Incidence and Severity of Potential Drug–Dietary Supplement Interactions in Primary Care Patients

An Exploratory Study of 2 Outpatient Practices

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Background: To explore the incidence and severity of potential interactions between prescription medications and dietary supplements.

Methods: A survey was conducted on dietary supplement use in 458 veteran outpatients currently taking prescription medications. Self-reported dietary supplement use was cross-referenced with each patient’s prescription medication list, and potential interactions were identified from several tertiary sources and medical literature searches.

Results: One hundred ninety-seven patients (43%) were currently taking at least 1 dietary supplement with prescription medication(s). The most common products included vitamins and minerals, garlic, Ginkgo biloba, saw palmetto, and ginseng. Among these, 89 (45%) had a potential for drug–dietary supplement interactions of any significance. Most of these interactions (n=84 [94%]) were not serious based on limited available evidence, giving an incidence of 6% (5/89) of potentially severe interactions among patients taking interacting drugs and dietary supplements and 3% (5/197) among patients taking coincident dietary supplements and medications.

Conclusions: Although the use of dietary supplements appears to be very common among patients who also take prescription medications, most potential drug–dietary supplement interactions found were not serious. However, literature support was sparse at best. Health care providers should continue to inquire about dietary supplement use and consider the potential for interactions, regardless of their severity.

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The use of alternative medicine has gained widespread public acceptance in the United States to treat an array of medical conditions and physical complaints and to promote good health. In 1993, Eisenberg and colleagues reported that approximately 1 of every 3 Americans has tried at least 1 form of alternative medicine. Five years later in a follow-up study, Eisenberg and colleagues reported an increase in the use of alternative medicine from 1990 to 1997, with a significant increase in herbal product and megavitamin use. More recently, Kaufmann and colleagues reported the use of vitamins and minerals and of herbal products in 40% and 14%, respectively, of their surveyed population.

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Alternative medications such as dietary supplements have been promoted as being natural and therefore safe and harmless; however, little or no regulation of the manufacturing of such supplements is available to direct consumers. In 1994, the Dietary Supplement Health and Education Act (DSHEA) was passed, giving the US Food and Drug Administration (FDA) authority to restrict the use of dietary supplements if such products proved unsafe. However, the premarketing requirements for dietary supplements continue to be less stringent than those of prescription medications, and at present the FDA does not authorize or test dietary supplements as they do prescription medications. Consequently, quality control issues such as toxicity, contamination, mislabeling, and misidentification of dietary supplements may be a problem.

An important finding of the follow-up study by Eisenberg and colleagues was the high prevalence of the concomitant use of alternative medications and prescription medications. It was estimated that approximately 15 million adults had consumed dietary supplements concurrently with prescription medications. Patients may not realize that combining these products with their prescription medications can result in drug–dietary supplement interactions. Like-
wise, physicians may not be aware that patients are taking such products, a point emphasized by Eisenberg and colleagues.2

The number of reports of clinically important interactions between dietary supplements and prescription medications is increasing.8 However, a paucity of information exists on how common this problem is in clinical practice. Therefore, to explore the occurrence of potentially significant drug–dietary supplement interactions within a defined population, we surveyed 458 outpatients visiting general medicine clinics at 2 Veterans Affairs (VA) medical centers. We cross-referenced self-reported use of dietary supplements with prescription of medications by VA health care providers. We report our findings and discuss important points that relate to the incidence and severity of potential drug–dietary supplement interactions in daily practice.

METHODS

STUDY SITES AND SURVEY DESCRIPTION

Because dietary supplement use is reported to be more common in the West than in other parts of the United States,4 we conducted the survey at 1 eastern (Pittsburgh, Pa) and 1 western (Los Angeles, Calif) VA medical center. Each facility is affiliated with a large teaching university, and each provides tertiary, primary, and specialty care.

The definition of dietary supplement for our study was based on the definition by the DSHEA as potentially any product intended for ingestion as a supplement to regular diet.4 Thus, we included any of the following as dietary supplements: vitamins or minerals (at any dose level), herbal products, and nutraceuticals. Combination products were, to every extent possible, categorized by their primary component(s). For instance, the combination product glucosamine and chondroitin (Osteo Bi-Flex) would be categorized by both of its primary components, glucosamine and chondroitin.

At each facility, a sample of patients waiting for general medicine clinic appointments was surveyed in 1999 for dietary supplement use. General characteristics of the VA populations at both sites are shown in Table 1. Four hundred fifty-eight patients completed questionnaires, including 260 patients from Pittsburgh and 198 from Los Angeles. The survey questions were similar to those used by Ly and colleagues10 and focused on present and past use of dietary supplements, products the patients were taking or had taken, place of purchase, monthly expenditures, sources of information concerning dietary supplements, and disclosure of dietary supplement use to primary care providers (Figure).

There were minor differences in the general protocol between the 2 sites. At the Los Angeles VA facility, surveys were self-administered by participating patients, with refusals to participate tracked (38/236 [16%]). In Pittsburgh, patients were asked if they would help with a survey and then asked questions by a survey coordinator. Refusals were reportedly infrequent but not formally tracked. Protocols at both centers had respective institutional review board approvals. The protocol allowed for patient and provider notification if any suspected severe interactions were found during the study.

DETERMINING INCIDENCE AND SEVERITY OF DRUG–DIETARY SUPPLEMENT INTERACTIONS

Records of oral prescription medications were searched from VA pharmacy files for each patient participating in the study. All prescription medications were cross-referenced to the dietary supplements being taken by the individual patients. The definition of a potential drug–dietary supplement interaction was modified from the following definition by a standard reference of a drug-drug interaction11: a pharmacological or clinical response to a drug and dietary supplement combination different from the anticipated effects of the 2 agents when given alone, and in which co-administration might result in an antagonistic, synergistic, or idiosyncratic effect. Potential drug–dietary supplement interactions were identified from several tertiary references,12–14 which were the primary sources for identification of potential interactions. In addition, newsletters, text-
Potential drug–dietary supplement interactions were classified as documented if an interaction was documented in actual case reports or clinical trials, or theoretical if an interaction was possible with pharmacodynamic properties suggesting an interaction, but had not been documented in the medical literature. Documented interactions were further classified as probable or possible. Probable interactions were defined as interactions with at least 3 individual case reports in the medical literature or evidence of the interaction found in a scientific study, and possible interactions were defined as interactions with fewer than 3 individual case reports documented in the medical literature.

In addition, we classified the clinical significance of potential drug–dietary supplement interactions as severe or not severe. Because of a lack of clear and widely accepted definitions of potential drug–dietary supplement interactions, we modeled our categories again on a standard reference for drug–drug interactions. An interaction was defined as not severe when the likely consequence of concurrent use would be expected to nominally affect therapeutic outcome, with little to no decline in a patient’s clinical status. A severe interaction was defined as one that, if it occurred, would likely require emergency or urgent intervention, with an outcome of hospitalization, a life-threatening event, or permanent physical or mental disability.

All 458 patients were prescribed pharmaceuticals, with an average of 7 oral prescription products per patient in Pittsburgh and 6 oral prescription products per patient in Los Angeles. Of these patients, 197 (43%) were taking at least 1 type of dietary supplement (Pittsburgh, 38%; Los Angeles, 49%). An additional 82 (18%) had taken such products in the past, but were not using them at the time of the survey.

Among the 197 patients taking supplements currently (Pittsburgh, 99; Los Angeles, 98), the average consumption was 3 supplements per day. A majority of current users were taking 1 or 2 products (Pittsburgh, 53 patients [53%]; Los Angeles, 55 [56%]), but many were taking 3 to 6 products (Pittsburgh, 41 [41%]; Los Angeles, 38 [39%]), with a small proportion consuming more than 6 per day (Pittsburgh, 6 [6%]; Los Angeles, 4 [5%]). Pharmacies and grocery stores were the most common places of purchase of dietary supplements. A monthly expenditure of less than $25 on supplements was reported by 82 [83%] of the patients surveyed from Pittsburgh and 71 [72%] of the patients surveyed from Los Angeles.

The most common reported sources of information about dietary supplements were friends or relatives (Pittsburgh, 50 [51%]; Los Angeles, 46 [47%]) and books or magazines (Pittsburgh, 50 [51%]; Los Angeles, 45 [46%]).

**Table 2** summarizes details concerning patients who reported taking dietary supplements at the time of the survey.

Among patients taking supplements, 48 (48%) of 99 Pittsburgh patients and 43 (44%) of 98 Los Angeles patients had potential drug–dietary supplement interactions of any significance (severe or not severe). Most patients had 1 or 2 possible drug–dietary supplement interactions, with 7 patients in Pittsburgh (7%) and 12 patients in Los Angeles (12%) having more than 3 potential drug–dietary supplement interactions. Most of the potential interactions found were with ginseng, garlic, Ginkgo biloba, and coenzyme Q. Few of these interactions were documented by even 1 case report, and even fewer were identified as probable by at least 3 case reports or any safety data from a clinical trial. Documented potential drug–dietary supplement interactions are described in **Table 3**. Theoretical drug–dietary supplement interactions (data not shown) were found with the following dietary supplements: bilberry, cayenne pepper, garlic, ginger, Ginkgo biloba, ginseng, goldenseal, hawthorn, pectin, St John’s wort, sassafras, saw palmetto, ascorbic acid (vitamin C), and vitamin E. Of all 89 potential drug–dietary supplement interactions, 5 (6%) were classified as severe (**Table 4**).

Of those who took supplements, 79 (70%) of the Pittsburgh patients and 39 (40%) of the Los Angeles patients had informed their primary care providers of dietary supplement use (data not shown). Of those patients who did not discuss their use of these products with
their primary care providers, 58 patients (59%) from Pittsburgh and 88 (90%) from Los Angeles reported that their primary care providers had never questioned them about the use of dietary supplements.

We found dietary supplement use to be very common among VA patients who receive prescription medications and who are followed up in general medicine clinics, with 43% currently taking at least 1 type of dietary supplement. This is greater than the 18% reported by Eisenberg and colleagues and the 16% reported by Kaufmann and colleagues. However, the sample populations from those studies were selected from the general population, whereas our population was taken from within ambulatory care clinics. Many respondents in the study by Eisenberg and colleagues, for example, reported seeing a physician, but it is unknown how many of these patients had chronic medical conditions and whether these conditions were being treated with prescription medications. Our study cohort consisted of many persons with multiple comorbid conditions and prescriptions for various medications, and our respondents were more likely to represent older men seen in general medical practice settings. Using a similar method, Ly and colleagues found that 23% of 124 elderly patients attending a geriatric clinic were taking a dietary supplement at a VA facility in our study (Los Angeles). However, this study included fewer patients and a more elderly patient population (average age, 78 years) in a different clinic setting. Thus, the results may not be directly applicable. In addition, in contrast to Eisenberg and colleagues, who questioned participants about high-dose vitamins only, our study included regular-strength vitamins and minerals. This would tend to increase our reported rates of dietary supplement use.

Although many ambulatory patients were using dietary supplements concomitantly with prescription medications, only about 5% to 6% of the potential drug–dietary supplement interactions might lead to a severe adverse clinical event. From another angle, only 2.5% of patients reporting use of supplements and prescribed medications together could be considered to be at high risk for a potentially severe interaction. Most of the potential drug–dietary supplement interactions were, in fact, likely to be minor or theoretical, although they could still be bothersome or partially interfere with or potentiate other therapies. Although our incidence rates may seem low at first glance, these results correspond reasonably well with the 2% to 3% estimate of severe drug-drug interactions noted by Peterson and Bates and approximate the range of incidence rates seen for potentially serious drug-drug interactions found in various ambulatory populations.

Since our study was initially completed in 1999, we considered that newer information on interactions might alter the incidence rate of potentially serious interactions. To address this, we completed a second MEDLINE search in late 2001 and also reassessed our findings using a more contemporary, comprehensive reference on drug–dietary supplement interactions. With this search, only 1 potential interaction—between St John’s wort and selective serotonin reuptake inhibitors—changed from being a theoretical interaction to a documented probable interaction. However, this potential interaction had already been considered as potentially severe—as a theoretical interaction—and did not change in our findings. On the other hand, problems with documenting and classifying dietary supplements and their efficacy and safety may lessen the ability to identify potentially severe interactions.

First, in contrast to prescription medications, dietary supplements are already assumed to be safe products, and according to the DSHEA, it is the responsibility of the FDA to prove products are unsafe before restricting their use. This process is the reverse of that used for approving prescription medications. Evidence-
based profiles of adverse effects and interactions of dietary supplements are limited in scope and are often incomplete and inconsistent, using case reports instead of properly conducted scientific studies to assess safety. Even with pharmaceuticals, for which there are much better data, it is problematic to standardize classifications for drug-drug interactions. The difficulty is vastly increased for dietary supplements because many of these products contain chemical identities for which there is little or no information available on efficacy and safety, not to mention their interaction potential with other dietary products or with prescription medications. Thus, because of this problem, we used standard references and additional, overlapping resources to help ensure the robustness of our findings.

Second, the contents in dietary supplements across products may not be consistent. For example, a study by Gurley and colleagues evaluated the content of ephedra alkaloids in 20 different dietary supplements. They found not only that the content of ephedra alkaloids varied widely among the products, but that significant lot-to-lot variations existed. Thus, studies on safety or efficacy may underestimate or overestimate the actual potential for clinically significant drug–dietary supplement interactions, depending on which particular brand of product and which lot is being assessed. Because of the lack of quality control, other issues such as contaminated and mislabeled supplements—and the subsequent potential adverse effects from those problems—should also be considered, although a discussion is beyond the scope of this report.

Third, different populations may have different types of potential interactions, probably with varying severity levels. Within our patient population, most potential interactions were with *Ginkgo biloba*, garlic, and ginseng. Other patient cohorts may use many different supple-

### Table 3. Documented Drug–Dietary Supplement Interactions Found in Surveyed Patients

<table>
<thead>
<tr>
<th>Dietary Supplement</th>
<th>Drug Class</th>
<th>Drug</th>
<th>Potential Effect</th>
<th>Classification of Documented Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Fluoroquinolones</td>
<td>Levofloxacin</td>
<td>Lowered absorption of fluoroquinolone</td>
<td>X</td>
</tr>
<tr>
<td>Coenzyme Q</td>
<td>Anticoagulants</td>
<td>Warfarin sodium</td>
<td>Lowered anticoagulant effect</td>
<td>X</td>
</tr>
<tr>
<td>Garlic</td>
<td>Anticoagulants</td>
<td>Warfarin</td>
<td>Lowered platelet aggregation; increased risk of bleeding</td>
<td>X</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Anticoagulants</td>
<td>Warfarin</td>
<td>Lowered platelet aggregation; increased risk of bleeding</td>
<td>X</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>Anticoagulants</td>
<td>Warfarin</td>
<td>Lowered platelet aggregation; increased risk of bleeding</td>
<td>X</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Calcium-flushing</td>
<td>Warfarin</td>
<td>Lowered anticoagulant effect</td>
<td>X</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Anticoagulants</td>
<td>Warfarin</td>
<td>Lowered platelet aggregation; increased risk of bleeding</td>
<td>X</td>
</tr>
<tr>
<td>Pectin</td>
<td>Cardiac medications</td>
<td>Warfarin</td>
<td>Lowered anticoagulant effect</td>
<td>X</td>
</tr>
<tr>
<td>Potassium</td>
<td>ACE inhibitors</td>
<td>Warfarin</td>
<td>Lowered INR; decreased platelet aggregation</td>
<td>X</td>
</tr>
<tr>
<td>St John's wort</td>
<td>SSRIs</td>
<td>Warfarin</td>
<td>Lowered INR; decreased platelet aggregation</td>
<td>X</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACE, angiotensin-converting enzyme; SSRIs, selective serotonin reuptake inhibitors; X, present.

*A documented interaction refers to having at least 1 case report in the medical literature.* Possible refers to finding fewer than 3 case reports in the medical literature, whereas probable refers to finding 3 or more case reports or having data from a clinical study. Theoretical drug–dietary supplement interactions (data not shown) were found with the following dietary supplements: bilberry, cayenne pepper, garlic, ginger, *Ginkgo biloba*, ginseng, goldenseal, hawthorn, pectin, St John's wort, sassafras, saw palmetto, ascorbic acid (vitamin C), and vitamin E.

†Category of potential interaction between St John’s wort and SSRIs changed from theoretical to documented and probable after initial classification based on updated literature search.

### Table 4. Examples of Potentially Severe Drug–Dietary Supplement Interactions Found in Surveyed Patients

<table>
<thead>
<tr>
<th>Dietary Supplement</th>
<th>Drug Class</th>
<th>Drug</th>
<th>Potential Interaction</th>
<th>Category*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Fluoroquinolone</td>
<td>Levofloxacin</td>
<td>Decreased absorption of fluoroquinolone</td>
<td>Documented probable</td>
</tr>
<tr>
<td>Potassium</td>
<td>ACE inhibitors</td>
<td>Warfarin sodium</td>
<td>Hyperkalemia</td>
<td>Documented probable</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>Warfarin sodium</td>
<td>Warfarin</td>
<td>Decreased INR</td>
<td>Documented possible</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Warfarin</td>
<td>Warfarin</td>
<td>Increased INR; decreased platelet aggregation</td>
<td>Documented possible</td>
</tr>
<tr>
<td>St John's wort</td>
<td>SSRIs</td>
<td>Warfarin</td>
<td>Increased levels of serotonin</td>
<td>Documented possible</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACE, angiotensin-converting enzyme; INR, international normalized ratio; SSRIs, selective serotonin reuptake inhibitors.

*Described in Table 3.

†Category of potential interaction between St John’s wort and SSRIs changed from theoretical to documented probable after initial classification based on an updated literature search.
ments, with varying incidences and severity levels of potential interactions. For instance, there are documented potential drug–dietary supplement interactions with kava supplements.\(^{39,40}\) Such potential interactions were not seen in our respondents who were concomitantly taking prescription medications, but might be found in other patient groups. Thus, the overall incidence of possible drug–dietary supplement interactions in the general population or across patients seen in various primary care clinics may differ from our results.

Our findings help provide a context for ongoing discussions about the risks of drug–dietary supplement interactions and raise some very pressing concerns regarding the case finding of potential interactions and subsequent adverse events. Approximately 15 million adults are estimated to have consumed some form of dietary supplement concurrently with prescription medications, and 60\% did not disclose this information to their primary care providers.\(^2\) In addition, a study in 1999 found that although patients are willing to disclose such information on the use of dietary supplements, they often do so only when asked directly by a clinician.\(^{41}\) Our results generally correspond to these findings, although fewer Los Angeles patients informed their physicians of dietary supplement use. This may be coincidental or may reflect some underlying attitude, but our expectation is that Californians would be more forthcoming about alternative medical practices than Pennsylvanians. Any other possibility for this discrepancy may be due to the methods of data collection at the 2 sites (direct questioning vs self-reporting). In any event, when patients do not disclose information to their clinicians, the likelihood of capturing adverse events as a consequence of concomitant drug and dietary supplement use decreases.

Unfortunately, our study also suggests that physicians infrequently ask about the use of dietary products, although previously disseminated research suggests that many people take dietary supplements and that potential exists for serious drug–dietary supplement interactions.\(^2\) Given the lack of questioning by clinicians, it is not surprising that patients rarely identified health care providers as their source of information about dietary supplements. Our study thus raises the rather vexing situation of “don’t ask; don’t tell” when it comes to dietary supplement use, a situation that further increases the likelihood that potentially serious drug–dietary supplement interactions may be underrecognized and underreported.

Regardless of the exact incidence, subsequent adverse events from drug–dietary supplement interactions are preventable, if recognized in time. Our results suggest that even a simple question such as “Are you buying any vitamins, minerals, or herbal or dietary products from your supermarket, pharmacy, or health food store?” could potentially benefit 2 or 3 of every 100 patients taking dietary supplements. The effect is likely to be larger, as seemingly minor interactions, should they occur, may still be problematic and interfere with other therapies and quality of life. Although obtaining this additional history may sometimes be difficult owing to time constraints during the patient visit, our data suggest that even cursory questioning can often provide valuable information, given the high incidence of dietary supplement use.

We acknowledge important limitations to our study. The surveys were conducted at 2 VA medical centers, with surveys given to a sample of patients visiting general medicine clinics. Refusal rates were formally measured at the Los Angeles site, although anecdotaly the refusal rate at Pittsburgh was lower. Our results are probably applicable to veteran outpatients, at least at those 2 facilities, but may not be generalizable to other sites or to other patient populations and/or groups with different conditions and diseases. On the other hand, if veterans at our centers are purchasing dietary supplements so frequently, even with the modest incomes seen among the general veteran population, we suspect that patients in the private health care setting are purchasing at least as much. In addition, if Eisenberg and colleagues\(^1\) are correct, and more than $20 billion is spent on dietary supplements annually in the United States, then other outpatient populations are likely at similar risk for potential drug–dietary supplement interactions. We were unable to assess types of severe interactions among different patient groups because of our finding of low incidence. However, it appears that patients taking dietary supplements and anticoagulants may represent a group at higher risk for potential drug–dietary supplement interactions. In future studies, we recommend a much larger and broader patient sample to better quantify the incidence of potentially severe interactions and to enable statistical analyses to better understand which persons may be at high risk for such events. Finally, we assessed the incidence of potential drug–dietary supplement interactions and did not measure actual effects, such as changes in drug serum levels or actual clinical events. Such observations, while desirable, would not have been feasible in our exploratory study; especially given the low incidence of potentially serious interactions.

We found that the use of dietary supplements among veterans at 2 geographically diverse VA medical centers was common, but potentially severe drug–dietary supplement interactions were infrequent and comparable in incidence to potentially serious drug–drug interactions.\(^28,30-34\) However, because safety problems may be underrecognized and underreported, we encourage all health care providers to question patients about dietary supplement use, especially because there are increasing reports of significant morbidity and mortality, with or without concomitant pharmaceutical use.\(^9\) In addition, health care providers should consider potential drug–dietary supplement interactions, regardless of the severity of the potential interaction, because even minor interactions can affect drug therapy and patient quality of life. Finally, it is important for health care providers to take responsibility in reporting potential interactions as well as adverse events in patients taking dietary supplements to the FDA to assist in monitoring the safety of these products.

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