# Risk of Concurrent Use of Prescription Drugs with Herbal and Dietary Supplements in Ambulatory Care

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## Abstract

**Introduction**: Little is known about the prevalence of herbal and dietary supplement (HDS) use among ambulatory patients who use prescription medications or about the risk of adverse drug events (ADEs) related to drug-HDS interactions. **Methods**: We conducted a secondary analysis of a study of patients who received prescription medications at four primary care practices. We used chart reviews and patient interviews to identify potential drug-HDS interactions, and we used MICROMEDEX to classify interactions. **Results**: A total of 101 of 657 patients (15.4 percent) reported using HDS, including echinacea (21.8 percent), ginkgo biloba (13.9 percent), glucosamine (13.9 percent), omega-3 fatty acids (12.9 percent), garlic (7.9 percent), St. John's wort (6.9 percent), and ginseng (6.9 percent). Although we found no increased rate of ADEs among HDS users compared to nonusers, 14 percent of users had potentially dangerous interactions with their prescription drugs. **Conclusion**: HDS use is common in adult ambulatory care. The risk of interactions between these agents and prescription medications is worrisome.

## Introduction

In 1994, Congress defined a dietary supplement as a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet. The "dietary ingredients" in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and substances, such as enzymes, organ tissues, glandulars, and metabolites. Dietary supplements can also be extracts or concentrates, and they may be found in forms such as tablets, capsules, softgels, gelcaps, liquids, and powders.[1]

The use of herbal and dietary supplements (HDS) has grown rapidly in the United States. In 2001, consumers spent $17.8 billion on dietary supplements, including $4.2 billion of this amount for herbs.[2] A comparison of the results of the National Health Interview Survey in 2002 with a 1997 survey of complementary and alternative medicine use[3, 4] found a 50 percent increase in Americans' use of herbal supplements, from 12.1 percent of adults in 1997 to 18.6 percent—or 38 million individuals—in 2002.[3]

Most dietary supplements are unlicensed, and manufacturers are not required to demonstrate efficacy, safety, or quality.[5] Although herbs are often promoted as natural and therefore

harmless, they are not free of adverse effects. An observational study showed that herbal supplements are associated with adverse events of all levels of severity and affect all age groups.[6] As the use of herbal medicine increases, so have reports of adverse drug events (ADEs) related to HDS. To date, research regarding drug-herb interactions is limited mostly to case reports and a few systematic reviews.[7, 8, 9, 10, 11, 12]

Despite concerns about possible harmful interactions between prescription drugs and HDS, little is known about the concurrent use of these products by ambulatory patients. Only one published study has investigated the potential prevalence of ADEs associated with HDS in ambulatory care settings. This study showed that 43 percent of patients seeking care at two Veterans Health Administration hospitals were taking at least one dietary supplement (including herbs, vitamins, and minerals) with prescription medications, and 45 percent had the potential for a significant drug-dietary supplement interaction.[13]

Because 60 to 70 percent of complementary and alternative medicine users do not discuss their use with a physician,[4] patients may have few opportunities to learn about potential interactions of herbal and non-HDS with their prescription medications. To increase understanding of HDS risk and to inform clinical practice, we conducted a secondary analysis of a study of ADEs among primary care patients.[14] The goals of the present study were to calculate the prevalence of HDS use among primary care patients taking prescription medications and examine the risk of drug-HDS interactions in this population.

# Methods

## Definition

We defined an ADE as an injury resulting from medical intervention related to a drug.[15] We interpreted this definition to include injuries resulting from an herbal or non-HDS and from a drug-HDS interaction.

## Study Sites

We studied four Boston adult primary care practices affiliated with a teaching hospital. Two practices were located at the hospital, and two were community-based. One of each type of practice used a basic computerized system for prescribing drugs, but there was no automatic drug allergy or interaction alert feature. The other practices used handwritten paper prescriptions.

The study protocol has been described in detail and reported elsewhere.[14] Briefly, study subjects included 661 adult patients who received prescription medications from internists at the study sites. All patients who received a prescription from participating physicians at an appointment were enrolled once during a 4-week enrollment period at each site. Patients were excluded if they were too ill to participate, hard of hearing, or unable to speak English or Russian. Data were collected from September 1999 through March 2000. The Beth Israel Deaconess Medical Center institutional review board approved the study in advance.

## Data Collection

One day after the patient's appointment, investigators sent patients a letter that described the study and requested their participation in a telephone survey. Ten to 14 days after the appointment, patients who agreed to participate were asked about medication-related symptoms and to read aloud their prescription bottle labels. Patients were also interviewed 3 months after the appointment regarding their symptoms. Patients were asked at 10 days and again at 3 months if they "regularly took any nonprescription drugs, such as herbal and other dietary supplements."

Three months after the appointment, a nurse examined subjects' medical records to identify any ADEs, drug allergies, comorbidities, demographic characteristics, number of medications, and duration of continuous care at the practice site.

Two physicians then reviewed the chart and survey data to ascertain the presence of ADEs. Physician reviewers attributed none of the ADEs of the original study to an HDS. However, the investigators did not evaluate the presence of potential ADEs related to drug-HDS interactions.

For the present study, we identified potential drug-HDS interactions by reviewing each patient's medication list. Interactions were classified according to the DRUG-REAX® system database from MICROMEDEX, which was available to clinicians at the four practice sites.[16] Potential drug-HDS interactions were classified by MICROMEDEX as "minor," "moderate," or "major" as follows:

**Major:** The interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects.

**Moderate:** The interaction may result in an exacerbation of the patient's condition and/or require an alteration in therapy.

**Minor:** The interaction would have limited clinical effects. Manifestations may include an increase in the frequency or severity of side effects but generally would not require a major alteration in therapy.

If we identified a potential drug-HDS interaction, we used two additional databases to confirm the reported interaction from MICROMEDEX.[17, 18] In all cases, the three databases gave consistent results.

## Statistical Analyses

We used Student's t-test and the chi-square statistic for continuous and categorical variables, respectively. Reported *P* values are based on two-tailed tests of significance. Logistic regression was used to examine factors associated with patients' use of any HDS. The model was adjusted for patient and practice attributes (i.e., age, sex, primary language other than English, ethnicity, years of education, type of practice, type of prescribing, number of medications, and duration of clinic care) found to be associated with ADEs in the original study.[14] A dichotomous variable for HDS use was included in the final model. SAS® (SAS Institute) version 8e was used for statistical analyses.[19]

# Results

## Herbal/Dietary Supplement Use

Of 1,202 potentially eligible patients in the original study, 661 (55 percent) completed the initial telephone survey and were enrolled. Of enrolled patients, 600 (91 percent) completed the telephone survey at 3 months. Chart reviews were completed for 653 patients (99 percent). We analyzed 657 of 661 potentially eligible patients for the present study because four patients did not answer the question regarding the use of herbal and other dietary supplements.

Of the 657 patients, 101 (15.4 percent) reported using at least one HDS (Table 1). Overall, patients used 39 different supplements. The most commonly used herbs were echinacea (22 percent), ginkgo biloba (14 percent), St. John's wort (7 percent), ginseng (7 percent), evening primrose oil (5 percent), and saw palmetto (4 percent). The most commonly used nonherbal dietary supplements were glucosamine (14 percent), omega-3 fatty acids (13 percent), garlic (8 percent), chondroitin (5 percent), coenzyme Q10 (5 percent), flax seed (4 percent), and cranberry (4 percent).

## Subject Participation and Characteristics

Table 2 shows the characteristics of HDS users and non-users. Compared to nonusers, more users were white (88 vs. 79 percent, $P = 0.04$), college educated (90 vs. 80 percent, $P = 0.02$), English speaking (98 vs. 91 percent, $P = 0.02$), and had fewer than 3 years of continuous care at the practice site (44 vs. 34 percent, $P = 0.09$).

In the multivariable analysis, HDS use was associated with college education [OR 2.25, 95 percent CI (1.09, 4.65)] and English speakers [OR 4.32, 95 percent CI (1.01, 18.49)] and was inversely associated with 3 years or more of continuous care [OR 0.80, 95 percent CI (0.66, 0.97)] (Table 3).

## Adverse Drug Events Among Herbal and Dietary Supplement Users

Twenty-nine (29 percent) of the 101 HDS users experienced an ADE, compared to 131 (24 percent) of the 556 nonusers ($P = 0.27$), a nonsignificant difference in univariate and multivariate analyses.

Although we identified no ADEs attributable to drug-HDS interactions, we identified 14 patients with 25 potential drug-supplement interactions among the 101 HDS users (Table 4). Potentially serious ("major") drug-herb interactions included St. John's wort with selective serotonin reuptake inhibitors (SSRIs) or with oral contraceptives, and ginkgo biloba with antiplatelet agents, nonsteroidal anti-inflammatory drugs (NSAIDs), or trazodone. Two of the 14 patients had multiple potential drug-supplement interactions.

## Table 1. Most commonly used HDS and non-HDS

| Supplement | Common uses | Supplement class | No. of HDS users | % HDS users[a] (N = 101) | % Patients (users + nonusers)[a] (N = 657) |
|---|---|---|---|---|---|
| Any supplement | | | 101 | 100 | 15.4 |
| Echinacea | Prevent common cold | Herbal | 22 | 21.8 | 3.3 |
| Gingko biloba | Enhance memory and concentration | Herbal | 14 | 13.9 | 2.1 |
| Glucosamine | Treat osteoarthritis | Nonherbal | 14 | 13.9 | 2.1 |
| Omega-3 fatty acids | Prevent cardiovascular disease | Nonherbal | 13 | 12.9 | 2.0 |
| Garlic | Prevent cardiovascular disease, improve hyperlipidemia | Nonherbal | 8 | 7.9 | 1.2 |
| St. John's wort | Antidepressant | Herbal | 7 | 6.9 | 1.1 |
| Ginseng | Stimulant | Herbal | 7 | 6.9 | 1.1 |
| Evening primrose oil | Treat premenstrual syndrome | Herbal | 5 | 5.0 | 0.8 |
| Chondroitin | Treat osteoarthritis | Nonherbal | 5 | 5.0 | 0.8 |
| Coenzyme Q10 | Various uses, including treatment of hypertension | Nonherbal | 5 | 5.0 | 0.8 |
| Saw palmetto | Treat benign prostatic hypertrophy | Herbal | 4 | 4.0 | 0.6 |
| Flax seeds | Prevent heart disease and cancer | Nonherbal | 4 | 4.0 | 0.6 |
| Cranberry | Prevent heart disease and cancer, treat urine infection | Nonherbal | 4 | 4.0 | 0.6 |
| Other[b] | | | 24 | 23.8 | 3.7 |

a Totals exceed 100% because 33 patients used multiple supplements.

b Other supplements included: arnica, bilberry, bromeline, chromium picolinate, comphrey, dehydroepiandrosterone, dong quai, ginger, goldenseal, grape seed, hawthorne, herbal tea, isoflavone, kava kava, L-carnitine, lecithin, lutein, lysine, melatonin, mistletoe, niacin, pyruvate, slippery elm, vitex, wild yam.

**Table 2. Characteristics of study sample, by HDS and non-HDS use**

| Characteristic | Total (N = 657) | Users (N = 101) | Nonusers (N = 556) | *P*-value[a] |
|---|---|---|---|---|
| Mean age (±SD) (yrs) | 52 (16.9) | 52.5 (15.9) | 52.6 (17.1) | 0.94 |
| Sex[b] | | | | |
| Male (%) | 34 | 33 | 34 | 0.82 |
| Female (%) | 66 | 67 | 66 | |
| Race | | | | |
| White (%) | 80 | 88 | 79 | 0.04 |
| Non-white (%) | 20 | 12 | 21 | |
| Primary language | | | | |
| English (%) | 92 | 98 | 91 | 0.02 |
| Non-English (%) | 8 | 2 | 9 | |
| Education level | | | | |
| <12 years (%) | 18 | 10 | 20 | 0.02 |
| ≥12 years (%) | 82 | 90 | 80 | |
| Mean (±SD) medications | 3.6 (2.9) | 3.6 (2.7) | 3.6 (2.9) | 0.89 |
| Years of continuous care | | | | |
| <3 | 36 | 44 | 34 | 0.09 |
| ≥3 | 64 | 56 | 66 | |

A Student's t-test for continuous and chi-square for categorical variables.

b Based on N = 656

**Table 3. Patient characteristics associated with HDS and non-HDS use**

| Characteristic | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|
| Age (years) | 0.99 (0.99, 1.01) | 1.01 (0.99, 1.03) |
| Sex | | |
| Female | 0.94 (0.60, 1.48) | 0.87 (0.55, 1.40) |
| Male | 1.0 | 1.0 |
| Race | | |
| White | 1.98 (1.05, 3.74) | 1.54 (0.80, 2.98) |
| Non-white | 1.0 | 1.0 |
| Primary Language | | |
| English | 4.78 (1.15, 20.00) | 4.32 (1.01, 18.49) |
| Non-English | 1.0 | 1.0 |
| Education level | | |
| >12 yrs | 2.24 (1.13, 4.45) | 2.25 (1.09, 4.65) |
| ≤12 yrs | 1.0 | 1.0 |
| No. of medications | 1.01 (0.93, 1.08) | 1.02 (0.95, 1.11) |
| Years of continuous care | | |
| ≥3 | 0.82 (0.69, 0.98) | 0.80 (0.66, 0.97) |
| <3 | 1.0 | 1.0 |

OR = odds ratio; CI = confidence interval

# Discussion

We examined the use of HDS among adult ambulatory patients using prescription drugs in a secondary analysis of a study of ADEs. We found that one in six patients used at least one dietary supplement along with their prescription medications. Echinacea, gingko biloba, glucosamine, omega-3 fatty acids, and garlic were the most commonly used supplements. Compared to nonusers, users had higher levels of education, were English speakers, and had fewer years of continuous primary care. A similar percent of HDS users had an ADE compared to nonusers (29 percent vs. 24 percent), a difference that was not statistically significant. However, we found potential drug-HDS interactions among 14 of 101 patients, and many of these interactions were potentially serious or life threatening.

## Table 4. Potential drug-HDS and non-HDS interactions

| Herb | Interacting drug | No. of interactions | Interaction severity[a] | Quality of documentation regarding interaction[a] | Description of interaction |
|---|---|---|---|---|---|
| St. John's wort | SSRIs | 1 | *MAJOR* | *Fair* | Increased risk of serotonin syndrome |
| | Oral contraceptives | 2 | *MAJOR* | *Good* | Decreased contraceptive effectiveness |
| | Benzo-diazepines | 1 | *Minor* | *Fair* | Reduced benzodiazepine effectiveness |
| | Statins | 1 | *Moderate* | *Fair* | Reduced atorvastatin & simvastatin effectiveness |
| Ginkgo biloba | SSRIs | 7 | *Moderate* | *Fair* | Increased risk of serotonin syndrome |
| | Antiplatelet agents[b] | 5 | *MAJOR* | *Fair* | Increased risk of bleeding |
| | NSAIDs | 2 | *MAJOR* | *Fair* | Increased risk of bleeding |
| | Nifedipine | 1 | *moderate* | *Fair* | Increased risk of nifedipine side effects |
| | Trazodone | 1 | *MAJOR* | *Poor* | Excessive sedation and potential coma |
| | Anti-convulsants | 1 | *Moderate* | *Fair* | Decreased anticonvulsant effectiveness |
| | Buspirone | 1 | *Moderate* | *Fair* | Changes in mental status |
| Garlic | Antiplatelet agents[b] | 1 | *Moderate* | *Fair* | Increased risk of bleeding |
| Ginseng | Nifedipine | 1 | *Moderate* | *Fair* | Increased risk of nifedipine side effects |

a Based on MICROMEDEX classification.

b Aspirin was the only antiplatelet agent used by supplement users.

Although the news media have publicized cases of ADEs related to HDS,[20] few prior studies have examined the prevalence of drug-HDS interactions.[13, 21, 22] The rate of potential drug-HDS interactions in our study (25 percent) was greater than previous reports of drug-HDS interactions.[13, 21, 22] The rate was similar to the high rate of drug-drug interactions in studies of outpatients, where researchers have reported potential ADE rates of 9.2 percent to 70.3 percent of any severity, and 1.2 percent to 23.3 percent for more serious events.[23, 24, 25, 26, 27, 28, 29, 30] Our study also contributes to the literature in demonstrating that many drug-HDS interactions are potentially serious or life threatening.

How can we account for the number of potentially serious drug-HDS interactions in this study? It is possible that the commercial databases for classifying these interactions overestimate the severity of interactions, in part, because they rely on case reports to identify such events—a reporting bias. Because HDS are unregulated, rigorous premarket testing is not required, and as a result, the clinical importance of HDS-related ADEs and interactions are not well characterized. Another possibility is that HDS-drug interactions represent a serious and under-recognized hazard in clinical care. If patients and clinicians were better informed about the prevalence and potential severity of these interactions, perhaps they would be more cautious about the concurrent use of prescription or over-the-counter (OTC) medications and HDS.

Our findings regarding the prevalence of HDS use are consistent with previous studies and market data. National estimates of herb use range from 9 to 19 percent.[4, 31, 32, 33, 34, 35, 36, 37, 38] National rates of concurrent use of dietary supplements and prescription medications are 16 to 18.4 percent.[4, 36] Based on market data, the largest-selling herbs during 1999-2000 were ginkgo biloba, St. John's wort, ginseng, garlic, echinacea, and saw palmetto (Information Resources, Inc. Jan 1, 1999). In the same year, ginseng, ginkgo biloba, glucosamine, St. John's wort, and echinacea were reported to be the most commonly used HDS.[36] However, our results are inconsistent with several ambulatory care studies that found rates of use of up to 57 percent.[13, 21, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48] Differences may be due to practice type,[22] patient population,[13,] geographic variation,[48] differing definitions of dietary supplements,[13, 21] or secular trends. For example, two studies included vitamins and minerals in their definition of dietary supplements, thus accounting for a greater prevalence of reported dietary supplement use.[13, 21]

Like previously published national studies,[31, 32, 36, 49] we also found that HDS use was common in middle age, among women, among those with more than a high school education,[31, 32, 49] and with concurrent use of prescription or OTC medications.[36] Our results also corroborate work showing that complementary and alternative medicine users are more likely to have a place to go for usual care, to have a customary medical care provider, and to have seen a medical professional in the past 12 months.[37] All the patients in our study had a usual primary care provider, although higher HDS use was associated with less than 3 years of continuous care.

Our study offers several implications for clinical practice. First, clinicians may benefit from more effective education about HDS. Despite the widespread use of supplements, some physicians lack knowledge about HDS.[50, 51, 52] Only about half of physicians in one study were able to identify potential interactions between herbs and conventional medications. Educating clinicians about herbs and dietary supplements could help reduce the chance of dangerous interactions.

Second, given the potential for interactions with conventional drugs, health professionals should ask patients about their use of HDS and non-HDS. Our findings support the Joint Commission requirement that HDS and non-HDS use be included in patients' medication lists.

Third, electronic order entry systems should include drug-HDS alerts for potentially dangerous interactions. Given the large number of different drug-HDS combinations, physicians would benefit from the support of electronic knowledge databases that include information about the most serious drug-HDS interactions.[53, 54, 55]

Our study has several limitations. First, because we studied only four primary care practices, our results may not be generalizable. Our sample included many white, English-speaking, college-educated patients in an urban setting. Supplement use by other ethnic groups and in other cultures might differ. Second, we relied on patients' self-reports of HDS use, and they may have underreported. Third, we may not have ascertained completely the contribution of HDS use to ADEs because this information may not have been recorded in the chart or elicited accurately in the patient interviews. Fourth, our study was powered to examine ADE rates in primary care practices with and without computerized order entry systems. Although we found a slightly higher rate of ADEs among HDS users than nonusers, the study had only 16 percent power to examine this association. A study with a larger sample size would allow researchers to evaluate the impact of HDS use on ADEs.

Our results suggest that the use of herbs and dietary supplements is common in adult primary care. Although we observed no increased rate of ADEs among patients using supplements compared to nonusers, we identified many potentially serious interactions between these agents and conventional medications. Improvements in eliciting information about the use of HDS and non-HDS and providing electronic decision support for interactions between supplements and medications may be important for preventing ADEs in ambulatory care.

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