that 23,005 (95% confidence interval [CI], 18,611 to 27,398) emergency department visits per year were attributed to adverse events related to dietary supplements. These visits resulted in an estimated 2154 hospitalizations (95% CI, 1342 to 2967) annually. Such visits frequently in-

Emergency Department Visits for Adverse Events Related to Dietary Supplements.Geller AI, et al. N Engl J Med. 2015 Oct 15;373(16):1531-40.

Health | Nation & World

Dietary supplements cause 20,000 ER visits a year, federal study finds

Originally published October 14, 2015 at 8:37 pm

The study is the first to document the extent of severe injuries and hospitalizations tied to dietary supplements, a rapidly growing $32 billion-a-year industry.

By ANAHAD O'CONNOR

The New York Times

A large new study by the federal government found that injuries caused by dietary supplements lead to more than 20,000 emergency-room visits a year, many involving young adults with cardiovascular problems after taking products marketed for weight loss and energy enhancement.

Background Data

- 166 million people use dietary supplements annually
- Other important statistics
  - Number of ER visits for all causes nationally: 136 million
  - ER visits associated with Rx drugs taken as prescribed: 731,000 (CDC, 2015)
  - Pediatric ER visits associated with 30 million children participating in organized sports: 775,000 (Johns Hopkins Medicine, 2015)
  - CDC estimates that each year roughly 48 million people get sick from a foodborne illness, 128,000 are hospitalized, and 3,000 die.
  - Allergic anaphylaxis rxns to food (FDA 2015):
    - 30,000 ER visits
    - 2,000 hospitalizations
    - 150 deaths

Table 1. Number of Cases and National Estimates of Emergency Department Visits per Year for Adverse Events Associated with Dietary Supplements (2004–2013).*

Characteristic	No. of Cases	Emergency Department Visits per Year	
		estimated no.	*estimated % (95% CI)*
All patients	3667	23,005	
Age (yr)			
≤4	988	4,965	21.6 (18.9–24.3)
5–10	126	697	3.0 (2.3–3.7)
11–19	308	1,866	8.1 (6.7–9.6)
20–34	930	6,433	28.0 (25.1–30.8)
35–49	558	3,505	15.2 (13.6–16.8)
50–64	399	2,682	11.7 (9.8–13.5)
≥65	358	2,857	12.4 (10.1–14.7)
Sex			
Female	2121	13,402	58.3 (56.4–60.1)
Male	1546	9,602	41.7 (39.9–43.6)

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Emergency Department Visits for Adverse Events Related to Dietary Supplements.
Geller AI, et al. N Engl J Med. 2015 Oct 15;373(16):1531-40.

Table 1. Number of Cases and National Estimates of Emergency Department Visits per Year for Adverse Events Associated with Dietary Supplements (2004–2013).*

Characteristic	No. of Cases	Emergency Department Visits per Year	
		estimated no.	*estimated % (95% CI)*
All patients	3667	23,005	
Mechanism of adverse event‡			
Adverse reaction	1152	7,663	33.3 (29.9–36.7)
Allergic reaction	796	5,434	23.6 (21.1–26.2)
Unsupervised ingestion by child	946	4,871	21.2 (18.4 –24.0)
Excess dose	375	2,330	10.1 (8.8–11.4)
Other	398	2,707	11.8 (9.9–13.7)
Patient outcome‡			
Discharged	3267	20,850	90.6 (88.0–93.3)
Hospitalized	400	2,154	9.4 (6.7–12.0)

Emergency Department Visits for Adverse Events Related to Dietary Supplements. Geller AI, et al. N Engl J Med. 2015 Oct 15;373(16):1531-40.

NEISS Database

- Contains Data from 63 participating hospitals as a representative sample of US Emergency Rooms
- First established by the CPSC to monitor consumer product related injuries sending people into ERs
  - Lawn mowers, toasters, cribs, car seats, highchairs, hair dryers … etc
- 2002 expanded to "The National Electronic Injury Surveillance System -- Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES)"
- Provides a "surrogate" measure of presumed serious injuries associated with consumer products

Limitations/Notable Observations (Geller et. al.)

- Outcome Severity not delineated
  - Not all ER visits are created equal

- No treatment information was listed

  "Most patients with palpitations, chest pain, or tachycardia associated with supplement-related adverse events were discharged from the emergency department (89.9%; 95% CI, 87.2 to 92.6)."

Limitations/Notable Observations (Geller et. al.)

- Age and reason for admission not delineated
  - ICU vs. Observation Ward

    "Hospitalization includes hospital admission, observation status admission, or transfer to another acute care facility"

- Not all allergy events associated with supplement suspected products/ingredients are created equal
  - As cited in the article approximately 10% of the allergic reactions were listed as "severe" and the balance were minor-moderate in nature
  - Confirmatory diagnosis for minor or severe allergic reactions is typically done on follow-up exams with primary providers not in the ER

Limitations/Notable Observations (Geller et. al.)

- Pediatric exposures:
  - CRCs are not provided because the products are classified as GRAS and CRCs are not warranted
  - Ingestions of DS may be over-represented due to lack of familiarity with ingredients causing parents, caregivers and even pediatricians to err on the side of caution and have a child seen in an ER after any unintended exposure
  - Micronutrient Events:
    - Not all Iron containing product exposures are created equal
      - Dose (typically low in pediatric supplements)
      - Form of iron: Carbonyl vs. Ferrous Salts

Limitations/Notable Observations (Geller et. al.)

- Confounding Variables in assessing role of a DS in "Adverse Reactions":
  - Many "adverse reaction" related diagnoses are diagnoses of exclusion
  - R/O of emergence of new disease or exacerbation/re-emergence of pre-existing disease
  - Product integrity issues, specification breaches, etc.
  - Alternative diagnosis not considered

Limitations/Notable Observations (Geller et. al.)

- Some products inclusions (identified in Supplement 1) were puzzling.

  "Additional products that are often used by consumers for complementary health but do not fall under the regulatory definition of dietary supplements (e.g., topically administered herbal or homeopathic products) were also included in the analysis."

  - eg, dimethyl sulfoxide, Calcium Polycarbophil, snake oil

Limitations/Notable Observations (Geller et. al.)

- Numerator and Denominator
  - What is the numerator for severe outcome cases as compared to the total visits and corresponding overall incidence rates?
- What is the incidence of AEs associated with dietary supplements properly manufactured and meeting all requirements of DSHEA??

"The safety of dietary supplements that are not known to be adulterated remains poorly described, however. Data are lacking to quantify the frequency of adverse events associated with dietary supplements in the United States."

Remaining Legitimate Issues (Geller et. al.)

- Exactly which products are involved in suspected events
- Unconventional/prohibited new ingredients
- Testing of products for adulteration to identify those events that involve products masquerading as appropriately designed, labeled and formulated DSs
- Difficulty Swallowing Issues
  - 41% of all micronutrient events (approx. 4,000) and 54.1% of events involving calcium

Clinician Role in Post-Market Surveillance (PMS)

Post-market Surveillance: "Best Practice" companies collaborate with clinicians to address the intent of the mandatory SAE reporting Laws

- PMS is a performance based process of incident investigation and signal detection
- Depends on a passive but sensitive surveillance system
- Clinicians play a vital role in monitoring, identifying and reporting suspected AEs involving supplements
  - Report to manufacturer, FDA or both????

PMS and Product Safety Profiling

1. Normalized Incidence Rates

2. Determining acceptable ranges and actionable variations

3. Determining expected events based on toxicology and product design

4. Identifying predictable events and their expected incidence rates

PMS and Product Safety Profiling

5. Incident integrity scoring (Consider that most consumer health care product events are spontaneously reported vs. clinical trial generated)

6. Identifying “Background Noise” or events occurring simultaneously but unrelated to product use

7. Identifying trends in low scoring unexpected events and considering potential relationship to product issues ie. “Sentinel Events”

PMS and Product Safety Profiling

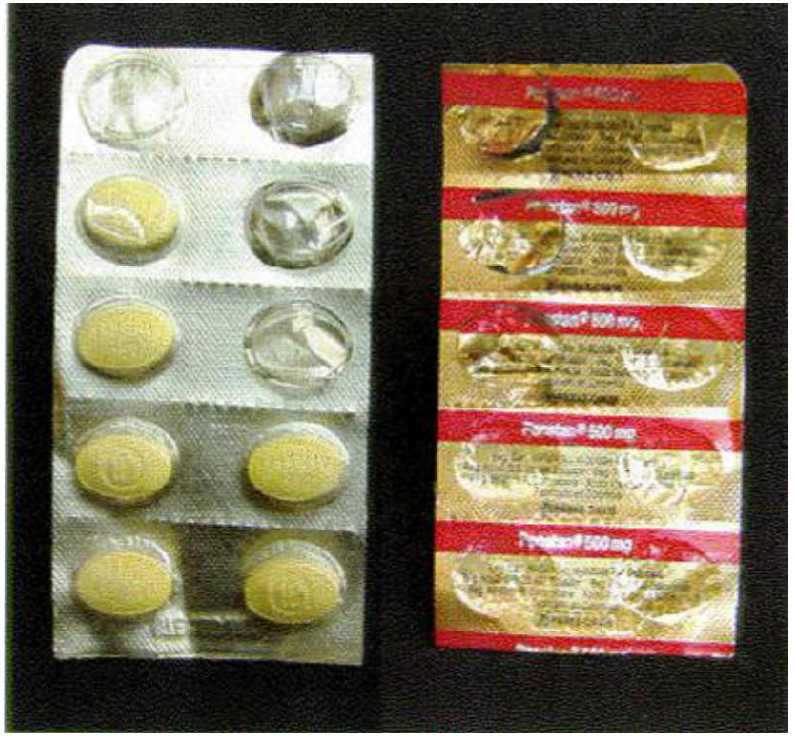
8. For suspected "Sentinel" events or for deviations in expected incidence rates do individual incidents represent:
   a) Quality Control issues/Contamination
      i. Before leaving the plant
      ii. After leaving the plant
   b) Direct but predictable or previously recognized adverse effects based on inherent toxicology/pharmacology of the product or an ingredient
      I. Dose dependent
      II. Dose independent (idiosyncratic)

PMS and Product Safety Profiling

8. For suspected "Sentinel" events or for deviations in expected incidence rates do individual incidents represent:
    c) Direct but previously unrecognized adverse effect of the product or an ingredient:
        i. Idiosyncratic, unpredictable in occurrence but predictably occurring at a low incidence rate within the population
        ii. Long Term effects secondary to chronicity of use

PMS and Product Safety Profiling

8. For suspected "Sentinel" events or for deviations in expected incidence rates do individual incidents represent:
   d) Interaction related event involving use of the product and:
      i. Other Drug
      ii. Disease
      iii. Food
      iv. Environment
      v. Biologic (gene expression)
      vi. OTHER CONSUMER PRODUCT CONCOMMITANTLY BEING USED
      vii. Old botanical or new use botanical
      viii. Counterfeit product



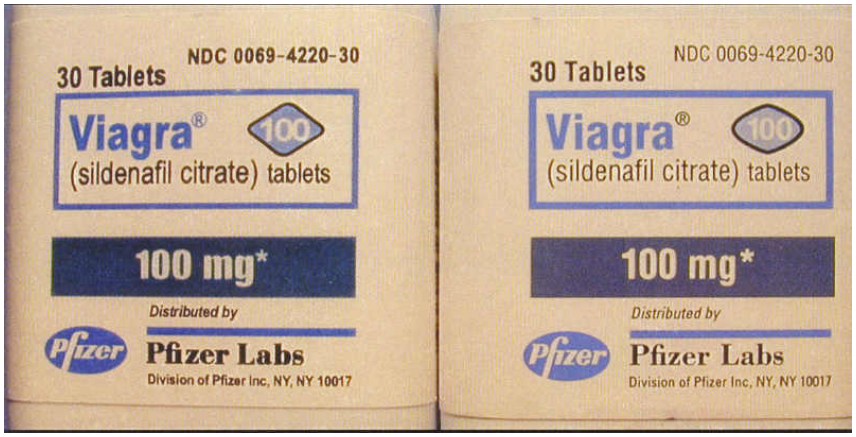
Ponstan is an anti-inflammatory product. This counterfeit was found in Columbia. First is the yellow powder; it consist of boric acid, floor wax, yellow highway paint. Pressed into tablets and placed in foil packs with labeling.

Source: Pharmaceutical Manufacturer Research Association

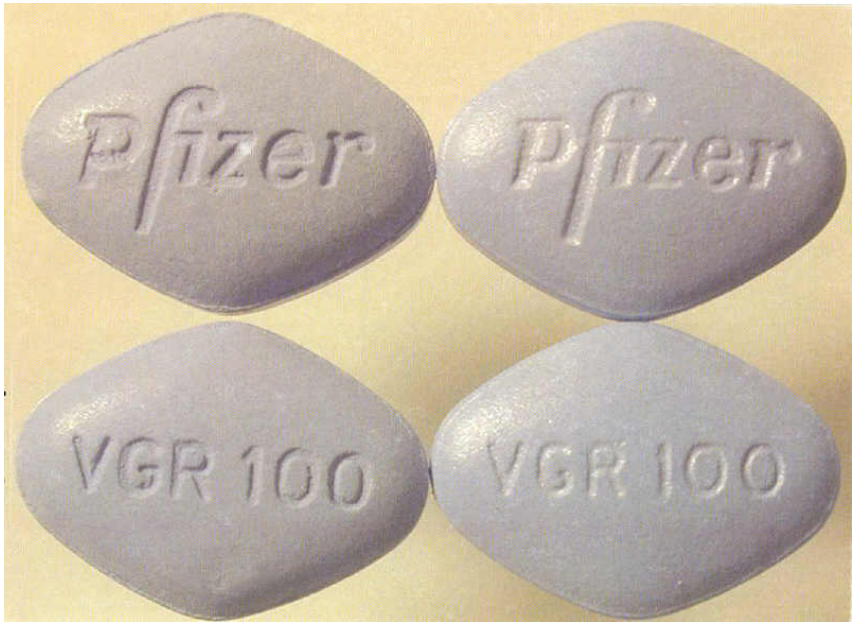
Courtesy: Marv Shepherd

Which one is the fake drug?

Viagra® (sildenafil)



FAKE AUTHENTIC



FAKE AUTHENTIC

Courtesy: Marv Shepherd

PMS and Product Safety Profiling

9. Are reported effects in any given category preventable?
10. Can reported effects in any given category be prevented, managed and/or mitigated through:
    a. Disclosure
    b. Education
    c. Reformulation
    d. New manufacturing process (change in solvents)
    e. New product design (multi-ingredient review)
    f. Dosage adjustment
    g. Market withdrawal or recall

DSHEA & DS Safety

- Key DSHEA product safety features:
  - Defines substance eligibility for inclusion in a DS
  - Has provisions for FDA evaluating and approving new dietary ingredients for inclusion in dietary supplements
  - Has specific GMP requirements for quality
  - As amended, has specific requirements for documenting and reporting of both serious and non-serious adverse events
  - Grants FDA specific authorities for declaring products adulterated or misbranded including recall and detention action
  - Contains specific requirements for labeling and claims
  - Contains provisions for civil and criminal penalties for violations

DSHEA, DS Safety, Clinician Context

- Top 3 focus areas in need of attention
  1) FDA Funding Limitations leading to Lack of Enforcement
     a) Allowing some rogue companies with products masquerading as supplements to remain in the marketplace
  2) Appropriate scientific investigations into botanical ingredient safety circumvented by innuendo
  3) Clinician context to guide individual patients:
     a) A vital component of rational risk/benefit assessment
     b) Referral to rational information re: supplement selection http://www.crnusa.org/CRNfactsheetconsumertips.html

Thank You!

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