

**Original Article****Dietary Supplement Polypharmacy: An Unrecognized Public Health Problem?****Nicole L. Nisly<sup>1</sup>, Brian M. Gryzlak<sup>2</sup>, M. Bridget Zimmerman<sup>2</sup> and Robert B. Wallace<sup>2</sup>**<sup>1</sup>Department of Internal Medicine, Carver College of Medicine, University of Iowa and <sup>2</sup>Department of Epidemiology, University of Iowa College of Public Health, Iowa City, IA, USA

Excessive and inappropriate use of medications, or ‘polypharmacy’, has been recognized as a public health problem. In addition, there is growing use of dietary supplements in the United States; however, little is known about the patterns of supplement use. Recent reports in the literature of cases of excessive or inappropriate use of herbal dietary supplements leading to the term ‘polyherbacy’. The clinical vignettes described in this article highlight the need for further research on the nature and extent of multiple and inappropriate dietary supplement use or ‘dietary supplement polypharmacy’. Clinical interviewing and population surveys both address this issue in complementary ways, and provide a further understanding of dietary supplement use patterns.

**Keywords:** complementary and alternative medicine–dietary supplements–drug interactions–herbals–polypharmacy

**Introduction**

Excessive and inappropriate use of medications has been recognized as a public health problem, resulting in an increased likelihood of adverse drug events, drug interactions, and inappropriate drug prescribing and increased costs (1). Multiple strategies have been developed to contain and recognize this problem, also known as polypharmacy. In addition, there is growing use of dietary supplements in the United States, with sales for the year of 2006 estimated at over \$21 billion (2). However, little is known about the patterns of dietary supplement use or how they interact with medications, although population surveys are addressing this issue (3–7). There are recent reports in the literature of cases of excessive or inappropriate use of herbal dietary supplements, leading to the term ‘polyherbacy’ (8) implying at

least potential similarity to the health problems associated with polypharmacy.

Dietary Supplements were defined by the Dietary Supplement Health and Education Act of 1994 as a product taken orally, and intended to supplement the diet. Dietary supplements include vitamins, minerals, herbs and other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars and metabolites. The Food and Drug Administration (FDA) regulates dietary supplements differently than prescription and over-the-counter drugs. Dietary supplement manufacturers are not required by the FDA to prove safety or efficacy and are not required to follow established drug product good manufacturing practices (GMPs), although dietary supplement-specific GMPs are being developed by the FDA (9). In December 2006, the Dietary Supplement and Nonprescription Drug Consumer Protection Act (10) was signed into law, requiring the FDA to establish systems of data collection on serious adverse reactions that people experience while using dietary supplements. Manufacturers and distributors of dietary supplements are now required by law to submit information to the FDA concerning adverse

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reactions reported to them by the public. This new regulatory requirement begins to address long recognized safety concerns over dietary supplement use.

Population surveys can provide substantial insight into the magnitude of herbal or dietary supplement use in the US. National surveys published recently documented use of dietary supplements ranging from 19% to 65% (3,6). However, published surveys may not be fully informative on patterns or extent of individual dietary supplement use, including multiple or excessive supplement use, appropriateness of use in accordance with evidence-based indications, or combinations of herbs with other supplements or medications. In part, this is due to limitations in the standardization of products and product names, the ubiquity of multi-ingredient preparations and the lack of assessment of changing use patterns over time. To our knowledge, there are no databases in the US of dietary supplement labels and detailed product information. The Office of the Director, Office of Dietary Supplements (ODS), National Institutes of Health has recently announced that it is seeking to partner with industry and academic institutions to develop such a database (11).

One complementary approach to population surveys is the qualitative study of representative individual case histories derived from a clinical setting, to better characterize individual patterns of use. In this report, we describe four cases illustrating examples of dietary supplement polypharmacy, which are derived from a Complementary and Alternative Medicine Clinic (CAMC) located in a large Midwestern academic medical center.

## Methods

The authors reviewed 150 case records of University of Iowa CAMC to select illustrative cases of dietary supplement polypharmacy occurring between September 2003 and September 2005. The cases selected below were chosen to provide significant illustrations of commonly reoccurring themes. They were selected based on the completeness of the medical record and illustrative potential. The CAMC can serve as an important setting to observe and document the behavior of individuals who use CAM, and dietary supplements in particular. It is a consultative service, housed in a large teaching hospital, in the Department of Internal Medicine. The majority of patients access the CAMC through self-referral, but roughly one third of new patients are referred by a physician or other health care professional. Most physician referrals are related to concerns over dietary supplement use, potential dietary supplement-drug interactions and dietary supplement polypharmacy. Nearly all CAMC patients are English-speaking and age 18 years or older; the CAMC serves nearly 600 patients

per year. CAMC appointments are lengthy, often lasting 60–120 min for new patients with extensive dietary supplement use. Nearly all CAMC patients share a strong interest in CAM use. While not all patients use dietary supplements, the majority use at least one supplement, with the average patient using three to five dietary supplement products, typically containing multiple active ingredients.

Clinic appointments involve a detailed dietary supplement use history, with direct validation via inspection of original product containers and labels by a physician or pharmacist. All patients are asked to bring their dietary supplements original containers to aid in identification. Initially, the comprehensive list of current and past supplement use was recorded manually on a form and incorporated into the medical record. Manufacturers' information and Internet web sites were used to aid in identifying product constituents. As electronic record-keeping was implemented, dietary supplement information was progressively incorporated into the electronic medical records. In September 2003, a computerized dietary supplement form was introduced, allowing patients or health professionals to enter the names, constituents, brand, dose, frequency of use, purpose and cost of each dietary supplement used. When patients performed the entry, the evaluating physician or pharmacist would later validate that data.

## Results

### Selected Case Histories Illustrative of Dietary Supplement Polypharmacy

The following are illustrative case histories of commonly observed behavioral patterns with respect to dietary supplement polypharmacy.

#### *Case 1—The Liver Function Abnormality Mystery: Consider Supplements!*

A 54-year-old woman with a history of large goiter and liver function abnormalities was referred by her physician to the CAMC to address her multiple dietary supplement use. She was noted to have moderate liver function abnormalities (ALT 3 times normal range) during a medical evaluation. After extensive evaluation of her liver dysfunction no apparent causes were found. She did not drink alcohol or take any medications, and was of normal body weight. Infectious, obstructive and autoimmune causes were ruled out. She was noted to consume a number of dietary supplements and referred to our clinic to address dietary supplement polyherbacy and its potential affect on her liver function tests. She brought all her supplements for review. At that evaluation, we addressed the purpose of her use of each supplement (Table 1).

**Table 1.** Dietary supplements and purpose of use

Dietary supplements	Purpose of use
Algae: multiple products containing <i>Blue-green algae</i> , <i>Chlorella</i> , <i>Spirulina</i> and <i>Norwegian kelp</i>	Thyroid health, goiter, iodine source
Allergy multi (Multivitamin complex for chemically sensitive individuals) and other individual supplements in addition to her multivitamin product: B complex, ester C, vitamin D, vitamin E, vitamin K, selenium	Vitamins and minerals
Boron, three different calcium preparations, two different magnesium preparations and silica	Bone density
Carotenoid complex: 25000 IU plus lutein, lycopene, alpha-carotene, alpha-lipoic acid, Antarctic krill, broccoli concentrate, pumpkin concentrate, carrot seed oil	Eye health, other
Digestive enzyme formula (two different kinds), probiotics (two different kinds)	Digestion
Oils: <i>Black currant</i> , <i>Evening primrose</i> , organic flax	Beneficial oils
Glucosamine and chondroitin sulfate	Joint health
<i>Siberian Ginseng</i>	Energy
<i>Ginkgo Biloba</i>	Memory
<i>Echinacea (angustifolia and purpurea)</i>	Colds and infection
Valerian extract	Sleep, occasional use
Turmeric	Cancer prevention, inflammation

She reported adding more and more dietary supplements over the years, as she read extensively and frequently researched the internet for information on these products. Ultimately she felt at a loss as to which supplements might be of benefit or which supplements to stop taking. This patient typically would use less than the recommended dose noted on the label, but at times would use a higher than recommended dose. She also would vary which supplement she might use in any given day. She expressed concern that her dietary supplement intake had gotten out of control and felt she may be addicted to using supplements as they gave her a greater sense of control.

After discussing the purpose for using each dietary supplement and concerns with dietary supplement polypharmacy and its potential effect on her liver dysfunction, she agreed to stop all supplements for the time being, with the exception of calcium and vitamin D, and one multivitamin a day. Until her follow-up visit she would increase her dietary intake of antioxidant foods, acidophilus and omega 3 fatty acids in place of her supplements, and practice mind-body techniques and exercise for health and stress reduction. We also offered a referral to counseling for anxiety management. Follow-up liver function tests were normal. We proposed to re-introduce a fewer number of supplements, based on evidence-based indications and safe dose ranges, one at a time, while we followed her liver function tests. She elected however to stay off the supplements over the next two follow-up visits, as she was happy with her dietary modifications. Based on the evidence presented above, we believe that her abnormal liver function tests were

a result of excessive supplement use and resolved completely with withdrawal of offending agents.

#### Comment

Following principles applicable to the management of polypharmacy, we recommended stopping all unnecessary supplements. Except for the calcium and vitamin D, none of her supplements were deemed essential, her pattern of use was erratic and she was unsure of benefits. By agreeing to guide her on the reintroduction of the dietary supplements once her liver function tests normalized, we provided a framework of partnership and respect. Nondietary supplement options were recommended to address her need for control and to manage her anxiety.

#### Case 2—Challenges from Different World Views: Intuitive Choice and Dietary Supplement Polypharmacy

A 56-year-old female was self-referred to the CAMC and brought a lengthy list of dietary supplements. She used different supplements each day and often would not follow the recommended doses in the bottles. An extremely important dimension of this patient's behavior was the method she used in selecting, which supplements she would use: The patient would choose the supplement to be used at a particular time by holding her fingers over the supplement container and allow the use of 'energy' or 'muscle strength' to guide her. If she felt her fingers stronger, the supplement would be chosen. This she called 'applied kinesiology', which was often utilized by the alternative health providers whom she had consulted with.

**Table 2.** Dietary supplements and purpose of use

Dietary supplements	Purpose of use
Thirty-four Homeopathic products (12). Examples of such remedies used includes: <i>Arsenicum ALB.</i> , <i>Aconitum NAP</i> , <i>Calcarea carbonica</i> , <i>Collisonia CAN.</i> , <i>Gelsemium SEMP.</i> , <i>Ignatia Amarra</i> , <i>Natrum Muriaticum</i> , <i>Nux Vomica</i> , <i>Phosphoricum Acidum</i> , <i>Plumbum Metallicum</i> , <i>Rhus Tox.</i> <i>Stramonium</i> , <i>Thuja Occid</i>	Multiple ailments, as dictated by energy or divine guidance
Botanical agents included: <i>Chanca piedra</i> , <i>Bladderwrack</i> , <i>Cat's claw</i> , <i>Chaste tree berry</i> , <i>Ginseng</i> , <i>Ginkgo</i> , <i>Grapefruit seed extract</i> , <i>Hawthorn</i> , <i>Horsetail</i> , <i>Olive Leaf</i> , <i>Pau D'Arco</i> and <i>Graviola</i> , among a total of 38 botanical products consumed	Gallbladder and liver detox, cancer prevention, hormonal health, heart health, parasites, infection, etc.
Flower essences (dilute preparations of flower extracts)	For prevention and treatment of multiple ailments
Oil essences (essential oils, used topically, for inhalation or orally in a dilute form),	For prevention and treatment of multiple ailments
Other non-botanical dietary supplements such as glucosamine sulfate and essential fatty acids	For prevention and treatment of multiple ailments

Often she would disregard the actual supplement identity and the dose being chosen and was unable to report which of the supplements or doses she used regularly. The total number of supplements used could not be estimated after multiple visits with a physician and pharmacist. A summary of her regimen occupied 17 pages. A selection of her supplements is listed in Table 2.

Of note, the practices described in this case are not intended to be representative of the complementary medicine technique 'Applied Kinesiology' (12,13), described at the International College of Applied Kinesiology web site as a complex technique to be used only by trained licensed providers, in conjunction with standard diagnostic methods.

It is also important to note that the diagnoses or medical problems noted in Table 2, were primarily self-diagnoses or diagnosis given to her by nonallopathic providers. She had known gallstones.

#### *Comment*

This is a striking example of dietary supplement polypharmacy. The use of 'energy guidance' and 'muscle strength testing', which she described as 'applied kinesiology', in her choice of supplement used could be considered very unusual by many health care professionals. However, variations of each approach are utilized by some alternative medicine providers and patients alike. Providers and patients will test the patient using applied kinesiology to determine current therapeutic needs. Based on these testing, dietary supplements are then recommended and often also sold to the patient by that provider. This form of dietary supplement use poses a potential safety challenge, as it does not involve scientific knowledge on potential benefits, drug interactions or side-effects for the dietary supplement used. Furthermore, it creates a challenge in the potential identification of side-effects, drug interactions, or benefits, as the user may not be able to describe what regimen they are using on a

particular day. Another dimension of the problem is that some alternative healers may instruct the patient to stop a prescribed medication, felt to be potentially harmful, based on 'muscle strength testing' or financially exploit a vulnerable individual, compelling the patient to purchase a supplement sold by the healer, presented as essential to balance one's energy.

#### *Case 3—The Case of the Dependent Adult at Risk*

An 83-year-old widowed man with a diagnosis of dementia, was brought to the CAMC by his two daughters to establish care, as he had just moved in from Florida. His daughters were the decision makers in his care and disagreed upon which course to take, thus the consultation to our clinic. His medical history includes two recent strokes, early dementia, and the use of multiple dietary supplements and warfarin. Despite recurrent strokes on aspirin and an antiplatelet aggregation agent (Ticlopidine), one of his daughters wished to stop his warfarin against medical advice and rely on the use of complementary therapies to prevent further strokes. She believed that the oral chelation therapy he had received by an alternative health care provider while living in Florida should have eliminated his thromboembolic risk. She felt that warfarin—which she described as a 'rat poison'—was detrimental for his health. Another daughter was concerned with potential complications such as recurrent stroke, if he stopped the prescribed agents. The patient deferred the decision to his daughters. As there was significant family disagreement on how to proceed, they presented for a consultation to our CAMC. He has not yet established care with a primary care provider.

Medications taken by the patient included Warfarin and Simvastatin (Table 3).

#### *Comment*

This case illustrates three complex medical issues. The first problem pertains to the increased risk for adverse

**Table 3.** Dietary supplements and purpose of use

Dietary supplements	Purpose of use
Oral Chelation Therapy containing: EDTA, N-acetyl-cystein, vitamin C, methyl sulfonyl methane	Cleaning of blood vessels
Another supplement product from the same company above contained multivitamins, minerals, aminoacids, inositol, <i>grape seed</i> extract, malic acid, PABA, boron, betain HCL, pancreatin, adrenal and thymus and pituitary substance, <i>buchu</i> leaf, <i>couch grass</i> , <i>garlic</i> powder, <i>juniper</i> berries and <i>hawthorn</i> berries	Heart and brain health and blood thinning
Coenzyme Q10	Heart and brain health
Flax seed oil	Blood thinning
Cyanocobalamine	Nervous system health

drug interactions in this older adult using both multiple dietary supplements and anticoagulation. Potential interactions include both decreased effectiveness with increased risk of thromboembolic events or increased risk of bleeding. Another concern is the potential risk of mad cow disease with the ingestion of bovine brain matter (pituitary substance). Clearly, the potential risk of recurrent thromboembolic event with the substitution of dietary supplements for warfarin is a concern.

A second issue illustrated here are the role of social forces in dietary supplement use in the setting of a dependent adult, who is not capable of making a fully informed decision. This is not an uncommon problem and it is truly concerning, not only at the end of life but it applies as well to the use of supplements in children, by often well intentioned caretakers who are misinformed and misguided. The ethical issues represented here are complex and deserve broader discussion and research. The third and broader issue illustrated here underlines the public health problem of unregulated and misinformed supplement use. This is an issue of outmost importance in public policy and education, which needs urgent attention from scholars, educators and policy makers. A concerted effort to promote and require education of health care professionals, CAM providers and the public in general on scientific evidence pertaining to safe use of dietary supplements is critical, given the substantial use of dietary supplements in this country.

#### *Case 4—Fear of Cancer Treatment: Seeking Dietary Supplements Instead*

A 45-year-old woman was referred by her oncologist to the CAMC with her third recurrence of head and neck cancer. A regimen of chemo-radiation had been proposed, as the new lesion, albeit very small, was not resectable due to its proximity to the carotid artery. The proposed treatment was thought to likely afford her significant odds of remission and prolonged survival. She is a single mother with poor social support, and receiving welfare. She was told by a local health food store owner that a natural regimen would be her best option and that she should avoid ‘toxic medical treatment’

at all cost. The patient thus was frightened by the prospect of side-effects of radiation and chemotherapy and that her choice to pursue the recommended medical treatment would ‘prevent her body from healing due to its inherent toxicity’, as her local health food store owner advised her (who was not known to be a trained CAM provider or herbalist). She came to the CAMC to discuss her treatment options. She estimated monthly cost for the dietary supplement proposed at over \$500 a month. This was beyond her means but she was willing to pay for that if it would save her life (Table 4).

#### *Comment*

Patients are often frightened and vulnerable by learning of a serious illness, even when that illness is treatable. They are easily swayed to seeking unproven treatments while giving up therapies, which have been shown to save or prolong life. This is often done under the guidance of unknowledgeable and commonly unlicensed self-proclaimed healers, who offer the promise of cure without risks, in contrast with evidence-based risk/benefit frank discussions of medical treatments. It is important to notice that the store owner derived significant financial gain for promoting the large number of supplements to a vulnerable individual, an often too common ethical dilemma in the promotion of dietary supplements but individuals (licensed providers or otherwise) who derive financial gain from their ‘health advice’. Another issue of significance here is the serious financial burden created by uncovered expenses with dietary supplements, to this socially vulnerable patient. Respectful, knowledgeable and culturally competent discussions that address the unmet patient needs (in this case fear, anxiety), often take place over several visits, and can help the patient understand the true risk/benefits of both medical and nonconventional treatments, enabling patients to make a safer informed decision.

#### **Discussion**

The clinical vignettes described in this article highlight the need for further research on the nature and extent of

**Table 4.** Dietary supplements and purpose of use

Dietary supplements	Purpose of use
Bowel cleanser: unmarked and unidentified container, given by the health food store <i>Psyllium</i>	Bowel detoxifier
Multivitamin preparation Vitamin C	Vitamins, cancer treatment
Yeast detox: caprylic acid, <i>echinacea</i> , <i>garlic</i> , <i>pau d'arco</i> , <i>slippery elm</i> <i>Candida</i> homeopathy preparation	Clear her body of yeast growth
Super algae containing <i>spirulina</i> ; pH Green Zone containing algae <i>spirulina</i> , <i>chlorella</i> and <i>alfalfa</i>	Boost the immune system, detox
Lymph gland cleanse containing the herbs <i>golden root</i> , <i>yarrow</i> , and <i>parthenium</i>	Clean the lymph system
Proactazyme containing the enzymes amylase, lipase, and protease Protease	Enzymes, detox, cancer treatment
E-Tea containing <i>burdock</i> , <i>sheep sorrel</i> , <i>slippery elm</i>	Detox, cancer treatment
Coral calcium	Cancer treatment, calcium
<i>Pawpaw</i>	Cancer treatment

multiple dietary supplement use. While polypharmacy has not been precisely defined in terms of the specific number of drug products used, the key elements for this diagnosis are the excessive and inappropriate nature of medications utilized with increased risk of adverse drug reactions (1). It has been estimated (4,15) that one out of every four adults taking prescription medications are also using dietary supplements concomitantly and are thus at risk for adverse drug interactions. The concept of dietary supplement polypharmacy described above and observed in our practice meets the criteria for medication polypharmacy. This health care problem is largely unrecognized and its prevalence among dietary supplement users is unknown. Based on our clinical observation coupled with data derived from the national surveys described above, this problem may be common, and of considerable public health significance.

Population surveys may have certain limitations, such as not reaching some respondents who are ill (and thus possibly more likely to seek alternative remedies), or who are unwilling to respond to these surveys. Also, many of these surveys provide somewhat limited lists of common dietary supplements and may not query the full range of products being consumed. In some instances, as noted in our vignettes, multiple constituents are likely to be included under one product label, which also may not be captured by the questionnaire. Nor can these surveys often validate the content of products or provide detailed lists of their constituents, having often been conducted by telephone.

Furthermore, in many surveys supplement use is captured in a single 'snapshot' in time, usually in the past month or year. This information is useful, but may not capture the frequently changing regimens that some individuals undertake, as seen in two of our cases. Our clinical experience suggests sporadic and limited-time

use for many products, at least among some patients. The details and complexity of dietary supplement use has escaped the scope of most surveys of dietary supplement conducted to date. New instruments and methods may be needed to capture the complexities of dietary supplement use and its potential clinical and financial burden (6).

The supplement use patterns described above may be surprising to some health practitioners. These findings highlight the need to re-evaluate the format and extent of clinical history-taking to include the potential for substantial and diverse supplement use, as well as other CAM usage. There has been an increasing awareness of CAM use, and numerous surveys have confirmed this growing phenomenon (4–6,9) and its clinical and public health importance (16). Despite this awareness, the movement to incorporate information on CAM usage in the medical evaluation (17) and records has been slow, as has been the professional education (18) oriented toward preparing physicians to guide patients in the use of CAM and dietary supplements. The principles described on each case discussion serve as models for the practicing physician caring for a patient using multiple dietary supplements. The counseling principles discussed after each patient case are summarized in Table 5.

### Limitations and Strengths of the Findings

This report has some limitations requiring discussion, most relating to generalizability of the patient histories. The setting of this CAMC experience in a single academic medical center and geographic area potentially selects highly interested users of dietary supplements, which may represent uncommon behaviors when compared with the general population. Thus, the extent of the consumption

**Table 5.** Counseling principles

Counseling patients using dietary supplements
1. Ask at each medical visit about the use of dietary supplements.
2. Document details of product ingredients, examine original product container.
3. If necessary set-up a special encounter to review all supplements used.
4. Evaluate and address unidentified needs such as depression, anxiety, cost issues.
5. Document dietary supplement use details on medical records.
6. Obtain access to up to date evidence-based information resources on dietary supplements for entire health care team.
7. Provide counseling on safety, efficacy and potential drug interactions.
8. Report suspected adverse reactions or drug interactions to MedWatch (16).

patterns described here cannot be extrapolated to the general population. However, these data include the details of dietary supplement use, and beliefs and behaviors regarding that use, not typically captured in clinical interviewing or national surveys. To our knowledge, there have not been detailed descriptions of patterns of dietary supplement usage in the indexed scientific literature.

## Conclusion

The hidden and growing phenomenon of dietary supplement polypharmacy adds a new layer of complexity to patient care and poses a significant public health problem, still largely unrecognized and poorly understood. There is growing awareness and education to contain and correct the problem of polypharmacy and its adverse consequences. Still, despite growing knowledge of the widespread use of dietary supplements, the health care profession has yet to assume a concerted effort in research, education, clinical practice guidelines and public policy to address this important and growing phenomenon. This article attempts to shed some new light on the practices of dietary supplement use, and highlights the need for further research as well as consumer and medical education, in this important area of health care. From a public policy standpoint, the recent establishment of an effective post-marketing surveillance and mandatory reporting mechanism to detect the adverse effects of dietary supplements (10,16,20) is timely and a step in the right direction.

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