How Physicians Should Evaluate Dietary Supplements

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ABSTRACT

Dietary supplements occupy a unique niche within the realm of modern medicine. These products are often used by patients at their own discretion, in an unmonitored setting, and without the input of their physicians. Although laws pertaining to dietary supplement labeling prohibit specific claims for the treatment or prevention of disease, these products are widely used as “alternative” or “complementary” therapy. Dietary supplements are readily available, not classified as over-the-counter medications, and not regulated as such. Patients and providers alike often assume these products are at least safe and possibly effective. Historically, dietary supplement pharmacodynamic and pharmacokinetic data have been limited and of meager quality. Information on dietary supplements in nonmedical literature is typically unreliable, and even in the medical literature, numerous studies have used products that were not well characterized. Although greater attention has recently focused on dietary supplement quality and integrity, complex issues persist and must be addressed when evaluating literature and advising patients. We seek to clarify many of these issues and make practical suggestions for the clinician.

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According to current United States law, dietary supplements are products taken orally and intended to supplement the diet by increasing total daily intake. These products may contain a vitamin, a mineral, an herb, or other botanical, amino acid, or substances such as enzymes, organ tissues, glandulars, and metabolites. Concentrates, metabolites, extracts, or combinations of these also qualify as dietary supplements. Individual dietary supplements may be classified in different ways, and therefore some ambiguities may result. For example, a vitamin and mineral may simply be vitamin E and calcium, respectively. A botanical is a plant-derived supplement (herbal and nonherbal examples are ginseng and soy, respectively), whereas glandulars are often derived from porcine or bovine tissue. Some classify supplements into broad categories: vitamin and mineral or nonvitamin, nonmineral. To augment confusion, many dietary supplements are sold as combination products containing an extensive number of the above ingredients.

DIETARY SUPPLEMENT REGULATION

Dietary Supplement Health and Education Act

Dietary supplements can be simplified into 2 categories: those marketed before 1994 and those marketed after the passage of the Dietary Supplement Health and Education Act. Basically, before 1994 dietary supplements had little regulation and could make health claims on labels. The Dietary Supplement Health and Education Act delineates Food and Drug Administration (FDA) authority and limitations in the regulation of dietary supplements. The Dietary Supplement Health and Education Act classifies dietary supplements as foods rather than drugs and outlines labeling requirements and regulations under which dietary supplements are to be marketed. Essentially, the act specifies that supplement ingredients marketed before the Dietary Supplement Health and Education Act need no FDA approval; however, the manufacturer must ensure the dietary supplement is...
The FDA has responsibility for taking action against any marketed dietary supplement that is unsafe. Manufacturers must ensure product label information is truthful and not misleading. The FDA monitors dietary supplement safety by following adverse event reports and reviewing labeling and specifying labeling requirements.

The Dietary Supplement Health and Education Act strictly prohibits any drug-like claims; therefore, dietary supplements cannot legally be marketed to treat, cure, diagnose, or prevent disease. Only “structure” or “function” claims are allowed. For example, a dietary supplement may be marketed to “improve joint health” but cannot claim to treat arthritis or joint pain. Dietary supplements are therefore not regulated by the FDA’s Center for Drug Evaluation and Research, as are prescription and over-the-counter drugs, but rather by the Center for Food Safety and Applied Nutrition. The Center for Food Safety and Applied Nutrition does require the following disclaimer on all dietary supplement labels making structure/function claims: “this product is not intended to diagnose, treat, cure or prevent any disease(s).” Supplements also are required to have a clearly readable label that, like food or (over-the-counter) labels, provides certain information. Labels must contain a recommended dose or “serving size” and list all ingredients. However, labeling is often confusing, because the quantity or identity of ingredients frequently are not clear, especially when compared with over-the-counter drugs. For example, a botanical name may be provided, with no mention of the specific plant part. An extract may have a milligram quantity specified with no clarification of how the quantity relates to the quantity of the original plant material or concentration of the active principle(s). The words “standardized,” “guaranteed potency,” and “high-performance liquid chromatography (HPLC) certified” commonly are used with no explanation as to methods of assessment or relation to the desired effects.

New dietary ingredients introduced to the market after 1994 are regulated under the Federal Food Drug and Cosmetic Act. Supplements containing new dietary ingredients require FDA notification at least 75 days before marketing. Some “gray areas” in the dietary supplement market exist as to what actually constitutes a new dietary ingredient. In essence, any dietary supplement containing ingredients without documentation of US marketing before 1994 requires FDA notification. The manufacturer or distributor notification must provide information that reasonably supports the safety of the dietary supplement. After notification, the FDA may object to the filing, request more information, or simply allow marketing without comment.

The Dietary Supplement Health and Education Act did not address the issues of dietary supplement efficacy and left proof of safety up to the manufacturer. To deem a product unsafe, the FDA must provide documentation as such. Few data exist on dietary supplements regarding safety or efficacy. Many infer safety on the basis of a long history of use. However, dietary supplements usually are not consumed in the same manner as “historical use.” Ginseng has been consumed for thousands of years in the form of a tea by steeping the raw herb in water. This form of a preparation would yield significantly different constituent compounds compared with a concentrated alcoholic extract manufactured and incorporated into a tablet. Thus, the safety and efficacy of currently marketed products cannot be guaranteed on the basis of historical use.

### GOOD MANUFACTURING PRACTICE GUIDELINES

To ensure the quality and safety of dietary supplements, the FDA has issued the Current Good Manufacturing Practices in 2007. These regulations greatly benefit consumers by requiring manufacturers to ensure the integrity of dietary supplement products. The Current Good Manufacturing Practices are being implemented in 3 phases, beginning with large companies in 2008 and including small-scale industry by 2010. Quality of manufacturing processes and the accurate listing of ingredients on the dietary supplement product label are addressed. According to the Current Good Manufacturing Practices, a manufacturer of a dietary supplement must take steps to ensure the ingredients used meet specifications; their facilities, personnel, and operational procedures preserve product integrity by preventing contamination or adulteration, and all of these procedures are adequately documented. The stipulations do not specify what tests must be used or quantify ingredient standardization. Rather, the Current Good Manufacturing Practices enforce basic controls and specifications for the ingredients, processes, personnel, and facilities used to maintain consistency and the identity of the finished product. Testing is used to confirm that dietary supplement materials used in processing meet the criteria set by the manufacturer, and that the manufacturing processes were sufficiently controlled to ensure the finished product meets specific requirements and was not unintentionally contaminated or adulterated during manufacturing.

### BOTANICAL DIETARY SUPPLEMENTS

Because of their complexity, botanical dietary supplements have several unique issues. Plant-based preparations may contain numerous compounds, even hundreds, with various pharmacologic activities, depending on the dose. Many botanical supplements report a standardized amount of an...
active ingredient, although in many cases the active constituents are not actually known. For example, despite the identification of a number of biologically active principles, the primary active ingredient in Valerian, a sleep aid, is unclear.\(^5\) Mechanisms of action for many compounds in botanical products are still being elucidated, and some may work in synergy.

A variety of factors can also alter the quantity of “active ingredient” within the raw plant material and finished product. Plants inherently have a degree of genetic variability, and conditions of growth also affect chemical composition of the plant. Duration and conditions of storage, harvesting, and processing all influence the final product. Methods used in manufacturing any dietary supplement can also vary the end product. Table 1 identifies potential factors that can alter chemical composition before or during manufacturing.

Published clinical trials and case reports involving dietary supplements often do not provide adequate description of the product. If botanical supplements are involved, the Latin binomial names of each plant in addition to common names should be listed. Manufacturer information and product lot number also should be documented. In clinical trials, analysis of active ingredients or marker compounds by an independent laboratory should be performed before using a supplement, as well as during and at the end of the trial to ensure quality of the product throughout the study. Ideally, products from a single manufacturer’s lot should be used, and storage conditions should be documented. If this information is not clearly described in the literature, the results cannot be generally accepted within the medical community or adopted into clinical practice. From this perspective, much of the older literature on dietary supplements is flawed because of product quality assurance. Numerous publications have documented variability in product ingredients versus label claims of a variety of dietary supplements.\(^6\)\(^-\)\(^10\)

Readers of the medical literature must carefully consider the possibility of both variable product quality and quantity in published trials or case reports. Without accurate product analysis, other elements of good clinical trial design can be undermined, and valuable resources wasted, with unreliable or inaccurate outcomes. All literature should be evaluated using these standards. Table 2 summarizes many of these issues related to clinical trials of dietary supplements.

For case reports, another consideration deserves mention. When serious adverse events are described, it is crucial that product characteristics are well documented. Unfortunately, investigators often do not have the product or access to appropriate analytic capabilities to perform a thorough product analysis. In such cases, depending on the nature of the evidence and the exclusion of other confounding causes, it may still be appropriate to file an adverse event report. Such cases must be regarded merely as signals of a possible problem, and not definitive, until a significant number of cases are reported and causality can be rigorously assessed.

### A Case in Point

Despite specific label regulation, patients often take dietary supplements to treat a variety of medical conditions, such as depression (eg, St John’s wort) or arthritis (glucosamine/chondroitin). Widely available in a variety of settings, dietary supplements may be perceived as safe by patients. Several of the issues surrounding botanical supplements are illustrated in the case of Ephedra, one of the oldest medicinal herbs. A member of the family Ephedraceae, *Ephedra sinica* is the primary species used in China for approximately 5 millennia.\(^11\)

The pharmacology of *Ephedra* is complex. With both traditional and recent popular uses, the established pharmacologic effects seem to be attributable to its ephedrine-type alkaloids, mainly (−)-ephedrine and (+)-pseudoephedrine. Ephedrine, a sympathomimetic agonist at both alpha- and beta-adrenergic receptors, enhances the release of norepinephrine from sympathetic neurons. Most of ephedrine’s

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**Table 1** Factors That May Alter Dietary Supplement Composition Before or During the Manufacturing Process

| Cultivation vs wild-crafting | Misidentification of the plant |
| Stage of growth at harvest | Environmental conditions (eg, soil, seasonal weather, nutrient exposure) |
| Method of harvesting and processing | With botanicals, use of improper plant part (leaf vs berry) |
| Environmental contaminants (insects, microbes, pesticides, heavy metals, dirt) | Improper storage methods |
| Variations in temperature, moisture or light | Use of solvents or other chemicals that may alter the active ingredients |
| Binders or fillers in the formulation altering bioavailability |  

**Table 2** Potential Limitations in Dietary Supplement Research Product Factors

| Source plant misidentification | Inadequate description of the raw materials |
| Product contamination (with other supplements or any pharmacologically active substances) | Inadequate analysis for active compounds |
| Use of inconsistent lots | The paucity of pharmacokinetic and pharmacodynamic information regarding dietary supplement and specific active ingredients |
| Study Factors | Lack of independent product characterization |
| Lack of adequate placebo controls or blinding | Insufficient number of subjects or inadequate randomization |
| Unwarranted extrapolation of conclusions based on 1 preparation |  

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therapeutic efficacy and most prominent adverse effects are due to these pharmacologic mechanisms. Effects of α- and β-adrenergic receptor stimulation include enhanced cardiac rate and contractility, peripheral vasoconstriction, bronchodilation, and central nervous system stimulation.11,12

The vasoconstrictor and bronchodilator effects of α- and β-adrenergic receptor stimulation account for the traditional use of Ephedra as a nasal decongestant and antiasthmatic. However, the vogue in the 1990s was the exploitation of Ephedra’s central nervous system stimulant and thermogenic effects. Ephedra-containing dietary supplements often were overused and abused, as is common with stimulant weight-loss products.11

Many cases of serious adverse effects and even fatalities have been reported that were linked with Ephedra or ephedrine administration.11-14 Hypertension was the most frequent adverse effect, followed by palpitations, tachycardia, stroke, and seizures. Ten events led to death, and 13 cases produced permanent disability.13 Many of these cases seem to involve misuse or predisposing factors. However, because of rapidly increasing numbers of adverse events related to the use of Ephedra, regulatory authorities acted to ban sales of Ephedra-containing products in the United States.15 Unfortunately, this is a story of a traditional herbal remedy that was aggressively marketed and indiscriminately used for its stimulant effects, leading to serious injuries and regulatory restriction.

ADULTERATED SUPPLEMENT PRODUCTS
In addition to the inherent complexities of botanical product identity, composition, and consistency, and the associated variability in these, some problems in the field have a more sinister origin. A number of incidences of intentional adulteration or “spiking” in the botanical dietary supplement industry are documented, with reports of preparations intentionally laced with pharmaceuticals to mimic an authentic material or give a desired effect.16-18 For example, a number of “herbal sexual enhancement” supplements have been “spiked” with prescription erectile dysfunction medications, such as sildenafil, tadafil, or synthetic derivatives.18,19 Weight-loss supplements “spiked” with sibutramine or other prescription stimulant drugs also have been identified, and “natural” supplements for arthritis have been adulterated with prednisone or nonsteroidal anti-inflammatory drugs.20 More ethical members of the industry have spoken out against intentional adulteration, recognizing the harm that may be inflicted on the industry.16 Consumers should be cautious and forewarned about possible adulterated products marketed by less established or “fly by night” companies that desire to turn a quick profit.

THE CLINICIAN AND DIETARY SUPPLEMENTS
Some researchers and clinicians alike have argued dietary supplements should be required to adhere to the same basic regulations as over-the-counter medications, thus classifying them as drugs. However, in the legislative push that resulted in the passage of the Dietary Supplement Health and Education Act, public opinion was strongly weighted toward less restriction and more availability of “natural” remedies, setting a precedent of limited regulation that is not likely to be quickly reversed. Thus, patient interest in dietary supplements is unlikely to diminish, and many feel very passionate about their right to use these products as they please. Clinicians must meet the patient on neutral ground with an open mind regarding dietary supplements. The following are some practical strategies to assist clinicians.

Communication is the first step to discovering a patient’s use of dietary supplements and may help avoid an adverse event or drug-supplement interaction that might have been prevented. Internists do not have to recommend or encourage dietary supplement use, and may even want to actively discourage use depending on the situation. At a minimum, clinicians must acknowledge patient use of these products and should recognize their potential to either help or harm patients. Internists must be prepared to evaluate patient dietary supplement use in a critical, but nonconfrontational manner. Providers should ask patients about dietary supplement use at every visit and recommend they bring dietary supplement products and their prescription or over-the-counter medications.

Second, the clinician’s education regarding dietary supplements is paramount. If a clinician is unaware of a possible side effect of a dietary supplement, it is unlikely to be considered as a cause. If an adverse event is suspected, with the product(s) at hand the clinician can document the manufacturer, listed ingredients, lot number, and other needed information. Various references on dietary supplements are available and have been reviewed elsewhere for quality and clinical applicability.21-23 Some are written with the basic scientist in mind, whereas others target clinicians. An enormous amount of information about supplements is available on the Internet at supplement manufacturers’ websites, blogs, and so-called unbiased sites. The clinician should be cautious regarding information gained on the Internet unless it is from a reliable source. The Office of Dietary Supplements and the FDA can both provide basic information. One particularly useful reference for clinicians with unbiased, reliable dietary supplement information is the Natural Medicine Comprehensive Database.24 Table 3 lists websites...
mentioned in this article. Many websites offering information on dietary supplements, unfortunately, are designed simply to promote products and thus cannot be considered unbiased. Some online sellers of dietary supplements offer a “suggested” list of supplements to take for almost any medical disorder, from eczema to angina. In addition, much of the lay literature, readily accessible via the Internet, makes exorbitant claims touting the benefits of dietary supplements. Unfortunately, misinformation and mystery are the current rule and not the exception.

Two final areas in which physicians can play a key role are adverse event reporting and literature evaluation. Physicians who encounter a patient who may have had an adverse reaction to a dietary supplement or possible supplement–drug interaction should report such cases to the FDA. Without proper reporting of these adverse events, no investigation will occur. Possible events can be reported online to the FDA at MedWatch. Unfortunately, most adverse events relating to dietary supplements are not reported, and much of this is due to lack of provider recognition. Physicians must thoroughly evaluate any publication for biases and product quality issues as previously discussed. Historically, reputed journals have published articles on dietary supplements without adequate discussion of these issues. Even when a dietary supplement is used in a trial of good quality with few limitations, the data cannot be readily extrapolated to another supplement as is often done with medication research. Table 2 outlines possible limitations regarding published literature and clinical trials. If any of these factors are present in a publication, the authors should specifically address them within the text.

CONCLUSIONS

The clinician will find challenges with patient use of dietary supplements to be greatly facilitated by attention to 4 key factors. Table 4 outlines the mnemonic CARE, which can be used to remember how physicians can improve their practice. The onus is principally on the individual clinician. Only with vigilance on the part of both clinician and researcher can deficient areas improve. With time, advances in the regulatory requirements (eg, Current Good Manufacturing Practices) will help ensure basic quality standards for many of the most popular products and enhance the likelihood that both the patient and physician have greater confidence the dietary supplement content conforms to the labeling. Physicians with only moderate knowledge of dietary supplements who always asks patients about dietary supplement use will do much to improve patient care. Also, clinicians who ask about dietary supplements will likely help educate patients about some of the issues discussed and demonstrate an interest in dietary supplements to patients and the possible effects they may have.

References


Table 4 CARE Mnemonic for Areas of Improvement with Dietary Supplement

| C | Communicate freely with patients about dietary supplements |
| A | Acquire knowledge of dietary supplements and find a reference that is accurate but easy to use |
| R | Report adverse events and possible drug–dietary supplement interactions |
| E | Evaluate the literature and examine publications for limitation |


