

Articles

Adverse events associated with dietary supplements: an observational study

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Summary

Background Adverse events associated with dietary supplements are difficult to monitor in the USA, because such products are not registered before sale, and there is little information about their content and safety.

Methods In 1998, 11 poison control centres in the USA recorded details of 2332 telephone calls about 1466 ingestions of dietary supplements, in 784 of which patients had symptoms. We used a multitiered review process (κ 0.42) to select 489 cases for whom we were at least 50% certain that their negative events were associated with dietary supplements. We aimed to assess the effects of multiple ingredients and long-term use, and collated data for patterns of use and information resources.

Findings A third of events were of greater than mild severity. We noted both new and previously reported associations that included myocardial infarction, liver failure, bleeding, seizures, and death. Increased symptom severity was associated with use of several ingredients, long-term use, and age. Paediatric exposures were more often unintentional than were adult ingestions, and treatment of disease was the reason for supplement use in at least 28% of reports. Most products and ingredients were not identified in the information database (Poisindex) used by poison control centres, and specific adverse events were reported variably among five additional sources.

Interpretation Dietary supplements are associated with adverse events that include all levels of severity, organ systems, and age groups. Associations between adverse events and ingredients are difficult to verify if a product has more than one ingredient, and because of incomplete information systems. Research into hazards and risks of dietary supplements should be a priority.

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See *Commentary* ???

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Introduction

Drawbacks to the system of surveillance of adverse events associated with dietary supplements¹ are cause for concern because there are an estimated 29 000 products on the market in the USA,² and there has been striking growth in use over the past decade.³ Results from previous studies have shown that dietary supplements can have serious adverse effects.^{4,5} Such effects—especially if they are rare—could remain undetected without adequate surveillance efforts.⁴ We have defined adverse events as those that are unwanted, that result in injury or illness, and that are of uncertain cause.⁶ Initial screening for these events requires sensitivity, and subsequent research needs specificity to establish a causal relation and to define subsets of adverse reactions (eg, adverse drug reactions) within the larger set of adverse events.

The 1994 US Dietary Supplement Health and Education Act¹ defines dietary supplements as orally ingested foods that include botanical products (such as herbal remedies), and non-botanical substances (such as glands, minerals, metalloids, aminoacids, vitamins, and microbial products), and traditional cultural remedies, including Asian herbal prescription medicines. Use of products from this highly diverse class of substances is often intended to maintain “structure and function”^{1,2} of the body, by contrast with prescription pharmaceutical drugs for treatment.^{1,2} An implication of the US dietary supplement act is that the burden of proof of safety has moved away from makers of US dietary supplements and the Act states that only dietary supplements that are “adulterated” present “a significant or unreasonable risk of illness or injury”. New dietary supplement ingredients introduced after the Act could “reasonably be expected to be safe”.¹ Dietary supplements do not have to undergo the mandatory prelaunch testing and postlaunch surveillance required of prescription drugs and other products, and there is no accessible and comprehensive register of supplement names and ingredients.

Adverse events associated with dietary supplements are recorded only through voluntary reporting, which is an inherently weak form of surveillance.^{4,7,8} Furthermore, the quantity and quality of rudimentary surveillance information on dietary supplements compiled by the toxic exposure surveillance system of the American Association of Poison Control Centres (AAPCC) was inadequate at the time of this study relative to that of other monitored substances, especially drugs.^{7,9,10} Without access to adequate information, poison control centres face obstacles in provision of services, and reporting of adverse events after dietary supplementation. Therefore, centres do not always detect adverse event signals, and the epidemiological studies generally used to investigate these events are not comprehensive.¹⁰ Thus, a cycle exists of inadequate incoming safety information and poor outgoing reporting of new data.

We aimed to obtain more information on adverse events associated with dietary supplements and to assess qualitatively the assumption that foods that are safe and free from adulteration¹ would not be hazardous—ie, would not be associated with moderate to severe adverse outcomes including death.

	Time participated (months)	Number of calls
San Francisco, CA	12	1062
Albuquerque, NM	12	603
National Capital, Washington DC	11	328
Fresno, CA	12	229
Baltimore, MD	12	177
Detroit, MI	11	124
San Diego, CA	10	116
New York, NY	11	84
Philadelphia, PA	8	77
Salt Lake City, UT	7	34
Boston, MA	4	64
Withdrawn (three centres)	3	93
Total	112	2991

Table 1: Contributions by individual poison control centres

Methods

We did a 1-year multicentre observational study of dietary supplement exposures reported to 14 poison control centres from Jan 1 to Dec 31, 1998. We invited 21 of the 65 centres in the USA to participate, on the basis of location, population size, or previous interest in the effects of dietary supplements. The Investigational Review Board of the New York Department of Health approved the non-interventional study design. Patient data were edited by the originating poison control centre to protect confidentiality. The figure shows data that were recorded and analysed.

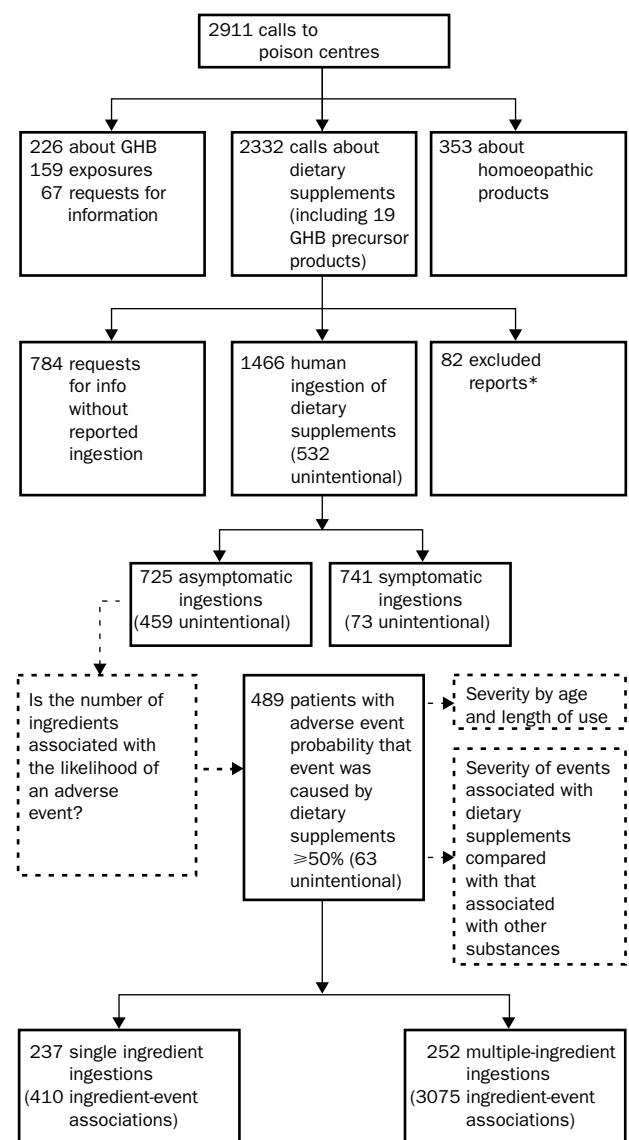
We included non-botanical and botanical ingredients for analysis, but excluded vitamins not already monitored unless they were formulated with other types of dietary supplement. When identified as such, foraged plants were excluded unless obtained from, or recommended by, a herbalist or commercial source. We included γ -hydroxybutyrate (GHB) precursor products,^{11,12} because they were sold legally as dietary supplements when the study began, and we did separate analyses for GHB. If a caller gave a trade name or acronym, we used the internet to search for chemical names, and if common plant names were reported, we categorised them using specific names from two herbalist resources.^{13,14} Some ingredient names were unidentifiable (eg, "other" and "trade secret enzyme"). We checked the availability of product and ingredient identities in the Poisindex reference database.¹⁵

We specifically searched reports of adverse effects to identify the most frequently recorded dietary supplement because we expected these supplements to be the most harmful or the most widely used. We therefore thought that these supplements would have the most information about adverse events. We used five reference sources for this search: three industry sources,^{14,16,17} a European monograph series,¹⁸ and a commercial database used by US poison control centres.¹⁹ These sources included access to Medline, a notable review series,²⁰ and European pharmacovigilance sources.^{14,18}

When poison specialists at the poison control centres took calls about dietary supplements from practitioners or consumers, they obtained information for the TESS (toxic exposure surveillance system) data form, which has a predefined hierarchy for organ systems.¹⁰ Occasionally, symptoms were further categorised—eg, one-sided weakness and slurring of speech in a patient were described as focal findings; or postingestion anxiety, tremors, and insomnia were interpreted as manifestations of, and added to, the predefined sign category of agitation. We added a form for study data to the TESS form, to promote uniform records that might not have been otherwise obtained. In particular, the study form assessed causality by standard methods.⁶ It included questions about confounding factors (such as medical

history, medication, or related substance abuse), as well as those analogous to the Naranjo scoring⁶ for adverse drug reactions, but adapted for our non-interventional screen. We also asked whether ingestion was intentional or not. If a patient was ill, we requested samples of the product they had taken, and these were analysed by chromatography or other assays, including drug and heavy metal screens for cultural remedies.²¹ We enlisted a coordinator in all poison control centres to assign probable cause ranks and to oversee quality of information.

We used categories of symptom severity and outcome that were based on definitions in the TESS database.¹⁰ A mild (AAPCC definition of minor) effect was defined as one that had minimum consequences and was generally transient; a moderate effect was longstanding, or was systemic, such as an isolated seizure; severe (AAPCC major) effects were life threatening, or resulted in significant residual disability, such as multiple seizures, respiratory compromise requiring intubation, or arrhythmia with hypotension. Deaths were included only if the patient died as a complication or direct result of the exposure. We defined hazard to be moderate or severe



Study profile

GHB= γ -hydroxybutyrate. *63 were exposures in animals.

	Total ingestion	Symptomatic ingestions	Symptom severity				Mild	Unintentional ingestion	Unintentional ingestion with symptoms (total [%])	
			Mild	Moderate	Severe	Death				
<1 year	65	10 (15%)	9		0	1	0	10%	40	4 (40%)
1–5 years	493	51 (10%)	47	2	2	0	8%	400	42 (82%)	
6–11 years	33	6 (18%)	5	1	0	0	17%	18	2 (33%)	
12–17 years	100	49 (49%)	33	14	1	1	33%	3	1 (2%)	
Adult 18–69 years	638	340 (53%)	226	92	20	2	34%	49	12 (4%)	
Elder adult >70 years	38	8 (21%)	3	1	3	1	63%	4	2 (25%)	
Unknown	99	25 (25%)	17	7	1	0	32%	20	0	
Subtotals	1466	489 (33%)	340(70%)	117 (24%)	28 (6%)	4 (1%)	149 (30%)	534 (36%)	63 (13%)	

Table 2: Age distribution among symptomatic exposures to dietary supplements by severity categories and unintentional circumstances

effects or death. Long-term (AAPCC chronic) use was defined by repeated doses for more than 8 h, which is consistent with the definition in TESS.¹⁰

We assigned probable cause scores using a multitiered review process. Clinicians at the originating poison control centre, the principal investigator, and two outside experts ranked probable cause on a five-point Likert scale (1, symptom was definitely related to use of a dietary supplement; 2, probably related; 3, at least 50% likelihood of being related; 4, probably unrelated; and 5, definitely unrelated).⁶ A third outside reviewer (a pharmacognocist) resolved issues when decisions were split, or provided an opinion if a reviewer omitted a rank. Average ranks were rounded to the nearest whole number, and any case with a final average score of 4 or 5 was excluded from analyses because symptoms were understood to be unrelated to dietary supplement use. Kappa statistics were used to assess inter-rater reliability between pairs of the four original reviewers.^{6,22} An expert in xenobiotics during lactation and pregnancy provided an over-riding decision about cases in whom these elements were present (F Nice, personal communication).

Eight of the 11 centres supplied severity scores for all symptomatic cases with symptoms reported during the time that they participated in the study. Outcomes from events not related to dietary supplements were qualitatively compared with those that were, because their review processes and sample sizes differed.

We used the Mantel-Haenszel test for trend (Statxact Cytel software version 4.0) to calculate exact p values with small expected cell sizes for proportions of ordinal outcome categories (mild to severe and death) for short-term versus long-term ingestion, and single-ingredient versus multiple-ingredient doses. Student's *t* test was used to compare mean numbers of ingredients or symptoms. All tests were two-tailed and significant at $\alpha=0.05$.

Role of the funding source

The Office of Dietary Supplements at the National Institutes had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

11 poison control centres completed the study, with a mean participation time of 10 months (SD 2.6) (table 1). Three centres withdrew after 1 month, but their data were retained.

Prospective collection yielded 2332 calls reporting 1466 ingestions, 36% (534) of which were unintentional. Half the exposures produced signs or symptoms (741), and reviewers decided that 66% (489) of these were related to ingestion of dietary supplements (mean kappa value 0.42, SD=0.09). The final distribution of ranks from 1 (definitely related) to 5 (definitely unrelated) was not skewed, with 4%, 23%, 39%, 28%, and 6%, respectively.

Data for patterns of use were reported in variable frequency between callers. Of patients whose sex was known, 54% (415) were women. Table 2 shows the distribution of patients' ages. Only 6 (9%) of the 67 children with symptoms under age 12 years developed more than mild symptoms, but 48 (72%) of these exposures were the result of unintentional ingestions. The frequency distribution of outcomes associated with dietary supplements seemed no less severe than those from other calls about events not related to dietary supplements (table 3).

Of 997 respondents, 276–341 (28–35%) reported that they intended to take the dietary supplement to treat disease; the upper end of the range includes conditions such as anxiety, benign prostatic hypertrophy, and pregnancy that were questioned to be diseases by a subsequent US Federal regulation.² Other intents included: dieting (140 [14%]); enhancement of athletic performance (104 [10%]); aiding sleep (97 [10%]); stress adaptation, antioxidation, or nutrition (86 [9%]); suicide (90 [9%]); stimulation of the immune system (44 [4%]); recreational stimulus (17 [2%]); and enhancement of cognitive performance (16 [2%]). Less than 1% of ingestions were for use of supplements as an aphrodisiac, as an abortifacient, treatment for menstrual symptoms, foiling of drug tests, and smoking cessation. Multiple intentions of use were possible, in addition to unintentional use (table 2).

Family or friends (379 [66%]) were the main influence that determined use in 572 respondents, whereas physician referral (39 [7%]) was reported more frequently than referrals from non-conventional caregivers such as herbalists (30 [5%]). Almost half of dietary supplement purchases were made from sources other than health food stores, such as pharmacies, grocery shops, and mail order or internet sources (665). Formulations associated with adverse effects (389) were pills, capsules, caplets, tablets, gels, and chewable substances (263 [67%]); liquid formulations (65 [17%]); powders, teas, or loose plant parts (44 [11%]); and lozenges (17 [4%]).

149 (31%) adverse events associated with dietary supplements were moderate or worse—ie, hazardous (tables 2 and 4, appendix 1 on our website²³). Most frequently associated with negative events were the botanical substances ma huang, guarana, ginseng, and St John's wort, and non-botanical substances chromium, melatonin, and zinc (appendix 2²³). Reviewers assessed the likelihood that a reported sign or symptom was related to dietary supplements, irrespective of the number of

	Mild	Moderate	Severe	Death	Total
Dietary supplements	286 (71%)	89 (22%)	22 (6%)	4 (1%)	401
Other substances	43 835 (72%)	14 994 (24%)	2246 (4%)	54 (<1%)	61 229

Table 3: Symptoms associated with calls related to dietary supplements or other substances in eight poison control centres in 1998

	Number of adverse events	Single ingredient
Neurological		
Coma	18 (4%)	12
Seizures	13 (3%)	6
Focal findings	1 (<1%)	0
Cerebral bleed	1 (<1%)	1
Cardiovascular		
Chest pain	20* (4%)	9
Conduction disturbances and arrhythmias	14† (3%)	4
Bradycardia	9 (2%)	6
Myocardial infarction	2 (<1%)	1
Haematological		
Bleeding with raised INR	3 (1%)	0
INR elevation with hepatotoxicity	5 (1%)	2
Hepatic (see also haematological)	11 (2%)	5
AST or ALT >1000 U/L	4 (1%)	1
AST or ALT >100 <1000	7‡ (1%)	3
Metabolic		
Electrolyte abnormalities	4 (1%)	1
Metabolic acidosis with anion gap	2 (<1%)	1
Hypersensitivity		
Throat, chest tightening, or bronchospasm	6§ (1%)	5
Anaphylaxis or angio-oedema	2 (<1%)	2
Respiratory		
Dyspnoea	20¶ (4%)	10
Respiratory depression	5 (1%)	2
Genitourinary		
Urinary retention	3 (1%)	2
Deaths	4 (1%)	3

AST=aspartate aminotransferase. ALT=alanine aminotransferase
 *Ten events were mild. †Two events were mild. ‡One event was mild.
 §Two events were mild. ¶Five events were mild. See appendix 1²³ for further details.

Table 4: Selected hazards associated with dietary supplements

ingredients in the ingested substance. Because we accounted for the number of single versus total ingredient cases, we have been able to assess cases in which multiple ingredients might confound effects. In fact, about half the ingestions (51%) were of substances that had more than one ingredient. Because more than one symptom can occur after an ingestion, the number of possible associations between an ingredient and a symptom from 489 ingestions was 2003 sole and 3485 total associations (including repeats).

Moreover, use of multiple ingredients seemed to be associated with a larger number of symptoms, as well as with more severe outcomes, than ingestion of single ingredient supplements. People with symptoms used more ingredients than did those without symptoms (mean difference 1.06,

95% CI 0.61–1.51; $p < 0.01$); patients with symptoms reported taking as many as 44 ingredients at the same time. Those who used multiple ingredients also had more symptoms on average than those who used single-ingredient supplements (mean difference 0.43, 0.19–0.67; $p < 0.01$). Furthermore, people who took combinations of ingredients had hazardous outcomes significantly more often than they did mild ones (mean difference in number of ingredients is 1.02, 0.14–1.90; $p = 0.024$).

We could not calculate precise dose-to-event response relations because information about dose size was rarely supplied. However, long-term use was associated with outcomes of greater severity than was short-term use, as well as a higher frequency of moderate and severe outcomes ($p < 0.0001$). Of adverse events reported by long-term users, 97 (57%) were mild, 54 (32%) were moderate, and 19 (11%) were severe or death. By contrast, 217 (77%) of events that occurred within 8 h of ingestion were mild, 51 (18%) moderate, and 12 (4%) severe or deaths.

In many instances, background information about dietary supplements and associated adverse effects could not be obtained (table 5). Less than half all ingredients (45%, $n = 1195$) and products (36%, $n = 1232$) reported to poison control centres were even listed in Poisindex, which is a main resource for the centres.¹⁹ This and other information resources corroborated 110 (34%) associations between supplements and adverse events that we noted ($n = 323$ table 5), and 63 (59%) organ system effects (107) for the 25 most frequently reported ingredients. The associations by organ system effects reported in table 5 are more conservative, because these categories should capture events regardless of discrepancies in terminology among resources. For example, drowsy might not be recognised as congestive heart failure, but both could be captured as cardiovascular effects. Overall, our resources identified more adverse events among the 15 most frequently reported botanical than the ten most frequently reported non-botanical ingredients (table 5). Identification of associations between dietary supplements and adverse events ranged widely between information sources (0–100%) for the 25 most frequently reported supplements (with six events or more; table 5).

Furthermore, there were 159 calls (154 about symptomatic ingestions) about the former dietary supplement ingredient GHB, that reported one death from cardiac arrest, coma (72), seizures (12), bradycardia (25), and withdrawal (nine). These symptoms were clinically

	Number	Number % identified in data source					Total ^{4,16-19}
		Commercial database ¹⁹	European ¹⁸ monographs	Industry-PDR (non-prescription and DS) ¹⁶	Industry-PDR (herbal medicines) ¹⁷	Industry-association ¹⁴ safety handbook	
Products reported to poison control centres ¹⁵	1232	446 (36%)	NA	NA	NA	NA	..
Total of all ingredients reported to poison control centres ¹⁵	1195	535 (45%)	NA	NA	NA	NA	..
15 most frequently reported botanical ingredients*†							
Ingredient name reported	15	15 (100%)	11 (73%)	5 (33%)	13 (87%)	13 (87%)	..
DS-organ system AEs	68	30 (44%)	16 (24%)	6 (9%)	22 (32%)	32 (47%)	49 (72%)
DS-symptom AEs	221	55 (25%)	22 (10%)	18 (8%)	30 (14%)	40 (18%)	91 (41%)
Ten most frequently reported non-botanical ingredients*†							
Ingredient name reported	10	10 (100%)	NA	2 (20%)	NA	NA	..
DS-organ system AEs	39	14 (36%)	NA	0	NA	NA	14 (36%)
DS-symptom AEs	102	19 (19%)	NA	0	NA	NA	19 (19%)
Total 25 most frequently reported DS ingredients*†							
DS-organ system AEs	107	NA	..	NA	63 (59%)
DS-symptom AEs	323	NA	..	NA	110 (34%)

DS=dietary supplement. NA=Not applicable. AE=adverse event. PDR=physician desk reference. *In 489 patients. †With six events or more. See appendix 2²³ for the most frequently reported dietary supplement ingredients.

Table 5: Products, ingredients, and adverse events reported in five data sources

indistinguishable from those associated with the 19 defined GHB-precursor dietary supplements included in the study, but how many effects were actually caused by the precursor molecules rather than GHB products is not clear.

Discussion

We have reported a large case series of adverse events associated with the diverse products classified as dietary supplements in the USA. Although other such large series exist,^{24–26} they might not be accessible through Medline,²³ only rarely describe the entire range of dietary supplements,^{25,26} and do not focus on products used in the USA. That a third of all adverse events in our study were linked to hazardous results—such as seizures, coma, myocardial infarction, arrhythmias, coagulation disorders, hepatic disease, anaphylaxis, and death—underscores the need for greater knowledge of adverse events associated with dietary supplement use. Furthermore, some people reported using dietary supplements to treat disease, which suggests that dietary supplements are being taken with the same intent as for drugs. Other patterns of supplement use resemble those for mainstream drugs (physician referral and purchase of pharmaceutical-like formulations from pharmacies), although this relation could be susceptible to selection bias. Overlap of some pharmacological profiles further blurs the boundary between prescription pharmaceuticals and dietary supplements.^{4,5} Together, these findings suggest that the regulatory distinction between prescription pharmaceuticals and dietary supplements might not be clear, or relevant, for consumers.

The hazards and history of GHB show the extreme end result of the confusion between dietary supplements and prescription pharmaceuticals. After GHB was abandoned in Europe as an anaesthetic drug in the 1960s because of convulsant effects, it was used as a dietary supplement in the USA during the 1980s.¹² Health hazards and deaths led to controls of the sale of the substance in 1990, which were extended almost a decade later to GHB-precursor products sold as dietary supplements, but which like this drug, are now abused substances.¹³

The severity of reported adverse events seemed to increase with age in our data. However, the lower severity of symptoms in children than in adults might be a result of the higher rate of unintentional ingestions than that reported for adults. Such ingestions are associated with less severe outcomes than those that are intentional, and a report of an unintentional ingestion might not even represent an exposure in children since their self reports are unreliable.^{10,27} On the other hand, the 70% rate of unintentional ingestions in preadolescents with symptoms emphasises the potential health hazards associated with packaging that is not child-resistant.²⁸

Other populations that seemed to be at risk of serious adverse events were users of aphrodisiacs such as yohimbine, women seeking alternative obstetric care including herbal abortion, dieters, bodybuilders, or those who wanted to enhance their athletic performance.^{4,5} Use of cultural remedies posed potential harm to 36 people captured in our study. Coma, seizures, drowsiness, bradycardia, conduction disturbances, hypertension, hepatotoxicity, and anticholinergic toxicity are all consistent with previously reported medical complications attributable to inherent toxicity, adulteration, or inadvertent plant substitutions.^{4,5,21,29,30}

Symptom severity was disproportionately greater with long-term than with short-term use of dietary supplements. This finding contradicted the expectation that symptoms would occur only if large amounts were consumed in a suicide attempt, the rates of which were close between

dietary supplements and other substances.¹⁰ Repeated use of supplements might have allowed attainment of steady state pharmacokinetics (after four half-lives),⁷ and increased toxicity in tissues.

The reliability of our results was limited by several factors. Practices varied between poison control centres,³¹ and various denominators across our data showed that topics researched by the centres were not consistent. Poison control centres provide clinical consultation services by telephone and usually have only remote access to patients and records, and thus there are poor opportunities for follow-up; for example, only 12 products were procured and submitted for analysis. Finally, we suspect that there was almost certainly under-reporting of adverse events and probable selection bias, because some centres that could scan their databases found reports that had been missed.

Further limitations were an absence of: a comprehensive register of dietary supplements; labelling regulations (in 1998); or prelaunch research and postlaunch surveillance, including mandatory reporting for adverse events related to dietary supplements. If such features existed, the quality of information databases used by poison control centres for dietary supplements would be more like those used for other products. If there was a comprehensive registry, centres could reliably retrieve all computerised records about supplements using a product class code, and they could search retrospectively to assess the size and direction of bias in our prospective collection. If a registry held information about listed ingredients and weights, we could ensure that all ingredients were accounted for, and we could characterise at least some dose-response relations between dietary supplement ingredients and adverse events. Identification of ingredients remains difficult a decade on from 1992.³² Even when we had a product in hand, ingredients were not always reliably listed on the label, at least not in 1998. In many instances, laboratory analyses were either impossible or impractical, especially when establishing the complete chain of evidence from the dietary supplement to the patient.³³ Formulations and use of multiple ingredients not only confounded the establishment of cause and effect, but could cause interactive fixed supplement effects (analogous to fixed drug effects),⁷ because the number of possible cause and effect combinations is enormous.

The amount of available information was greater when multiple reference sources were used, but time restrictions in clinical practice rarely allow for this to happen. European¹⁸ and US industry resources^{14,16,17} did not adequately describe the full range of adverse events associated with dietary supplements relevant to practice in the USA,³⁴ and focused mainly on botanical products. A commercial database used by poison control centres¹⁹ was more useful than industry resources, but has the drawback of not allowing full access to non-subscribers. An absence of information to substantiate the cause of an adverse event^{14,16–19} contributes to errors in our review process because reviewers are more confident to declare probable cause when there is a known precedent for the association.

Despite these difficulties, our methods accounted for the inadequacies of reporting adverse events associated with dietary supplements. Inter-rater reliability was moderately strong⁵ and ranks were reasonably normally distributed. We provided reviewers with information much the same as that used in scoring systems that identify adverse drug reactions.⁶ Our review process not only identified eight cases of historical challenge-dechallenge-rechallenge by non-interventional methods, but also excluded more than 250 cases that were probably unrelated. Another strength of our study was the inclusion of intent of use. Although we

cannot be certain that any exposure reported to a poison control centre is real, unintentional ingestions are particularly suspect in young children.^{10,26} Another rigorous part of this study was the separate analysis of multiple versus single ingredients. Inclusion of cases with multiple ingredients allowed a more sensitive screen for adverse effects and a way to distinguish effects caused by confounding ingredients or by interactive effects from those related to only one ingredient.^{4,5,7}

We cannot report population-based risks of dietary supplements from our data because the numerator (adverse events with both selection bias and under-reporting), and the denominator (dietary supplement use in the population) are unknown.^{8,35} Centres that participated in our study contribute about 12% of all cases reported by the 65 centres in the USA, and in 1998 all reported a mean penetrance of 8.7 people who use centres per 1000 in the population (range 3.7–16.9).¹⁰ Yet, there are too many unknown variables to estimate the overall risk of dietary supplement use.

We can conclude that at least some dietary supplements have potential for substantial hazard.³⁶ These hazards raise issues about the regulatory and practical distinction between dietary supplements and drugs. The fact that callers from the same catchment areas reported adverse events related to supplements with outcomes no less severe than those for all other product exposures offers no reassurance. Specifically, these data warrant concern about the absence of child-resistant packaging for dietary supplements, about prenatal and perinatal exposure, about the ingestion of multiple ingredients, about long-term consumption, and about the quality of surveillance efforts. As a minimum, the difficulties we have described suggest the need for a comprehensive register of dietary supplements, strengthened surveillance (particularly mandatory reporting of adverse events), enforceable definitions of what constitutes a risk to safety, and what circumstances warrant product recall. Safety research should become a priority in investigations of dietary supplements to clarify hazards and possible risks for this recently defined class of foods.

Contributors

M Palmer compiled the database, contracted services, analysed data, and wrote the manuscript. B M Sprague managed the database. R Ko reviewed the protocol and did chemical analyses. C Haller, P McKinney, W Klein-Schwartz, A Tschirgi, S C Smolinske, A Woolf, G Everson, L S Nelson, T Dodd-Butera, W D Bartlett, and B R Landzberg supplied information about cases and reviewed the study protocol. All authors reviewed the manuscript.

Conflict of interest statement

None declared.

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