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Dietary Supplements

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CONTENTS

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Objectives

Understand the current terminology defined by the National Center for Complementary and Alternative Medicine (NCAAM) in relation to dietary supplements and complementary and alternative medicine (CAM).

Describe current regulatory issues and trends relating to dietary supplements, including labeling requirements, advertising, product quality, legal actions, and adverse event reporting.

Identify potential safety problems with dietary supplements including adverse effects, interactions with prescription medications, and issues involving either intrinsic or extrinsic ingredients.

Test Your Knowledge Questions

1. Which of the following claims for a dietary supplement would most likely cause the US Food and Drug Administration (FDA) to consider that the supplement should be regulated as a drug rather than as a dietary supplement?

A. Supports strong bones and teeth
B. Treats influenza
C. Promotes urinary health
D. Improves immune function

2. Which of the following best describes dietary supplement use in the United States?

A. Only a minority of the population uses dietary supplements.
B. Most patients report their dietary supplement use to their primary care providers.
C. Most patients think that their health care providers are knowledgeable about dietary supplements.
D. Many patients using prescription medicines concomitantly use dietary supplements.

3. Even if Current Good Manufacturing Practices (CGMPs) promulgated by the Dietary Supplement Health and Education Act of 1994 (DSHEA) are properly implemented, which of the following is still likely to occur?

A. A dietary supplement product adulterated with a prescription drug such as sibutramine is being marketed and sold.
B. A dietary supplement product is analyzed and found to have much less of the active ingredient than what is indicated on the label.

C. A dietary supplement product is analyzed and found to have much more of the active ingredient than what is indicated on the label.
D. A dietary supplement product is marketed and sold, but there are no studies to confirm its efficacy for any condition.

Test Your Knowledge Answers

1) The correct answer is B. Under the DSHEA, manufacturers of dietary supplements may make statements regarding product ability to affect structure or function of the body. Manufacturers refer to these as "structure-function claims," which are regulated by the FDA for labeling and the US Federal Trade Commission (FTC) for merchandizing and marketing. Any claim regarding diagnosis, treatment, cure, or prevention of a disease is disallowed and subject to fines and prosecution. Therefore, a claim to support strong bones and teeth would be allowed as a structure claim, if true. The claims to promote urinary health and support the immune system would be function claims. The claim that a product treats influenza is an obvious claim regarding treatment of disease and would thus be disallowed.
2) The correct answer is D. Surveys have shown varying percentages of the US population using dietary supplements. Data from a large nationwide survey published in 2016 indicated that the use of dietary supplements remained stable between 1999 and 2012, with 52% of US adults reporting use of any supplements in 2011–2012.1 Many persons using dietary supplements do not report this use to their allopathic health providers. Patients may not disclose supplement use because they do not think of supplements as products that may interact with their medications or because they believe that the health provider will be judgmental about their use. Abundant data indicate that the latter belief is overwhelmingly the most common reason why patients do not disclose the supplements they use, and there is strong evidence to validate patients' fear of reprisal. Although most patients think that their healthcare provider should be knowledgeable regarding dietary supplements, only about half of patients in a recent survey reported that providers actually were knowledgeable. In contrast, surveys of healthcare providers indicate that they are often reluctant to recommend CAM modalities even though they report having good to excellent awareness of the potential benefit of these modalities. Many patients using dietary supplements also use prescription medications; this concomitant use could result in supplement interactions with medication or increased incidence of adverse events.
3) The correct answer is D. The DSHEA mandates that CGMPs be set up for the dietary supplement industry. Under these CGMPs, process controls are supposed to be in place at each step of manufacturing. Thus, the dietary supplements arriving on the shelf should contain the correct ingredients in the correct amounts and should be free of adulterants. There should be consistency between lots in terms of content. Unfortunately, the FDA does not have sufficient resources to inspect all manufacturing plants and final products. However, examples of random

testing of the authenticity of dietary supplements sold in large national retail chains by New York State agencies caught national attention in 2015 and led to legal action against the retailers, which ultimately paid large settlements.2 The CGMPs do not address whether there are any data supporting the efficacy of dietary supplements.

Introduction

Dietary supplements are widely used by consumers and are probably used by some patients receiving nutrition support. Nutrition support clinicians are in an important position to not only identify patient use but also provide information to patients and other healthcare providers about dietary supplement indications, efficacy, safety, and legal regulation. This chapter provides an overview of the subject. More complete information on specific dietary supplement ingredients is available from specialized resources (Table 19-1). A relatively small number of ingredients account for a large portion of the most popular dietary supplement products.

TABLE 19-1 Select Resources on Dietary Supplements

Reference books:

- Barnes J, Anderson LA, Phillipson JD, eds. Herbal Medicines. 3rd ed. London, UK: Pharmaceutical Press; 2007.
- Coates PM, Betz JM, Blackman MR, et al, eds. Encyclopedia of Dietary Supplements. 2nd ed. London, UK: Informa Healthcare; 2010.
- Cupp MJ, Tracy TS, eds. Dietary Supplements: Toxicology and Clinical Pharmacology. 2nd ed. Totowa, NJ: Humana Press; 2007.
- Dasgupta A, Hammett-Stabler C, eds. Herbal Supplements. Hoboken, NJ: Wiley; 2011.
- Mason P. Dietary Supplements. 4th ed. London, UK: Pharmaceutical Press; 2011.
- Pathak Y, ed. Handbook of Nutraceuticals. Boca Raton, FL: CRC Press; 2010.
- Stargrove MB, Treasure J, McKee DL. Herb, Nutrient, and Drug Interactions: Clinical Implications and Therapeutic Strategies. St. Louis, MO: Mosby Elsevier; 2008.
- Tracy TS, Kingston RL, eds. Herbal Products: Toxicology and Clinical Pharmacology. 2nd ed. Totowa, NJ: Humana Press; 2010.
- Ulbricht CE. Natural Standard Herb and Supplement Guide. St. Louis, MO: Mosby; 2010.

Online resources:

- American Botanical Council:

– www.herbalgram.org

– www.herbmed.org

- ConsumerLab: www.ConsumerLab.com

- Federal Trade Commission: www.ftc.gov
- Food and Drug Administration Dietary Supplements section: www.fda.gov/Food/DietarySupplements/default.htm
- National Institutes of Health Office of Dietary Supplements: http://ods.od.nih.gov
- National Sanitation Foundation (NSF):

– Home page: www.nsf.org

– Search for NSF Certified Dietary Supplements: www.nsf.org/certified/dietary

- Natural Medicines: https://naturalmedicines.therapeuticresearch.com
- Natural Products Association: www.npainfo.org
- Pharmacist's Letter: http://pharmacistsletter.therapeuticresearch.com
- QuackWatch: www.quackwatch.org
- US Pharmacopeia: www.usp.org

Current Use in Adults

In the United States, annual sales of dietary supplement products exceed $36 billion.3 The reported prevalence of dietary supplement use varies by the population evaluated and the products included in the survey. As noted earlier, US survey data indicates that the use of dietary supplements remained stable between 1999 and 2012, with 52% of US adults reporting use of any supplements in 2011–2012.1 National Health and Nutrition Examination Survey data published in 2011 suggests that approximately 53% of adults use dietary supplements.4 Other surveys confirm similar rates of dietary supplement use among older adults.5

However, clinicians may be unaware of their patients' use of dietary supplements. The results of a 2002 study in a community hospital indicate that, of the patients taking dietary supplements, less than half reported their supplement use to their primary providers. Documentation of dietary supplement use in the medical record was found to be insufficient in a prospective study of interviewed patients.6 Product description, product name, and frequency of use were often missing from documentation. In another investigation, reported use of a supplement 2 to 3 days prior to surgery was also not recorded in the medical record.7

Dickinson and colleagues surveyed physicians and nurses about their own use of supplements. They found that dietary supplements are used regularly by 37% to 59% of physicians and 59% of nurses, with most of those surveyed also recommending dietary supplements to their patients.8,9

Definitions

For purposes of this chapter, the ingredients that can be found in dietary supplements are divided into 3 groups based in part on the raw material sources. The first group comprise ingredients accepted as nutrients that have been recognized with Dietary Reference Intake (DRI) values (Table 19-2). The second

group is herbal ingredients that contain parts or extracts of medicinal plants (Table 19-3). Lastly, are the other dietary supplement ingredients that are not officially recognized as nutrients and are not of botanical origin (Table 19-4). The official regulatory framework surrounding dietary supplements, including definitions, is important for better appreciating their role in patient care.

TABLE 19-2 Common Nutrient Supplement Ingredients

			Major Adverse Effects		
Ingredient Name	Common Uses[a]	Daily Dose[b]	Side Effects	Interactions	Comments
Arginine	Athletic performance, wound healing	2–3 g	GI discomfort, headache	Antihypertensives, blood thinners	Avoid use status post myocardial infarction; caution in hepatic/renal impairment.
Ascorbic acid	Wound healing	100–1000 mg	Diarrhea, kidney stones	Aspirin, estradiol, iron, indinavir	Dose cautiously in glucose-6-phosphate dehydrogenase deficiency; use with caution in renal impairment.
Biotin	Alopecia, brittle nails	300 mcg	NK	Antiepileptics	High-dose pantothenic acid reduces biotin absorption.
Calcium	Osteoporosis	400–2000 mg	Hypercalcemia, constipation	Bisphosphonates, digoxin, fluoroquinolones, levothyroxine	Use with caution if at risk for calcium oxalate stones.
Cholecalciferol	Osteoporosis	10–25 mcg (400–1000 IU)	Hypercalcemia, kidney stones	Antiepileptics	
Choline	Athletic performance, dementia	250–500 mg	GI discomfort	NK	Lecithin (phosphatidylcholine) has a less fishy odor.
Chromium	Diabetes, depression	200–500 mcg	Hypoglycemia	Insulin	Trivalent form and chloride salt are preferred.
Copper	Hypercholesterolemia	1–2 mg	GI discomfort	Penicillamine, iron, zinc	Available as chloride, acetate, or sulfate salt.

Folic acid	NTD prevention	400–1000 mcg	NK	Phenytoin, methotrexate	Assess vitamin B_{12} status. Supplementation >DRI may lead to inappropriate methylation, imposing health risks.
Iron	Fatigue	60–180 mg	GI discomfort, esophageal ulcers	ACE inhibitors	Fumarate or sulfate if inorganic. RDA is 8 mg for men and postmenopausal women and 18 mg for nonpregnant women.
Pyridoxine	PMS, depression	50–150 mg	Neuropathy	Isoniazid, hydralazine	Allergic reaction and photosensitivity are rare.
Selenium	CVD, rheumatoid arthritis, cancer	50–100 mcg	Hair loss, nail dystrophy	Clozapine	Sodium selenite or selenomethionine are preferred forms.
Taurine	Athletic performance, CVD	0.5–2 g	NK	NK	Nonprotein amino acid
Zinc	Diarrhea, wound healing	25–100 mg	Immunosuppression, anemia, and neuropathy from copper deficiency	Fluoroquinolones	Sulfate or chloride are preferred forms. RDA is 11 mg for men, 8 mg for women.

ACE, angiotensin-converting-enzyme; CVD, cardiovascular disease; DRI, Dietary Reference Intake; GI, gastrointestinal; NK, none known or not known; NTD, neural tube defect; PMS, premenstrual syndrome; RDA, Recommended Dietary Allowance.

[a]In addition to prevention/treatment of nutrient deficits.

[b]Elemental doses are listed for minerals.

TABLE 19-3 Popular Herbal Supplement Ingredients

Ingredient Name	Common Uses	Daily Dose	Major Adverse Effects	
			Side Effects	Interactions
Black cohosh *(Cimicifuga racemose)*	Menopausal symptoms	40–80 mg	Headache, GI discomfort	Tamoxifen
Chamomile *(Matricaria recutita)*	Indigestion; insomnia	400–1600 mg	Allergic reactions, drowsiness	Benzodiazepines
Echinacea *(Echinacea purpurea, Echinacea pallida, Echinacea angustifolia)*	Upper respiratory infection	600–1600 mg	Allergic reactions, headache, GI discomfort	Acetaminophen, steroids, and other immunosuppressants
Feverfew *(Tanacetum parthenium)*	Migraine prevention	125 mg	Allergic reactions, joint pain, mucositis, photosensitivity	NK
Garlic *(Allium sativum)*	Hyperlipidemia	600–900 mg	Bleeding, body odor, GI discomfort	Anticoagulants, saquinavir
Ginger *(Zingiber officinale)*	Nausea, vomiting	1000 mg	Heartburn	Anticoagulants
Ginkgo *(Ginkgo biloba)*	Vascular insufficiency	80–240 mg	Allergic reactions, bleeding, GI discomfort	Anticoagulants
Ginseng *(Panax ginseng, Panax quinquefolius)*	Panacea	100–200 mg	Headache, insomnia, GI discomfort	Antihypertensives
Goldenseal *(Hydrastis canadensis)*	Dyspepsia, diarrhea	400–800 mg	GI discomfort, hypoglycemia, mucositis, photosensitivity	Anticoagulants
Green tea *(Camellia sinensis)*	Weight loss	100–750 mg	Stimulant	Warfarin
Hawthorn *(Crataegus monogyna)*	Heart failure	160–900 mg	GI discomfort, headache, insomnia	Antihypertensives, digoxin
Milk thistle *(Silybum marianum)*	Liver disease	200–400 mg	Anaphylaxis, GI discomfort	NK
Saw palmetto *(Serenoa repens)*	Benign prostatic hyperplasia	320 mg	Dry mouth, GI discomfort, headache	NK
St. John's wort *(Hypericum perforatum)*	Depression	240–1800 mg	Dry mouth, GI discomfort, confusion, hypomania, photosensitivity	Antiepileptics, cyclosporine, digoxin, indinavir, oral contraceptives, triptans, warfarin
Valerian *(Valeriana officinalis)*	Anxiety; insomnia	400–1200 mg	Drowsiness	Benzodiazepines

GI, gastrointestinal; NK, none known.

TABLE 19-4 Other Popular Supplement Ingredients

Ingredient Name	Common Uses	Daily Dose	Major Adverse Effects[a]		Comments
			Side Effects	Interactions	
Beta-carotene	Cardiovascular disease	5–15 mg	Diarrhea, joint pain	Colestipol, ethanol, orlistat	Avoid in smokers (increased risk of lung cancer and cardiovascular mortality).
Chitosan	Hypercholesterolemia	1.3 g	Bleeding, GI discomfort, hypoglycemia	Antiplatelets	Avoid in people with shellfish allergy; may interfere with vitamin absorption.
Chondroitin	Osteoarthritis	800–1200 mg	GI complaints	Warfarin	May be natural (cartilage, trachea) or synthetic.
Coenzyme Q	Hypertension, heart failure	100–600 mg	Headache, fatigue	Warfarin	Synthesized by body; decreases with age.
Creatine	Muscle mass/strength	2–5 g	GI complaints, muscle cramps, renal impairment reported	Caffeine	Synthesized by body; influences creatinine levels.
Curcumin	Wound healing, inflammation	NK	GI irritation (usually when combined with black pepper)	NK	A component of turmeric.
Fish oils	Cardiovascular disease	1–4 g	Anticoagulant	Antiplatelets	Contents may vary with fish sources used.
Glucosamine	Osteoarthritis	1500 mg	GI complaints, proteinuria	Antiplatelets, diuretics	Source may be natural (shellfish).
Lutein	Ocular disorders	2–20 mg	NK	NK	Carotenoid found in a variety of foods.
Lycopene	Cancer, cardiovascular disease	2–30 mg	GI discomfort	Antiplatelets	Carotenoid found in tomato products.
Melatonin	Sleep disturbances	0.5–5 mg	Dysphoria, headache, infertility	Antiepileptics, sedatives, warfarin	Pineal gland hormone.
MSM	Allergic rhinitis, osteoarthritis	0.5–2.5 g	GI discomfort	NK	An oxidation product of dimethyl sulfoxide.
Resveratrol	Cancer, cardiovascular disease	NK	NK	Antiplatelets	Oral bioavailability unclear.

GI, gastrointestinal; MSM, methylsulfonylmethane; NK, none known or not known.

[a]Data on adverse effects and interactions are limited for this category of dietary supplements.

The controlling legal definition of dietary supplement is that which the US Congress included in DSHEA,10 which amended the FDA authority under the Federal Food, Drug, and Cosmetic Act (FDCA).11 This legal definition is broad and includes products taken by mouth that contain one or more of the following “dietary ingredients”: a vitamin; a mineral; an herb or other botanical; an amino acid; a dietary substance for use by humans to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any ingredients previously described. A dietary supplement must be labeled as such and may be in tablet, capsule, powder, softgel, gelcap, or

liquid form. Supplement means that the product is not represented for use as a conventional food or as a sole item of a meal or the diet.12

In addition to defining the term, Congress included dietary supplements under the general category of foods for purposes of the FDCA.12 Hence, dietary supplements do not undergo the stringent and expensive premarket approval process required for prescription or over-the-counter drugs. Congress also excluded dietary supplements from the definition of food additives,13 which means that manufacturers are exempt from the food additive premarket approval provisions of the FDCA as well.

In addition to the legal definition of dietary supplement, nutrition support clinicians and other healthcare providers should be aware of several other terms that may arise in a discussion of dietary supplements. For example, the National Institutes of Health (NIH) defines complementary and alternative medicine (CAM) as a group of diverse medical and healthcare systems, practices, and products that are not generally considered part of conventional medicine (also called allopathic medicine).14 Complementary medicine refers to practices and products used together with conventional medicine, whereas alternative medicine refers to systems, practices, and products that are used as a substitute for conventional medicine. Integrative medicine (also called integrated medicine) refers to a practice that combines both conventional and CAM approaches for which there is evidence of safety and effectiveness.14 The National Institute for Complementary and Alternative Medicine (NCCAM) is a branch of NIH that provides grants for research investigating whether CAM modalities have proven benefits. NCAAM also serves as an educational resource for the public.

Both conventional and CAM practitioners may use dietary supplements as part of a patient's biologically based treatment. What defines a dietary supplement product is the legal definition (as previously described), not who recommends it.

Naturopathy is a medical system that aims to support the body's ability to heal itself through dietary and lifestyle changes with therapies including the use of herbal supplements, massage, and joint manipulation.14 Phytotherapy is the science of using plant-based medicines to prevent or treat illness.15

The terms nutraceutical and functional food are often used in the context of dietary supplements. Nutraceutical can refer to nutrients or other active food ingredients delivered in a pharmaceutical dosage form. By contrast, an active ingredient delivered within a food matrix, whether added or natural, may be considered a functional food; these functional food ingredients may be nutrients, herbals, or other compounds.16 For example, vitamin C tablets might be described as a nutraceutical, whereas orange juice may be considered a functional food because it is high in vitamin C. The Academy of Nutrition and Dietetics (AND) defines functional foods as foods that "move beyond necessity to provide additional health benefits that may reduce disease risk and/or promote optimal health." According to AND, this definition would include conventional foods, modified foods (fortified, enriched, or enhanced), medical foods, and foods for special dietary use, such as infant foods and weight loss foods.17 Notably, the terms nutraceutical and functional food have no legal meaning under the FDCA, and the FDA has

regulatory authority over nutraceutical and functional food products either as dietary supplements or as foods.18

Dietary supplements are also distinguished from medical foods, such as enteral nutrition formulas. The Orphan Drug Act legally defines medical food as a "food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."19 The original reasoning behind orphan drugs and this subcategory of orphan foods was to ease premarket development costs for those products not anticipated to recoup costs due to minimal need.20 Examples include liquid protein and other modular components used in enteral nutrition, some oral nutritional drinks, and a few vitamin products approved for use as medical foods. Medical foods are exempt from both food labeling21 and dietary supplement labeling requirements. Therefore, even though a medical food product might look like a dietary supplement in terms of content, different regulations apply because it is labeled as a medical food.

Homeopathy is a system of medicine that originated in Europe in the late 18th century. It is based on the "principle of similars," or "like cures like," which is described by practitioners of homeopathy as the observation that while high doses of pharmacologically active substances cause symptoms when administered to healthy people, those same substances when prepared in very dilute form may relieve similar symptoms in conditions resulting from different etiologies.22 Homeopathic remedies are not dietary supplements under the legal definition of the FDCA. Although 2 products may contain similar ingredients, they may also be subject to different regulations depending on whether the product is officially recognized as a homeopathic medicine or a dietary supplement. Articles listed in the official Homeopathic Pharmacopeia of the United States are categorized as drugs by the FDCA.23 These products have official monographs that provide drug information in the Homeopathic Pharmacopeia of the United States.22 However, whereas the premarket approval process for most new drugs is governed by the FDA, the homeopathic products' premarket approval process is controlled by the Homeopathic Pharmacopeia Convention of the United States, which is comprised of scientists and clinicians trained in homeopathy.22

Regulatory Issues

US Food and Drug Administration Oversight

Under the DSHEA, the manufacturer is responsible for ensuring that a dietary supplement is safe before it is marketed. The FDA is responsible for taking action against an unsafe product and its manufacturer after it reaches the market. Generally, manufacturers do not need to register dietary supplement products with the FDA nor obtain FDA approval before producing or selling dietary supplements unless the product contains a new dietary ingredient (NDI).24 NDI refers to any ingredient not previously marketed in the United States before the enactment of the DSHEA (October 15, 1994).25 A dietary supplement product on the market is considered adulterated if it contains an ingredient that was not

present in the food supply prior to the DSHEA or a known ingredient that has been chemically altered and the manufacturer markets it without giving prior notification to the FDA.26 If a product includes an ingredient formerly unknown to the food supply, the manufacturer must make an NDI submission to the FDA that includes premarket safety data. The agency has rejected some submissions for failure to adequately identify the ingredient or failure to provide sufficient safety information.27 For more information on premarket notification requirements for NDIs, see the FDA's online guidance.28 In addition, compilations of dietary supplement regulations are available for reference.29,30

History of Federal Dietary Supplement Regulation

The Pure Food and Drug Act of 1906 prohibited "adulterated or misbranded" products from reaching consumers. The FDCA (1938) required products to be safe, and subsequent amendments created the requirement of efficacy.14 In the 1960s and early 1970s, the FDA attempted to increase regulation of vitamin and mineral formulations under its authority to regulate special dietary foods.31 In 1966, the FDA issued regulations that created several new requirements for vitamins and mineral formulations, including the requirement that products carry a statement that "there is no scientific basis for recommending the routine use of dietary supplements."29 In response to strenuous objections, these regulations were stayed, and the agency eventually revoked them. In response to the FDA's attempts to assert its control over the dietary supplement industry, critics supported legislation that would severely limit the FDA's role in regulating dietary supplements. In 1976, amendments to the FDCA substantially limited the agency's authority to regulate the composition of dietary supplements.31

The FDA again attempted to increase regulation of dietary supplements in the 1990s. The Nutritional Labeling and Education Act (NLEA) of 1990 addressed the regulation of labeling and claims of food and food products, including dietary supplements. At that time, a review of over-the-counter products revealed a lack of safety and efficacy documentation, which meant that many dietary supplement products would have to be pulled from store shelves.14 The dietary supplement industry argued that herbs, botanicals, and their components would not have been adequately quantified on labels under the nutrition labeling rules of the NLEA.32 Further debate resulted in the Dietary Supplement Act of 1992, which delayed the NLEA and exempted dietary supplements from the purview of the legislation.

This legislative history is the backdrop for the Congress passing the DSHEA in 1994 despite strong objection from the FDA. Passage of the DSHEA established an inclusive definition of dietary supplements, which covers a wide range of products. Dietary supplements were relegated to the category of "foods," not drugs or food additives, both of which require submission of premarket safety data to the FDA. Congress specifically allowed structure/function claims that previously would have made the product a drug for regulatory purposes. This allowance placed the burden on the FDA to show that a product is unsafe after it is already being sold instead of requiring the manufacturer to demonstrate safety prior to a product's sale.31 While the legislative intent was to improve access to dietary supplements for consumers and prevent burdensome and time-consuming premarket requirements, a consequence has been that dietary supplements are less regulated than medications and food additives.

Despite the length of time that the DSHEA has been in place, several studies demonstrate that the public does not understand how dietary supplements are regulated; in particular, they believe that the FDA or another government agency approves dietary supplements before they can be sold.33 Safety considerations have led to recommending a return to more stringent regulation.34

Labeling Requirements and Claims

Labeling Requirements

The DSHEA amended the FDCA to add specific requirements for dietary supplement labels and ingredient declarations.35 The FDA has jurisdiction to promulgate rules to prevent the misbranding of dietary supplements. These rules, which have been in effect since 1999, require dietary supplements to carry a Supplement Facts label that meets specific requirements.36 Among other requirements, Daily Values must be listed for dietary ingredients present in a significant amount and for which a daily consumption value has been established. This daily reference value (ie, the Daily Value) does not necessarily reflect the Recommended Dietary Allowance (RDA) or Adequate Intake (AI) level for those nutrients that have DRIs. If no Daily Value has been established for an ingredient, the ingredient must still be listed but identified as having no such recommendation.35 The label must also contain contact information identifying a "responsible person" who can receive serious adverse event reports.37 Manufacturers must ensure that product label information is truthful and not misleading.22 For a complete description of labeling and claims requirements, see the FDA's Dietary Supplement Labeling Guide intended for industry.17

Under federal law, scientific literature from a peer-reviewed publication that is used in connection with the sale of a dietary supplement is exempt from labeling requirements if the report is reprinted in its entirety; is not false or misleading; does not promote a particular manufacturer or brand; is presented with other items on the same subject matter to give a balanced view of available scientific information; if displayed in an establishment, is physically separate from the dietary supplements; and does not have appended to it any other information.38 This provision is referred to as the third-party literature exemption, but there is no requirement that the publication be prepared by an independent party with no financial interest in the successful marketing and sale of the product.31

In addition to federal regulations, states may have additional laws regarding the labeling and sale of dietary supplements. For example, the New York State Attorney General investigated several retailers for violating New York law by falsely labeling dietary supplements and selling adulterated herbals,39 including supplements containing wheat, which could be harmful to those with wheat allergy, celiac disease, or gluten sensitivity.

Claims

Federal law allows dietary supplements to carry a variety of different types of claims. Some require approval by the FDA prior to use and some do not. All must comply with pertinent statutes and regulations. Three types of claims—nutrient content, structure/function, and health—are described

subsequently, but many other types exist. A complete description of all types may be found on the FDA's website.17

Nutrient Content Claims

Manufacturers are required to accurately describe the nutrient content of a dietary supplement. If claims regarding the content do not meet statutory requirements, the product may be deemed misbranded within the meaning of the FDCA.40 A product is misbranded if any of the following are true:

- The labeling fails to list (1) the name of each ingredient in the supplement and (2) the quantity of each ingredient or, if it contains a proprietary blend, the total quantity of all the ingredients in the blend.
- The product is a botanical product and the labeling fails to identify the part of the plant from which the ingredient is derived.
- The product is purported to conform to the specifications of an official compendium but fails to do so.
- The product fails to have the identity and strength that the supplement is represented to have or fails to meet the quality, purity, or compositional specifications based on the assay or method the supplement purports to meet.

Structure/Function Claims (Statements of Nutritional Support)

Under the FDCA, drugs are defined as articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease and articles (other than food) intended to affect the structure or any function of the body.23 However, the DSHEA specifically allows dietary supplements to make structure/function claims if they meet certain statutory criteria, including a disclaimer statement that the product is not intended to prevent or cure a disease. Before the DSHEA, herbal supplements (but not vitamin/mineral supplements) were classified as drugs if they made structure/function claims.31

These structure/function claims, or statements of nutritional support, tend to be nonspecific (eg, "helps support the immune system"). Premarket notification or approval by the FDA is not required to use these types of claims. The label can include one of these claims if either of the following is true:

- The benefit is related to a classic nutrient-deficiency disease, describes the role of the ingredient in affecting structure or function in humans, and characterizes the mechanism by which the ingredient acts to maintain such structure or function.
- The claim describes general well-being from consumption of a nutrient or dietary ingredient; the statement is truthful and not misleading and contains the following disclaimer in full: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease."41

Health Claims

A health claim is an explicit or implied characterization of a relationship between a substance and a disease or a health-related condition. This type of claim requires significant scientific agreement and must be authorized by the FDA. A health claim describes the effect a substance has on reducing the risk of or preventing a disease (eg, “calcium may reduce the risk of osteoporosis”). By contrast, a structure/function claim describes the role of a substance intended to maintain the structure or function of the body (eg, “calcium for bone and colon health”) and does not require approval by the FDA before use.42,43

As noted earlier, although homeopathic remedies (eg, cold remedies) may contain the same ingredients as a dietary supplement, they are not recognized legally as dietary supplements. Therefore, homeopathic remedies can make more specific claims about treating or curing illness than dietary supplements without having to demonstrate scientific evidence to the FDA.44

Advertising and Promotion

The FTC is responsible for ensuring that dietary supplement advertising is truthful, not misleading, and based on sound scientific evidence. The FTC publishes an Advertising Guide for Industry to assist those who sell or market dietary supplements with compliance.45 The FTC can send warning letters to companies making potentially misleading statements in their advertisements. If a clinician believes advertising is false, misleading, or without scientific proof, complaints can be filed online with the FTC (www.ftc.gov/complaint). In 2010, it was reported that over the past decade the FTC had brought more than 100 law enforcement actions challenging claims about the effectiveness of a wide variety of supplements, including cold and flu products, weight loss products, and supplements claiming to treat serious diseases, including cancer and AIDS.46 For a discussion of current actions brought by the FTC against Internet supplement advertisers, see the FTC press releases found on the FTC website.

However, despite the FTC’s role in preventing deceptive advertising, the public is inundated with marketing about dietary supplements that may not be accurate or based in science. The advertising and sale of dietary supplements on the Internet is common in today’s economy and estimated to account for at least 4% of total dietary supplement sales.47 When dietary supplement advertisements dominate search engine results, consumers and health professionals may be challenged to find resources that provide reliable information. Several sources are available (Table 19-1), and some perform better than others.48

Adolescents have been identified as a group at risk for susceptibility to questionable advertising in fashion, sports, and lifestyle magazines because they reportedly desire to improve their physical appearance or performance and because teenagers often identify with celebrities and sports figures.49 One study of advertising in magazines with a high adolescent readership showed problems with the accuracy of information about dietary supplements in these publications.46

Product Quality

The quality of dietary supplement products has long been an area of concern given the minimal regulation of dietary supplements since the passage of the DSHEA in 1994. The DSHEA gave the FDA the authority to promulgate rules to prevent dietary supplement products of poor quality.50 However, rules relating to CGMPs for dietary supplements took time to develop. The final rule governing CGMPs was published in June of 2007, but compliance dates exempted smaller manufacturers until June 2010.51,52 For a complete history of dietary supplement CGMPs, see the FDA's website.53 Prior to adoption of the final rule, general food Good Manufacturing Practices applied to dietary supplements; however, unlike foods, most dietary supplements are taken in the form of tablets, gelcaps, and capsules, which means the physiological processes involved in taking supplements can be very different from food intake.

The CGMPs require that process controls are in place at each step of the manufacturing process, regardless of whether one company or multiple firms are involved, to ensure that the product contains what it purports to contain. These controls include establishing and meeting specifications to ensure that the finished supplement contains the correct ingredient, purity, strength, and composition intended consistently and reliably each time.52 While establishing standardized CGMPs for dietary supplements is an important step in promoting product quality, the onus remains on the manufacturer to ensure that these processes are established and being followed. The FDA has limited resources to inspect manufacturing plants and products for compliance with CGMPs. However, if a violation is found, the agency can take steps to remove the offending product from the market. (See Practice Scenario 19-1 for discussion of an adulterated dietary supplement.)

Practice Scenario 19-1

Question: What steps would you take in the case of a woman who is admitted to the hospital with unexplained rapid heartbeat and high blood pressure and indicates that she used weight loss supplements in the recent past?

Scenario: A 45-year-old woman with a history of obesity and fluctuating weight is admitted for unexplained hypertension and tachycardia. She says she has used a weight loss product that is labeled "100% natural." The dietitian reviews the label and confirms the "100% natural" claim but notes that the label does not list any ingredients known to cause the patient's symptoms. A call to the hospital pharmacist identifies the product as a dietary supplement and not a drug. After searching online for further product information, the dietitian locates the US Food and Drug Administration (FDA) website and discovers that the FDA has warned consumers about tainted weight loss products containing sibutramine, a prescription medication that was taken off the market in 2010. The supplement used by this patient is one of the products identified as containing sibutramine.

Intervention: The dietitian informs the patient to stop taking the supplement and explains the rationale for stopping. The dietitian also discusses with the medical team the results of the search and the advice

given to the patient and reports the adverse event using the FDA's MedWatch Safety Information and Adverse Event Reporting Program (www.fda.gov/medwatch/report.htm).

Answer: (1) Discuss the supplement with the pharmacist. (2) Investigate supplement on the FDA's website and other reliable sites (refer to Table 19-1). (3) Communicate all information to the patient and medical team. (4) Report the adverse event on MedWatch.

Rationale: The FDA has reported incidents of weight loss products marketed as "100% natural" being adulterated with prescription medications including sibutramine, which was removed from the market in 2010 for safety reasons. Sibutramine is known to substantially increase blood pressure and/or pulse rate in some patients and may present a significant risk for patients with a history of coronary artery disease, congestive heart failure, arrhythmias, and stroke. Sibutramine may also interact with medications in a life-threatening way.

Adverse Event Reporting

In 2006, Congress amended the FDCA to require dietary supplement manufacturers to report any serious adverse events that come to their attention to the FDA.54,55 A serious adverse event is defined as an event that either results in death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect, or any event that requires a medical or surgical intervention to prevent one of these outcomes.55 If a consumer or clinician reports such an event to the manufacturer identified on the label of the suspect product, the manufacturer is bound by law to file a report of the event to the FDA through the agency's MedWatch reporting system.55 At this point, the agency can take appropriate steps to investigate the product and consider requiring the manufacturer to remove it from store shelves, if appropriate. However, submission of a serious adverse event report by a manufacturer does not constitute an admission that the product caused the event.55

Only serious events, as defined by law, require this type of reporting to the FDA. While manufacturers must keep records of both serious and nonserious events for 6 years and make them available to the FDA if the plant is inspected, nonserious events are not reported publicly for healthcare professionals to review. For example, if a product causes mild rash in many people but no hospital admissions or other serious event criteria apply, the general public is not given access to this information. Because of this reporting system and the lack of premarket testing reports, the availability of minor adverse reaction data is limited with dietary supplements. Clinicians who believe a patient's illness or injury might be related to the use of a dietary supplement should report the event directly to the FDA. Previously reported adverse events are also published on the FDA's website for review by clinicians.56

In February 2010, Senators John McCain (R-AZ) and Byron Dorgan (D-ND) introduced a bill that proposed to amend the FDCA to tighten regulation of dietary supplements on the basis that these products may pose safety risks unknown to consumers.57 While this bill did not become law, it reflected the efforts of those who believe increased regulation of dietary supplements would benefit the public. The bill would have required dietary supplement facilities to register with the FDA and obligated manufacturers to submit a compilation of all nonserious adverse events to the FDA.

Efficacy of Dietary Supplements

Given the diversity of dietary supplement ingredients, one cannot generalize about the clinical efficacy of all dietary supplements as a group. Thousands of marketed products contain countless ingredients, often in a variety of combinations. Data on efficacy vary with the individual ingredient(s) in a product. As with any therapeutic intervention, the value of a dietary supplement ingredient or a specific combination of ingredients in a dietary supplement product is based on an evaluation of known benefits and risk.

For the patients' benefit, clinicians should thoroughly and critically evaluate research data before making recommendations about incorporating a dietary supplement into clinical practice. The trials used to evaluate clinical efficacy should meet accepted criteria for a well-designed study. Well-designed clinical intervention studies provide the highest level of data to support the effectiveness of therapeutic interventions. Once published, such studies can provide information on indications, contraindications, dosing, and monitoring of a dietary supplement. Because national regulatory frameworks for dietary supplements vary, it is important to pay close attention to the description of the pharmaceutical quality of the product used in each study.

Epidemiologic data and case reports on the use of a dietary supplement ingredient are less valuable than research trial data in making clinical decisions about efficacy. Information on traditional use—including dietary patterns that include a given component—cannot necessarily be extrapolated to the use of dietary supplement ingredients in a pharmaceutical regimen. Common uses of popular dietary supplement ingredients (Tables 19-2, 19-3, and 19-4) are supported by widely varying levels of evidence. Although the body of peer-reviewed literature studying the use of individual dietary supplement ingredients or specific combinations of ingredients is growing, many marketed products are not yet supported by evidence. Differentiating the available evidence from the marketing hype is important for consumers and clinicians alike.58 Ideally, adequate efficacy data would be available to evaluate whether a dietary supplement does what the claims say it does. However, once a product is in the marketplace, a patient could choose to use it even in the absence of any supporting data. In such a case, it would be valuable to know that the product is at least reasonably safe and of high quality. (See Practice Scenario 19-2 for an example of questionable use of a dietary supplement.)

Practice Scenario 19-2

Question: What advice would you give to the medical team treating a young woman admitted with a severe Crohn's disease flare who refuses conventional medications in favor of using aloe vera?

Scenario: A 25-year-old woman with an established history of Crohn's disease, a body mass index of 17.5, and a weight loss of 10 pounds over the last 3 months is admitted to the hospital with an acute Crohn's disease flare and iron deficiency anemia. In taking her history, she tells you she is refusing anti-inflammatory medications in favor of natural dietary supplements because of the potential side effects of the medications. She is taking aloe vera on the advice of a natural medicine practitioner. The medical

team assumes taking aloe vera orally is not harmful and agrees to allow the patient a trial period of treatment with the aloe vera. The patient and team mutually agree that if her condition does not improve, the patient will try conventional medications used for treating Crohn's disease. The team asks you for information on the appropriate dosage of oral aloe vera.

Intervention: Tell the team that oral aloe vera is relatively contraindicated given the patient's current presentation.

Answer: (1) Research information on oral aloe vera use. (2) Communicate results of search to patient and team. (3) Recommend against its use in this patient.

Rationale: Aloe vera is used topically to treat minor wounds, minor burns, and other dermatological conditions. Its traditional use in oral form is for managing constipation, for which there is supporting scientific evidence. There is no convincing evidence of any benefit of oral aloe vera for inflammatory bowel disease; its use has not been compared with conventional treatments for Crohn's disease. Risks of oral aloe vera supplementation include exacerbating abdominal pain, cramping, diarrhea, and significant electrolyte imbalances. The risk of harm outweighs any potential benefit, and the medical team should be advised that oral aloe vera is not safe for this patient.

Safety of Dietary Supplements

Given the presence of biologically active ingredients, the safety issues for dietary supplements share many similarities with the issues for more closely regulated pharmaceutical products, but dietary supplements also involve a few unique safety concerns. As with other pharmaceutical products, adverse effects resulting from the intrinsic (ie, labeled) ingredients may occur. These effects may be predictable and dose-related; unexpected allergic or idiosyncratic reactions; or interactions with prescribed medication. The risk to the patient may vary by age, sex, genetics, nutritional status, conditions or disorders, and treatments. Adverse effects may influence any organ system—for example, the influence of a supplement containing kava on the liver may range from mild transient transaminitis to fulminant hepatic failure, or influence of ginkgo on the skin may range from a self-limited rash to exfoliative dermatitis.

Safety evaluation based on epidemiologic data or traditional use data may fall short of identifying or predicting potential adverse effects. The doses, matrixes, and chronicity of exposure using pharmaceutical dosage forms may mean that outcomes from using these products are unlike outcomes associated with traditional use, findings from epidemiologic data, or even results from short-term, clinical intervention trials. Unfortunately, well-designed and adequately powered clinical trials to evaluate adverse effects of dietary supplements are uncommon.59 As a result, adverse effects of dietary supplements are not as well characterized, recognized, or reported as they are with medications. When adverse effects are identified, reported, and documented, it is not always clear whether the findings can be attributed to the labeled ingredients or to poor product quality. In either case, knowledge about the

potential harm a dietary supplement may cause a patient allows for informed decision-making about the product's use. Some ingredients are recognized to have risks that outweigh benefits (Table 19-5).

TABLE 19-5 Dietary Supplement Ingredients Where Risk Outweighs Benefita

Ingredient Name	Potential Danger
Androstenedione	Carcinogenicity
Bitter orange *(Citrus aurantium)*	Cardiotoxicity, hypertension
Blue-green algae	Hepatotoxicity, neurotoxicity
Blue cohosh (*Caulophyllum thalictroides)*	Cardiotoxicity, hypertension
Calamus *(Acorus calamus)*	Carcinogenicity, nephrotoxicity
Chaparral *(Larrea tridentata)*	Hepatotoxicity
Coltsfoot *(Tussilago farfara)*	Carcinogenicity, hepatotoxicity
Comfrey (*Symphytum* spp.)	Carcinogenicity, hepatotoxicity
Dong quai *(Angelica sinensis)*	Anticoagulant, carcinogenicity
Ephedra [ma huang] *(Ephedra sinica)*[a]	Cardiotoxicity, hepatotoxicity
Germander *(Teucrium chamaedrys)*	Hepatotoxicity
Germanium	Nephrotoxicity
Kava *(Piper methysticum)*	Hepatotoxicity
Lobelia *(Lobelia inflata)*	Coma, hepatotoxicity, neurotoxicity
Pennyroyal *(Hedeoma pulegioides; Mentha pulegium)*	Multiorgan dysfunction, neurotoxicity, abortifacient
St. John's Wort *(Hypericum perforatum)*	Multiple drug interactions by interfering with liver's microsomal mixed oxidase enzyme system
Sassafras *(Sassafras albidum)*	Genotoxicity, hepatocarcinogenicity, abortifacient
Skullcap (*Scutellaria* spp.)	Hepatotoxicity
Snakeroot or boneset *(Eupatorium perfoliatum)*	Carcinogenicity, hepatotoxicity, nephrotoxicity
Valerian root *(Valeriana officinalis)*	Hepatotoxicity
Wormwood *(Artemisia absinthium)*	Neurotoxicity
Yohimbe *(Pausinystalia yohimbe)*	Cardiotoxicity

[a]Ephedra is banned for sale in the United States by the US Food and Drug Administration (FDA). All other ingredients listed in this table are commercially available in stores and pharmacies and online. Note the advisory warnings on FDA's Food and Dietary Supplement Division (http://www.fda.gov/Food/DietarySupplements).

The safety of multi-ingredient products is not always known because the study of such products has been limited.60 To determine the maximum safe levels of dietary supplement ingredients, one must account for the interindividual variability of intake of foods fortified with nutrients or other ingredients.61 This risk assessment approach can be most easily conducted for nutrient ingredients. Toxicological data on many of the plant sources of herbal ingredients are still lacking.62

In sum, the incidence of adverse effects with a dietary supplement product or ingredient is difficult to ascertain because the United States has a voluntary system of reporting that captures very few events and there is little valuable denominator data on overall use.63 Some of the best data come from poison control centers, with estimates of about 30% to 40% of referred dietary supplement exposures being associated with adverse effects.60 About one-half of calls to poison control centers concerning dietary supplement exposures described symptoms, with 62% of these considered "probably" associated with the supplement.64 Dietary supplements ranked second behind antidepressants in adverse-reaction hospitalizations following exposures as evaluated by poison control centers.65 Adverse effects related to dietary supplement interactions with medications are not always delineated, but they need to be

taken into account. Dietary supplements and herbals are a leading cause of liver injury and account for 20% of the cases of hepatotoxicity in the United States.66 Many herbals that are linked to liver injury; for example, the weight loss supplements containing green tea extracts may be associated with acute hepatitis. Multi-ingredient dietary supplements and body building supplements containing anabolic steroids that can cause hepatotoxicity are other common culprits.67

At least 43% of ambulatory adults regularly use dietary supplements concurrently with prescription medicine, but dietary supplement information is not always included in medication histories in institutional or community settings.68 Among adults using prescription drugs, 32% to 39% are also taking a dietary supplement.69,70 Among patients with 2 or more chronic medications, 44% reported use of herbal dietary supplements.65 Among women age 75 years and older using prescription medication, 60% combined them with dietary supplements.5 An estimated 12% to 45% of individuals using dietary supplement products with prescription drugs are at risk for a drug-supplement interaction, with 6% to 29% of these interactions considered potentially serious or clinically significant.71–74

Approximately 90% of dietary supplement users thought that pharmacists should routinely be checking for interactions.67 The information on documented interactions or potential interactions is limited but continues to grow.72,75 These may occur within the gastrointestinal lumen, but they are more likely occur at the level of transporters and metabolizing enzymes found in the intestinal epithelium and the liver. Many of the dietary polyphenols as well as botanicals found in dietary supplement products are substrates for—or influence expression and activity of—drug transporters and drug metabolizing enzymes.76–82 For example, soy isoflavones (eg, daidzein, genistein) can significantly upregulate 2 drug transporters and 5 enzymes.83,84 Also, catechins found in green tea can significantly influence drug transporters in enterocytes and hepatocytes.85 Nutrient transporters (eg, thiamin, folic acid) can also be reduced by polyphenols.86 Even specific probiotic strains may play a role in altering transporter function responsible for drug and nutrient absorption.87 Cautious interpretation and extrapolation from in vitro and in vivo data are necessary until more human data become available.

In contrast to prescription and nonprescription medication, dietary supplements may be associated with adverse effects that are extrinsic to the labeled ingredients. This problem relates to the quality of the product and may be caused by misidentification of the raw material or ingredients, or the presence of impurities, which may be introduced by adulteration (eg, prescription drugs), substitution (eg, different plant), or contamination (eg, heavy metals, pesticides). CGMPs are intended to reduce the likelihood of this group of adverse effects.

Plant-derived (ie, botanical) ingredients can vary widely in their chemical content, depending in part on soil and environmental conditions. Quality assurance of dietary supplement products containing botanical ingredients should take Good Agricultural Practices into account, with manufacturers requiring an independent certificate of analysis for all raw materials purchased (botanical or otherwise) that provide thorough documentation of composition including concentrations of any contaminants.88 The ability to analyze dietary supplement ingredients containing or extracted from plant sources is improving. To monitor the quality of these herbal ingredients requires validated and adopted standard assays for chemical constituents (ie, marker compounds) as well as evaluation of contaminants.89–91

Ideally, quality control methods would occur with raw materials as well as finished products.87 Any manufacturing practice that cannot confirm the identity, purity, strength, and quality of a dietary supplement product falls short of maximizing patient safety. Multiple independent testing programs that provide data on quality of dietary supplements are accessible to the public. Manufacturers may choose to submit their products for independent testing, and the results are published in reports available to consumers. However, only a small proportion of products on the market are independently tested. Independent testing programs include the US Pharmacopeia Dietary Supplement Verification Program, ConsumerLab.com, the National Sanitation Foundation, and the Natural Products Association (formerly the National Nutritional Foods Association), which offers a third-party CGMP certification program specific to dietary supplements that includes the FDA CGMP requirements. Aside from general tests and assays, many dietary supplement ingredients have officially recognized monographs in the US Pharmacopeia that can be used to better identify high-quality products.92

The Clinician's Role and Implications for Nutrition Support Practice

Open dialogue between clinicians and patients, including regular discussions with patients about their medications and dietary supplements, is vital in communicating health-related information. It is recommended that clinicians have a good working knowledge of common dietary supplements based on validated sources of information.93 One goal is to support informed decision making by the patient. Another goal is to prevent adverse outcomes associated with dietary supplement use, keeping in mind that the risk for adverse reactions is increased for individuals receiving concurrent drug therapy or undergoing surgery. The involved clinician should be willing to evaluate the dietary supplement literature and report any observed adverse effects, including interactions with other therapies, when needed.92 Of patients regularly using dietary supplements, 93% think it is important for their healthcare providers to be knowledgeable about them; however, only about half felt that their providers actually were familiar with such products.67

For a practitioner to be able to counsel patients on the use of dietary supplements, he or she first needs to be familiar with common ingredients, their safety and efficacy, and any potential interactions between the supplements and medications. Clinicians should frequently ask patients about supplement use; collect data on the patient's current or proposed use of vitamins, minerals, herbals, and other dietary supplements, including the specific regimen and the reason/indication for each product used; and carefully evaluate indications, dosing, and safety and efficacy data. The assessment of the patient's intended or current use of supplements provides the clinician an opportunity to counsel the patient on safety issues related to supplement use. Clinicians should approach the subject of supplement use with a "buyers beware" perspective. Documenting the patient's use of supplements in the health record allows practitioners to continually monitor the patient for potential adverse reactions. Patients who have taken their supplements consistently with other medications should be counseled to check with a provider before making any changes in dose or discontinuing use of the product. One study demonstrated that certain ethnic groups (eg, Asian Americans and Hispanics) may be less likely to disclose dietary supplement use to healthcare providers.69 The authors suggest that this is associated with limited English-language ability and lower socioeconomic status, which may inhibit members of these groups from seeking medical attention. Other potential influences on patient disclosure include

the responses from their healthcare provider—negative responses may discourage patients from speaking openly about supplement use.69 Deficits in consumer knowledge about dietary supplement safety, efficacy, and regulation can be significantly improved through education by clinicians.31

Given the limited evidence on safety and efficacy, clinicians have had little guidance in directing patient use of dietary supplements. Weiger et al developed a systems approach to guiding clinicians to "recommend," "accept," or "discourage" dietary supplement use.94 A recommendation for a specific dietary supplement should be based on evidence that supports its efficacy and safety. Supplement acceptance can be considered if evidence of the efficacy of the product is questionable but its safety has been established. Clinicians should discourage use of supplements when evidence demonstrate a lack of efficacy and potential harm, but they should give this advice in a professional manner to foster open communication and not cast dispersions or judgment.95

Among the oncology populations, patients may opt for alternative treatments instead of conventional therapy. Michaud and colleagues have presented an algorithm for evaluating dietary supplement use in oncology patients, which may also be applied to other medical situations.96 Oral supplement products increase the potential risk for interactions between drug and nondrug therapies for oncology patients. Under safety review, each supplement should be evaluated to identify any ingredients that may have antioxidant, anticoagulant, procoagulant, immune modulator, or hormonal properties, particularly if there are established safety concerns or known drug interactions. If the supplement potentially has any of these characteristics, the clinician should address the patient's risk level. Even if the safety concern is only hypothetical concern or based on questionable data, individuals at risk should be discouraged from using the product. If the supplement seems to pose no risk to the patient's safety, clinicians should proceed to evaluate the efficacy of the product. If there is decisive evidence for lack of efficacy, use of the product should be discouraged. If convincing evidence supports efficacy, use of the product may be recommended. When efficacy evidence is lacking or questionable, clinicians must use clinical judgment to assess whether use of the supplement is acceptable. Supplements falling into this category may warrant continued follow-up and especially close monitoring.95

AND recommends that dietetics professional consider several factors before they decide to sell supplements.97 Providers should avoid selling products that are beyond their scope of practice or are not compliant with institutional policies regarding sales and distribution of dietary supplements. They should acknowledge the patient's choice and avoid any potential bias in persuading patients to choose specific dietary supplements. Accurate and relevant educational information should be included when providing/selling dietary supplements. If the providers gain financial revenue from the sale of the product(s), they need to disclose this fact to their patients via face-to-face interaction or in written documentation that is easily understood and readily available. Information about comparable products on the market should also be presented. Legal issues, including malpractice, are a concern for providers who choose to sell dietary supplements. It is further recommended that providers have a grasp of federal and state regulations pertaining to licensure and business practices.

Recommendations for individual patients do not preclude setting institutional protocols or policies that address dietary supplements. The Joint Commission has set forth recommendations for health-system formulary implementation on the use of dietary supplements, but it is otherwise silent on specifics.

The American Society of Health-System Pharmacists (ASHP) has issued clinical practice recommendations on the use of dietary supplements in response to the increased frequency of use.98 Because of safety concerns, ASHP discourages use of supplements in situations where irrevocable consequences may occur, such as use in conjunction with immune suppression, chemotherapy, HIV infection, anticoagulation therapy, or use of hormonal contraceptives. Health-system formularies should have established criteria for inclusion of dietary supplements, and these products should undergo the same scrutiny as prescription and nonprescription medications to decrease institutional liability. ASHP suggests discontinuing use of patient self-administered dietary supplements on admission, especially as diagnostic workup continues. Allowing patient dietary supplement use during hospital admission should require documentation in the medical record, including a physician order and the supplement name. In addition, a pharmacist should review and verify the ordered supplement before dispensing it.97 The safety of hospitalized patients may be compromised if written policies about dietary supplements are inadequate.99 (See Practice Scenario 19-3 for an example of dealing with dietary supplements in an inpatient setting.)

Practice Scenario 19-3

Question: What dietary supplement would you recommend for a patient with heart failure and with history of gastric bypass surgery 5 years earlier?

Scenario: A 57-year-old man presented with new onset mild heart failure, leukopenia, and peripheral neuropathy. He reported that he had never been fully compliant with advice to take a multivitamin with minerals and a calcium supplement following his gastric bypass procedure. The team immediately ordered the oral multivitamin supplement on the hospital formulary and ordered a laboratory micronutrient panel for bariatric patients to check for deficiencies (ie, thiamin, vitamin B12, vitamin C, vitamin D, iron, copper, selenium, and zinc). The results of the panel revealed deficiencies of thiamin, copper, zinc, and vitamin D. The neurology team is concerned with the patient's neuropathy and calls the nutrition support clinician to ask whether the formulary micronutrient product contains the necessary amount of copper for repletion. The clinician checks with the pharmacy for the supplement label information and learns that the current formulary product supplied by the wholesaler to the pharmacy and dispensed contains the following:

- Vitamin A (no beta-carotene): 5000 IU
- Thiamin mononitrate: 1.5 mg
- Riboflavin: 2 mg
- Niacinamide: 20 mg
- Pyridoxine: 0.1 mg

- Calcium pantothenate: 1 mg
- Vitamin C: 37.5 mg
- Vitamin D: 400 IU

The clinician quickly realizes that this supplement is not the appropriate multivitamin/mineral product for the patient. The content of vitamin A (salt not described) exceeds the Dietary Reference Intake (DRI) of 900 mcg (5000 IU = 1500 mcg); the content of pyridoxine, pantothenic acid, and vitamin C are below the DRIs; and the form of vitamin D is not described for the dose (400 IU = 10 mcg).

Intervention: Initially, the nutrition support clinician recommends a complete therapeutic multivitamin/mineral preparation. She also investigates the product on formulary to determine the product composition and identify whether it contains adequate amounts and forms of the nutrients to replete the identified deficiencies. Additionally, she considers the costs and benefits of repleting individual deficiencies using single ingredient products of appropriate dose and salt.

Answer: (1) Identify a therapeutic multivitamin/mineral product containing adequate amounts to meet the patient's specific needs. (2) Communicate the information to the patient and the team. (3) Consider approaching the institution to add this standardized product to the formulary, knowing that patients with certain nutrient deficiencies may require amounts greater than the DRI.

Rationale: The composition of the formulary oral micronutrient supplement did not meet the patient's needs. The patient was deficient in copper, which the supplement available on formulary did not contain. An individual oral copper supplement containing 2 to 8 mg of copper that is not the sulfide or oxide forms would be most appropriate. A set of criteria for selecting an appropriate multivitamin/mineral product should be determined and shared with the purchasing officer.

Summary

The popularity of dietary supplement products containing nutrient, herbal, and/or other ingredients remains unabated. The well-informed nutrition support clinician understands what constitutes a dietary supplement and how these products are regulated. Whenever required to do so, the responsible clinician will determine clinical effectiveness and safety of specific dietary supplement ingredients through a careful review of evidence-based compilations and the primary literature. Patients should be supported in making fully informed decisions about dietary supplements.