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AUTHOR

Cynthia Sheppard Solomon, BSPharm, RPh, FASCP, NCTTP, Clinical Assistant Professor, Internal Medicine and Neurology, Wright State University Boonshoft School of Medicine, Dayton, OH

PEER REVIEWER

Brian Hocum, PharmD, Adjunct Faculty, Washington State University College of Pharmacy, Spokane

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RELIAS MEDIA

Homeopathic Remedies and Dietary Supplements in 2018: Weighing Benefits and Risks

Myth or Fact?

"Even though a supplement or homeopathic prep may not help, at least it won't hurt…?"

Reaching for supplements or a readily available homeopathic preparation sounds easy. However, despite a lot of promotion and hype, these products may not provide the answer to better health, and in fact, some may be dangerous. Today, many patients seek to improve their health through supplementation and healthy remedies, not realizing that some products may have harmful characteristics, may interact with prescription or over-the-counter medications, may be contaminated or adulterated, and may not provide promoted benefits. Yet, more than half of Americans are choosing to use supplements, either daily or occasionally. Healthcare professionals must strive to understand how to assist patients in making decisions about healthier living, including providing them with accurate, factual advice on dietary supplements and homeopathic preparations.

By making a commitment to learn techniques for gathering facts, then passing along relevant evidence to patients, clinicians can effectively build a trusted partnership with their patients. Clinicians need to be able to identify where a product falls on the spectrum of fact vs. fiction before having a conversation about the product with patients. First, healthcare professionals should seek credible information on products, especially evidence-based research, if it exists. This may involve collecting information during or after the patient's appointment.

Active biological substances often have both beneficial and harmful characteristics. Despite the heavy promotion of safety associated with health-focused products, ingredients in both dietary supplements and homeopathic products are not necessarily innocuous. Clinicians should provide honest expression of the facts, weighing the benefit vs. risk with each product. Blanket answers, such as "at least it won't hurt," may be irresponsible, especially if the provider has not evaluated a particular therapy. Clinicians can demonstrate commitment to their patients by showing that they are willing to learn about unfamiliar supplements and to consider possible alternative treatments, as appropriate.

Dietary supplement and homeopathic product manufacturers often make little effort to identify potential interactions with prescription and over-the-counter medications, increasing the relevancy of buyer beware. Patients can

EXECUTIVE SUMMARY

More than half of Americans are using supplements or over-the-counter medications. Practitioners need to understand how their patients are using supplements and be able to provide accurate, factual advice on dietary supplements and homeopathic preparations. Consumers are bombarded with sophisticated television advertisements for a multitude of products inferring a wide range of expectations.

- Dietary supplements — which include vitamins, minerals, herbs, botanicals, and amino acids — are subject to the Dietary Supplement Health and Education Act of 1994.
- The supplements are not intended for prevention, treatment, or cure of diseases. No research reports or manufacturer-generated production reviews are required, but the U.S. Food and Drug Administration does regulate the good manufacturing practice of supplements.
- Homeopathic treatments follow the premise that small doses treat or potentially cure illness while high doses of the same substance can cause illness. The Australian National Health Medical Research Council concluded that there is no reliable evidence that homeopathic remedies are effective for any health condition.
- The Ask-Tell-Ask model from the University of California – San Francisco is a building block for asking patients open-ended questions. The National Institutes of Health Office of Dietary Supplements offers tools for developing patient-focused conversations.

protect themselves by having clinicians as advocates to clarify, make recommendations, and partner.

This article will discuss ways that primary care providers can communicate better with patients while raising their own awareness of homeopathic products, dietary supplements, and medical foods. The article will evaluate each category for benefits and risks and provide details on how to research each product for available information. Finally, the article will assess various recommendations, including examples in weight loss, energy enhancement, and performance products.

Specific Regulations

Dietary supplements, which categorically are meant to supplement the diet, are subject to the Dietary Supplement Health and Education Act of 1994 (DSHEA) — Public Law 103-417, 103rd Congress. DSHEA states that certain items fall under the category of dietary supplements, including vitamins, minerals, herbs, botanicals, and amino acids, alone or in combination, and are to be ingested. Creams, ointments, parenteral preparations, and products administered by other routes are not dietary supplements.

Dietary supplements are not intended for prevention, treatment, or cure of diseases.[1] The regulation suggests that the risk of dietary supplements is negligible, but one should not depend on them for treatment or mitigation of disease. Although no research reports or manufacturer-generated production reviews are required to be filed for market approval, the U.S. Food and Drug Administration (FDA) does regulate the good manufacturing practice of supplements.[2] However, the burden of proof lies with the U.S. government to establish false or misleading information or processes. The FDA can get involved after marketing, when a suggestion of harm occurs in a significant number of users. A manufacturer may state that a dietary supplement is useful in providing nutritional support as long as that claim does not imply disease. If a product includes a disease claim, the product is subject to regulation as a drug, with the manufacturer required to file for a new drug application, unless the claim is an authorized health claim for which the product qualifies. The Federal Trade Commission is responsible for overseeing supplement advertisements and labels.[3] Within the past several years, the FDA has tightened good manufacturing practice requirements.

In general, dietary supplement ingredients are hard to monitor, difficult to identify, and often are associated with false claims. (*See Table 1.*) There have been many confirmed reports of counterfeit and adulterated products, requiring patients to seek care in emergency departments. Since no premarketing assessment regarding content is required, heavy metals, dirt, and other extraneous substances also can be found in some products. Providers and patients can report problems with specific products to the FDA MedWatch system at 1-800-FDA-1088.

The effects of dietary supplements are difficult to monitor, as consumers often do not view them negatively, choosing to keep their use private when speaking with healthcare professionals. Historically, clinicians have not sought information from patients about intermittent or regular use of supplements when collecting medication histories. This lack of sharing can lead both patients and clinicians into sketchy territory when adverse effects or drug-herb or drug-drug interactions occur. (*See Table 2.*) Older adults commonly search the internet for information on dietary supplements. In a recent study, 80% of the 338 retail websites used to seek information on the eight most widely used supplements made at least one claim suggesting the therapy could treat, prevent, or even cure specific conditions.[4,5]

Clinicians also need to be aware of a volunteer program that evaluates quality assurance of unregulated dietary supplements. Several organizations have created verification emblems to signify that ingredients advertised on the product label actually are contained in the product in the quantities as listed. (*See Table 3.*) Although this verification does not prove safety or effectiveness, it provides assurance that buyers are purchasing products that contain the ingredients listed on the product label.

Table 1. FDA Statements on the Risks of Taking Supplements

Key areas of concern, possibly leading to harmful consequences:
- Combining supplements
- Using supplements with prescription or over-the-counter medications
- Substituting supplements for prescription medicines
- Taking too much of certain supplements, including vitamin A, vitamin D, or iron
- Taking supplements at the time of surgeries

Ways to be a smart supplement shopper:
- When searching for supplements on the internet, use noncommercial sites (e.g., NIH, FDA, USDA) rather than depending on information from sellers.
- If claims sound too good to be true, they probably are. Be mindful of terms like "works better than," "totally safe," and "no side effects."
- "Natural" does not always mean safe.
- Ask a clinician if the supplement you are considering would be safe and beneficial for you.

Source: National Institutes of Health. Office of Dietary Supplements. Dietary supplements: What you need to know. Available at: https://ods.od.nih.gov/HealthInformation/DS_WhatYouNeedToKnow.aspx. Accessed Nov. 6, 2018.

Homeopathic Preparations

Samuel Hahnemann, a German physician in the late 1700s, is considered the father of homeopathy. Discouraged by medical methods such as bloodletting and purging, Hahnemann gave up his clinical practice, and chose to translate medical and scientific textbooks for a living. He found a medical text touting treatment with substances that might cause disease in a healthy person when given in high doses, but that could be used to treat the same illness when given in small amounts. The concept of "let likes be cured by likes" had been studied since early Greek times.[6] Hahnemann was determined to experience this phenomenon by ingesting cinchona tree bark (quinine), causing fever, chills, and diarrhea, which was malaria-like. He believed this process could cure many diseases.[7] Over the next several decades, many followers practiced these experiments, trying to meld them into orthodox medical practice.

Homeopathic treatments follow the premise that small doses of certain substances treat illness and potentially cure disease, while high doses of the same substance cause illness. (*See Table 4.*) Ingredients may include poisons (i.e., white arsenic), plants (i.e., poison ivy), heavy metals, crushed whole bugs, and other unique substances. Homeopathic products do not have to be ingested. Some can be found as ointments, sublingual tablets, injections, drops, gels, creams, and tablets. Production usually includes dilutions in tinctures of alcohol or purified water solutions,[8] with specific nomenclature (one 10th dilution is identified as 1x). Remedies often follow product categories, such as respiratory, otolaryngology, musculoskeletal, and pain disorders. Prescription and over-the-counter products exist.

Homeopathic regulations originated with the Federal Food, Drug, and Cosmetic Act of 1938. Remedies were allowed to be marketed without FDA safety and efficacy evaluation. If a homeopathic product was recommended for treatment of a serious disease, such as cancer, it would be sold by prescription.[8] Generally speaking, there is little evidence to support the effectiveness of any homeopathic remedy for specific treatments.[8] The safety of these products, often found as mixtures, is not clear. Often, toxic ingredients are included, supposedly in very small quantities, although that is not always the case. When substantial amounts of active ingredients are used instead of very small amounts, the potential for side effects, drug interactions, and poisoning increases. In the past decade, homeopathic ingredients have been found in higher quantities than advertised on packages.

Homeopathic agents must be listed in the Homeopathic Pharmacopeia of the United States (HPUS). The HPUS Compliance Policy Guide currently identifies the regulatory framework, including which ingredients are considered prescription and which are over-the-counter. Of some 1,350 drugs listed in the HPUS, about 440 are prescription in some form or potency.[9] One example of a homeopathic injection that currently is available only as a prescription is Zeel Solution, which is a mixture of 15 homeopathic medications in dilution.[10] Being listed in the HPUS does not extrapolate into significant safety and effectiveness. Ingredients can come from plants (i.e., poison ivy, onion varieties, or belladonna), minerals (i.e., white arsenic), or animals (i.e., cobra venom or crushed whole bees), and can be administered by mouth or injection or applied topically in forms like creams, balms, gels, or nasal sprays. Originally, the FDA exempted homeopathic preparations from premarket analysis, as long as the ingredients were listed in the HPUS and followed the stated procedures for strength, quality, and purity.[11] Early on, products were not too numerous, and use was not widely popular. However, in the past several decades, use has increased substantially, as has concern for the safety of increasingly numerous products. Users of homeopathy often choose to self-prescribe for colds or musculoskeletal pain,[11] and thus, may have adverse side effects. By 2016, the Federal Trade Commission required safety and efficacy claims in this group of products, similar to over-the-counter, FDA-approved drugs. It also required that manufacturers be able to substantiate health claims made about their products.[8]

Now with a market share greater than $3 billion, this group of products is no longer an outlying small subset. Recent studies, including those published in the *British Medical Journal* and the Cochrane Database of

Systematic Reviews, as well as research from Harvard University, have found no better efficacy than placebo effect, even when more than 60 studies were evaluated.

Example of Issues Associated With a Homeopathic Remedy

L.O., a 10-year-old female with asthma, currently takes an asthma preparation that contains arsenic album, ipecac, Sambucus nigra, and Lobelia inflate, as necessary, for cough and inability to breathe, especially at night. The child had the product with her at school. When she presented to the school nurse after being unable to breathe easily in class, the nurse had concerns about whether the product was beneficial for the condition. Because the child was not breathing well on her own, was coughing, and gasped for breath, she was taken to the local emergency department for evaluation, where clinicians assisted the parents in making preventive and acute changes in therapies. The parents discontinued the original treatment.

This product contains:

- aqueous arsenic trioxide dilution — creating "arsenic album," often used in homeopathic mixtures for digestive disorders, food poisoning, insomnia, allergies, anxiety, depression, and obsessive-compulsive disorder;
- Ipecac;
- *Sambucus nigra* (elderberry);
- *Lobelia inflata* — puke weed (Indian tobacco): taken by mouth; side effects include nausea, vomiting, diarrhea, cough, dizziness, tremors, tachycardia, dramatic hypotension, coma, death.[12]

The National Center for Complementary and Integrative Health noted that little evidence exists to support homeopathic claims where side effects and drug interactions are commonly seen, especially when excessive amounts (more than the tiniest quantities) of active ingredients are found.[8] Such is the case involving 10 infant deaths from homeopathic teething products in the fall of 2016 and into the spring of 2017. The FDA concluded the manufacturer had mislabeled the amount of belladonna alkaloids in several teething tablets and gels. Both scopolamine and hyoscyamine are chemicals found in belladonna (deadly nightshade). After the FDA issued instructions about discontinuing treatment with this dangerous substance, the manufacturer decided it would no longer sell and distribute its products in the United States.[13]

In December 2017, after alerting consumers to toxic ingredients, such as the case of high levels of belladonna in baby teething homeopathic remedies, the FDA proposed a new risk-based enforcement approach to homeopathic remedies initiating closer scrutiny of substances with the greatest potential risk.[8,14,15] The alert focused on safety concerns for vulnerable populations; products not meeting legal standards for quality, strength, or purity; and products unproven but intended to treat serious diseases/conditions.

In 2015, the Australian National Health Medical Research Council concluded there is no reliable evidence that homeopathic remedies are effective for any health condition.[8]

Some products labeled as homeopathic may not comply with the definition. In 2012, authors of a systematic review demonstrated that many homeopathic products containing ingredients such as heavy metals (like iron or mercury) may not be diluted, and these higher doses may cause serious adverse effects.[8]

Table 2. Potential Interactions Between Dietary Supplements or Homeopathic Preparations and Prescription Products

Some herbal ingredients implicated for potential risk:[44,45]

- Flaxseed
- Evening primrose oil
- St. John's wort
- Peppermint
- Senna
- Echinacea
- Hawthorn
- Green tea
- *Ginkgo biloba*

Five dietary supplements of concern for potential interactions:[44]

- Glucosamine
- Cod liver oil
- Omega-3 fish oil
- Calcium carbonate
- Multivitamins

Adverse effects of homeopathy:[6,8,11]

- Some products may not be diluted as stated on the label, and may contain larger quantities of toxic substances, causing side effects or drug interactions.
- Taking remedies containing heavy metals, such as mercury or iron, that are not highly diluted or replacing an effective conventional treatment with an ineffective homeopathic product can cause adverse effects.
- Liquid homeopathic products may contain alcohol at higher levels than conventional FDA-approved drug products.
- Homeopathic aggravation, which is a temporary worsening of existing symptoms after taking a preparation, can occur.
- Check for specific warnings from the FDA regarding remedies that have been problematic and have been found to be harmful.
- Do not replace conventional immunizations with homeopathic ones.

Table 3. Verification Symbols for Quality Assurance

Verification marks from the three organizations below ensure that an independent group has evaluated the product to confirm that ingredients listed on the label are in the bottle in the amounts listed. However, it does not ensure safety or efficacy. For example, when the verification mark from the U.S. Pharmacopeia (USP) is displayed, it shows that the manufacturer has submitted a product for evaluation voluntarily.

- Consumer Lab: www.ConsumerLab.com
- The US Pharmacopeia: www.USP.org
- National Science Foundation: www.nsf.org

Table 4. Differences Between Homeopathic Medicines and Dietary Supplements

- Homeopathic medicines are regulated as drugs, according to the Federal Food, Drug and Cosmetic Act. Over-the-counter homeopathic products must have a therapeutic indication (for self-limiting, self-diagnosable condition) on the product label.
- Dietary supplements are regulated by the Dietary Supplement Health and Education Act (DSHEA). These products cannot make claims for the diagnosis, relief, cure, or mitigation of symptoms of an illness.
- Both categories of products may have little proof of safety or efficacy associated with their use.

Source: Consumer Healthcare Products Association. Facts About Homeopathic Medicine. Available at: https://www.chpa.org/homeopathic.aspx. Accessed Nov. 6, 2018.

Case Report

A 40-year-old Hispanic male has a diagnosis of osteoarthritis (OA) based on the American College of Rheumatology criteria, with a visual analog scale pain rating of 7–9 five days per week. He has patellofemoral pain syndrome on radiograph, no history of secondary OA, and is 15 pounds overweight. He is a smoker and has stage 1 hypertension; his blood pressure at home this week was 144/94 mmHg. He takes acetaminophen or Percocet every 6 to 8 hours, enalapril, and hydrochlorothiazide. He has been taking "Botany Bay" to relax when the pain is bad, but he says it is no longer easy to purchase on the internet.

The clinician's first step is to identify the ingredients in Botany Bay to learn what this patient is using. An internet search led to a Reuters report from Feb. 21, 2018, stating that the FDA recalled certain kratom-containing dietary supplements distributed under several brand names, all made by one manufacturer.[16,17] Kratom is an ingredient in Botany Bay, and it was listed on an import alert on dietary supplements. The FDA implemented a kratom purge after a *Salmonella* outbreak.[17] The FDA recalled products containing the increasingly popular opioid-like substance, and indicated that kratom-containing dietary supplements manufactured by a Missouri company were destroyed.[17]

Kratom (*Mitragyna speciosa*) is a tropical tree that is native to Southeast Asia.[18] Kratom often is promoted misleadingly to ease pain and reduce symptoms of opioid withdrawal.[18] It contains compounds with psychotropic effects and can be found listed as Thom, Biak, Ketum, Kakuam, Ithang, and others. Kratom can act similarly to opioids and stimulants, causing sedation, pleasure, and, at times, a decreased pain effect. No evidence of efficacy currently exists. Kratom currently is not an illegal Schedule 1 drug, and often is sold as a dietary supplement. Shown to have additive effects similar to morphine, kratom can lead to addiction and death. The FDA has data on numerous deaths, and acknowledges there is no therapeutic benefit as a dietary supplement. Although the FDA has not completely banned kratom, the agency issued a series of warnings in 2017. Kratom has been associated with at least 44 deaths, many related to adulterated or contaminated products or its use in combination with illicit drugs, benzodiazepines, opioids, alcohol, and other medications, including cough syrups.[18]

The FDA and the Centers for Disease Control and Prevention continued to follow this alert for months after the original press release. The number of products recalled had spread to multiple manufacturers.[19] A June 29, 2018, update suggested the FDA's outbreak investigation had concluded. The FDA reminded consumers that raw products contaminated with *Salmonella* can make people sick and advised consumers to avoid kratom.[19]

By accessing updated information about products in a timely way, the clinician can identify problems and immediately discuss ingredients with patients. Clinicians can search for product information by combining the proprietary product name with the word "supplement" in a search engine.

The FDA can issue warnings or recall products when it can identify toxic ingredients that are confirmed by reports of harm, or when instances of contamination, adulteration, or counterfeit ingredients are involved. This does not always mean that people stop purchasing the products via the internet or in illicit trade. In fact, persistent consumers often can continue to access toxic substances that have been banned or restricted by the FDA. In recent years, FDA has pulled kratom, DMAA (1,3-dimethylamylamine), kava kava, contaminated probiotics, and other products found to create undue harm.[20] Despite a ban initiated in 2013, DMAA was identified in an August 2018 FDA warning as a substance marketed in dietary supplements. In the case of kratom, when the manufacturer refused to voluntarily

withdraw the products, the FDA used its authority under the Food Safety Modernization Act to issue a mandatory recall order to protect U.S. consumers from contaminated food products. In addition, the FDA deemed kratom a "drug sold outside the FDA approval process."

Communicating With Patients

The Ask-Tell-Ask model from the University of California at San Francisco is a building block of primary care. Asking open-ended questions and assessing patients' existing knowledge prior to sharing new information can be helpful and successful when identifying and collecting patient information on supplement use. The technique allows clinicians to ask patients what they are willing to do, thus achieving positive health-focused goals.[21]

Before discussing remedies and supplements with patients, it is helpful for providers to know where they stand on supplement use. Many clinicians have not had special training on these types of products and may not recognize the ingredients or specific issues the patient is trying to address. Consequently, providers may be uncomfortable when patients raise the issue. Identifying individual implicit bias and working to address the bias can enlighten clinicians and allow for productive conversations with patients about specific concerns and desires. The majority of patients use at least one integrative care product or supplement, but do not disclose this use to their physicians. Clinicians can affect the patient exchange positively by being fair-balanced, open-minded, and honest in assisting patients with questions about supplement use. Motivational interviewing may be effective when communicating with patients about risks and benefits of various therapies.

Communicating Risks and Benefits

The Office of Dietary Supplements within the National Institutes of Health offers tools for developing patient-focused conversations about these products at www.ods.od.nih.gov.

Clinicians can raise the trust level in the patient-physician partnership by asking patients why they are considering a particular remedy and helping them recognize benefits and risks, interactions, or contraindications. Existing diseases or conditions, such as diabetes, heart disease, hypertension, atrial fibrillation, or pregnancy, can make the difference in how these topics are addressed.

Patients will benefit from understanding that many product claims are exaggerated. Often, the "miracle" products can have hidden or unexpected interactions. Potential harm can occur from the large "mega" doses sometimes recommended by manufacturers or "guru clinicians" who are pushing certain products. Patients need to know the importance of having limits on dosing — more is not necessarily better, and, in fact, small amounts may be just right for good health. Unlike the marketing for dietary supplements, marketing for homeopathic remedies promotes that the products contain tiny doses of active ingredients. However, the actual preparations can contain much larger doses of potentially harmful ingredients.

Consumers should not exceed recommended daily allowances of vitamins or minerals such as vitamin D or calcium. New data from the U.S. Preventive Services Task Force confirms that there is insufficient evidence to assess the balance of benefits and harms for men, premenopausal women, and postmenopausal women to use calcium and vitamin D supplements to prevent fractures.[22]

The use of high-dose vitamin C to prevent colds actually can cause serious problems with kidney stones or gastrointestinal ulceration. Only 65 to 90 mg a day is needed to protect the immune system. In this case, more is not better. Older patients or children taking chewable multivitamins always should rinse out their mouths after chewing tablets that contain vitamin C, as it can remove tooth enamel.

Products may not always be what they seem. Several studies have tested protein supplements for content and found significant heavy metal contamination. Arsenic, cadmium, lead, and mercury have been reported in numerous popular protein supplements, contributing to the concerns of adulteration and contamination of products, which are not evaluated by a governmental agency prior to marketing.[23] Thinking protein shakes are a great snack, patients may regret their choice when they begin to feel lethargic and fatigued, a sign of heavy metal toxicity, after long-term regular use.

Several widely publicized male performance enhancement products contain proprietary mixtures of dozens of substances. The mix may have a specific name, making it very difficult to know the actual contents. Several of these products have been documented to include testosterone-like or Viagra-like substances, or they may include other harmful substances, banned drugs, or FDA-approved prescription products in violation of DSHEA. When a patient already takes a prescription product such as sildenafil, the possibility of drug interactions occurring with supplements increases.

Supplements for Daily or Intermittent Use

The American Cancer Society Nutrition and Physical Activity Guidelines suggest there is no evidence that phytochemicals taken as supplements are as beneficial for long-term human health as the vegetables, fruits, beans, and grains from which they are extracted.[24]

But for some, perhaps older adults, calcium, vitamin D, or vitamin B12 might be helpful when the daily diet is not consistent or nutritious. Providers should review the latest meta-analyses and updates on new research. If patients have special issues, allergies, or other health concerns, they may be candidates for multivitamins or an added amount of some ingredient, such as fiber. Clinicians should discuss these items with patients to determine individual benefit.

Dietary supplement advertisements or product labels that promote a specific disease treatment are cause for concern. Replacing already proven prescription medications used to treat common illnesses with unproven dietary supplements can increase

health risks. Substituting a dietary supplement advertised as potassium chloride for the prescription potassium chloride can cause significant harm to patients because the two products are not equivalent. If cost is an issue, accessing affordable medication assistance programs can make a difference. There may be many patients in a clinical practice with hidden needs. The healthcare team should constantly assess opportunities to personalize the approach.

Supplements such as ginseng or glucosamine may manipulate blood glucose levels or other conditions, making a person with chronic illness more vulnerable. Advertisements that promote supplements as curing or treating chronic illness or a medical condition usually have not been evaluated for that claim. If the ingredient or product has been shown to have some special ability to cure, mitigate, or treat an illness, the dietary supplement manufacturer would have to file a new drug application with the FDA. FDA procedures for drug approval, including safety and efficacy, require significant review of these substances. Dietary supplements and herbs are not to be used as treatments. Although general health claims are allowed, medical claims are not.

Research of homeopathic preparations has shown that active ingredients may be diluted so greatly that it is difficult to extract and identify them in the lab. Products in this category often are found on store shelves beside FDA-approved over-the-counter drugs, contributing to misleading perceptions about effectiveness. According to the Federal Trade Commission, "homeopathic product claims are not based on modern scientific methods."[8,25]

Omega-3 polyunsaturated fatty acid dietary supplements include a combination of eicosapentaenoic acid (EPA) and docosapentaenoic acid (DPA), which are found in many fatty fish. Omega-3 prescription products often are recommended for patients with high triglyceride blood levels. The theory of benefit in heart disease has been studied in large randomized, controlled studies, including a recent Cochrane review.[26] Increasing doses of EPA and docosahexaenoic acid have not been shown to make a difference in cardiovascular death, coronary deaths or events, stroke, or heart irregularities. Although there appears to be some benefit in patients with high triglyceride levels, the combination of ECA and DPA has been associated with increased low-density lipoprotein levels.[26] Recent preliminary findings are interesting in patients with mild anxiety taking omega-3 fatty acids. Although these studies have shown no effect in moderate or severe anxiety, there continues to be ongoing research with the use of higher doses.

Eating garlic in bulb form or taking an added supplement of allicin (the active ingredient in garlic) each day has not been shown to achieve the theoretical benefits of garlic.[27] The dose needed to show benefit is more than a person reasonably can eat and likely will create severe abdominal problems, including nausea. No garlic supplement has been shown to provide cholesterol-lowering or other immune benefits in randomized, controlled trials. There is a clear risk of bleeding when garlic is combined with warfarin or other herbs, such as *Gingko biloba*, which has blood-thinning qualities.[28] Garlic supplements also have been associated with decreasing the effectiveness of HIV medications.

Probiotics have been the subject of significant questions regarding efficacy and contamination. In 2014, a newborn in a Connecticut hospital received a contaminated probiotic while being treated per hospital protocol. The infant acquired necrotizing enterocolitis and died. Although the proprietary mix was supposed to contain three live strains of bacteria, it also contained the mold *Rhizopus oryzae*. Little evidence currently exists to demonstrate significant benefit associated with treating infants with probiotics.[29] After the infant died, health officials formally issued a warning to use caution in children's use of probiotic supplementation. For healthy adults, consuming yogurt with live cultures may provide adequate nutritional benefits. However, the FDA warned healthcare providers about using dietary supplements containing live bacteria or yeast in patients with compromised immune systems.[29] Dietary supplements are not subject to FDA's premarket review or approval requirements for safety and effectiveness nor to the agency's rigorous manufacturing and testing standards for drugs, including testing for extraneous organisms. However, the FDA is aware that in the practice of medicine, some providers recommend products that are marketed as dietary supplements for use as drugs (e.g., to treat, mitigate, cure, or prevent a disease or condition) even though the products are not evaluated as such.[30]

Cinnamon (active component: cinnamaldehyde) has been touted for lowering blood sugar and reducing lipid levels at a daily dose of 1 to 6 grams.[31] However, these results have not been replicated.

Performance Enhancers

Coaches and trainers may recommend supplements to athletes to boost their abilities to perform.[32] However, these supplements may cause serious consequences, and in many cases, have been shown to contain toxic contaminants.[33] Illicit drugs, banned substances, and prescription ingredients may be found in varying quantities to help boost metabolism or increase hormone levels. Healthcare professionals should consider the complexities of performance enhancers, their physiologic and psychotropic effects, and potential interactions. The hype of supplement labels and internet promotion to enhance metabolism[34] motivates users to choose popular performance supplements, even combining them for similar effects.[35] The negative acute and long-term effects are well documented, sometimes leading to deadly heart and respiratory consequences.[36]

Products marketed to improve strength or endurance commonly are adulterated. Monitoring current FDA alerts is critical. Caffeine and caffeine-like substances are a type of potentially harmful ingredient that boosts metabolism and is an amphetamine-like alternative that can cause tachycardia, irritability, coma, and death. Powdered caffeine products have a narrow range of positive effects, and it does not take much powder to cause death.[37]

Weight Loss, Energy, and Performance

Amino acids, protein, creatine, caffeine, and caffeine-like amphetamine alternatives can boost metabolism while they increase the heart rate and respiratory rate and generally affect multiple organ systems. Chromium, promoted for weight loss, can increase metabolism. However, claims that patients taking it can eat anything and still lose weight are not true. To lose and maintain weight, eating fewer calories and increasing activity are the keys. At doses of 200 mcg per day, chromium is associated with heightened lung cancer risk.[24]

Bitter orange, an ephedra alternative, has been found to contain synephrine, which increases heart rate while raising blood pressure. Bodybuilding products containing DMAA, an illegal ingredient similar to bitter orange and ephedra and touted as a natural stimulant, cause great concern when patients take them alone or with caffeine or caffeine alternatives. In 2012, a marathon runner died after consuming a powder containing DMAA. Inadequate oversight, along with internet sales to consumers wanting to try hyped substances, puts patients at risk.

Homeopathy and Supplementation

Treating migraine headaches, cramps, neuralgia, and other chronic problems, such as lower back or shoulder pain, can be very challenging. Treating pain is one of the target categories for homeopathic remedies. For centuries, homeopathic remedies in China and India have contained ingredients such as cobra venom.[38,39] In 1939, the *New England Journal of Medicine* published the first article discussing the use of cobra venom in the relief of intractable pain.[40] Cobra venom is a neurotoxin and paralyzes respiratory muscles.[40] Researchers are continuing to investigate various mechanisms to reduce pain by administering venoms from different snake species.[41]

Another area of contention regarding dietary supplements is using them for treating concussions. Online advertisements for preventing concussions, reducing the effects of concussions, or improving recovery from concussions have increased in the past five years, with manufacturers overstepping regulations to suggest benefit. Many of the products include ingredients with skullcap, curcumin, creatine, and vitamins C, D, and E. Additionally, resveratrol, omega-3 fatty acids, and melatonin have been studied in animals or are under investigation for possible benefits. Several studies in humans are underway, but are not yet complete.[42,43] These therapies should not replace a focused evaluation of a concussion by a healthcare professional using conventional treatments recommended to achieve a full recovery.

A recent conclusion of a study on drug-supplement interactions in older adults suggested that primary care providers routinely should ask questions of patients about use of supplements and herbs to mediate and avoid potential interactions with prescription medications.[44] Medication-related problems are more common among older adults because of comorbidities and reduced clearance of pharmacologically active compounds.[44,45] In a recent cross-sectional survey, an estimated one out of three persons was at risk of potential drug-supplement interactions.[45] Some of the most common supplements associated with potential interactions are calcium, vitamin D3, peppermint, St. John's wort, glucosamine, omega-3 fish oil, and *Ginkgo biloba*. Clinicians can affect outcomes positively by recommending patients discontinue unnecessary therapies with which significant interactions and adverse effects are likely.

Medical Foods

Medical foods are specially formulated for the dietary management of a disease that has distinctive nutritional needs not met by diet alone. Intended

Table 5. Additional Resources

BeSafeRx
https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/buyingmedicinesovertheinternet/besaferxknowyouronlinepharmacy/default.htm

National Center for Complementary and Integrative Health
https://nccih.nih.gov/

National Institute on Aging
www.nia.nih.gov

Office of Dietary Supplements
www.ods.od.nih.gov/factsheets/list-all

U.S. Food and Drug Administration
www.fda.gov

National Institutes of Health
www.nih.gov

Cochrane Library
www.cochranelibrary.com

American Pharmacists Association
www.pharmacist.com

Dietary Supplement Health and Education Act of 1994
https://ods.od.nih.gov/About/DSHEA_Wording.aspx.

to be used under physician supervision, medical foods are not registered with, reviewed by, or approved by the FDA.

Case

E.G. is a 74-year-old female with seasonal rhinitis, dyslipidemia, OA in her fingers and wrists, and hemorrhoids. She takes fluticasone nasal spray BID, celecoxib 100 mg BID, atorvastatin 10 mg QD, and pramosone ointment as needed for hemorrhoids. Three weeks ago, she began experiencing yellowing of her skin, increased blood pressure, forgetfulness, and elevated liver transaminase levels. She states that nothing has changed in her life, but that she is taking a food recommended by her rheumatologist and she needs to call the pharmacist for more. The patient still had the prescription bottle, which identified the medical food as limbrel/flavocoxid, a plant blend probably containing cyclooxygenase (COX)-1 and COX-2 inhibitors. The mixture contains baicalin and catechin flavonoids, which elevate serum aminotransferase and can cause acute liver toxicity and acute hepatitis with jaundice.

The FDA banned limbrel/flavocoxid in December 2017, as a result of cases of reported acute liver toxicity. The proprietary mixture of plants and herbs includes *Scutellaria baicalensis* (skullcap) and *Acacia catechu* (catechin), both of which are linked to acute liver toxicity.[46,47]

The flavocoxid case demonstrates that some patients do not consider a medical food worthy of sharing, which is understandable. Questioning can enlighten both the physician and the patient and greatly clarify the situation. Patients always should be coached to bring all medication bottles, along with any products they take daily or occasionally for their health.

Summary

Dietary supplements and homeopathic remedies are here to stay. Additional investigation is needed, but the majority of these manufacturers do not pay for research efforts. Instead, the National Institutes of Health, foundations, independent agencies, and nongovernmental organizations cover the costs. Many powerful lobbies and wealthy manufacturers are helping to support the myths.

Primary care providers should be aware of the FDA website BeSafeRx, which is an online campaign to identify and avoid fraudulent online pharmacies. See Table 5 for a list of websites that may be helpful to clinicians. In addition, it is important to check supplement verification systems such as U.S. Pharmacopeia, NSF International, and Consumer Lab, as well as look for the VeriSign seal when confirming valid online pharmacies. It is important that providers learn as much as possible and be aware of the gaps in understanding about many of these substances. By implementing these strategies, providers can help ensure positive outcomes possible and trusting relationships with their patients.

Sources of Dependable Information

Registered pharmacists can serve as key partners in the search for credible, accurate information on remedies and supplements. Patients should avoid purchasing from online sources unless the site includes the VeriSign seal, indicating it complies with U.S. federal drug and pharmacy laws. The FDA advises against conducting blind searches on the internet. Clinicians should connect to respected organizations; look at clinical guidelines and review randomized, controlled trials; and perform online searches of federal agency sites, academic associations, and Google scholar to make decisions regarding worthiness of treatments. Using modern techniques of motivational interviewing and ask-tell-ask, clinicians can elevate the partnership tremendously.

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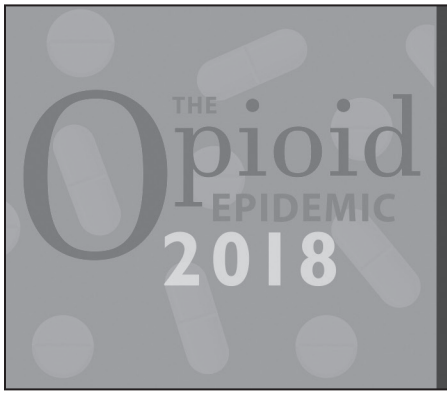

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CME Questions

1. Which of the following is *not* part of dietary supplement regulations, as stipulated by the Dietary Supplement Health and Education Act?
   a. The FDA is not required to evaluate pre-marketing research collected from manufacturers for their specific products.
   b. The Federal Trade Commission, overseeing the product label, assures purity and strength of the active ingredients.
   c. Dietary supplements are exclusively taken by mouth, and are not injected or topically applied.
   d. Good manufacturing practices must be followed by manufacturers, but FDA approval is not required prior to bringing the product to market.
2. Healthcare professionals can assist patients to make healthy decisions about dietary supplements and homeopathic remedies in all but which of the following?
   a. By being able to discuss various options factually and honestly with patients
   b. Making decisions for the patient to save him/her from being confused about the benefits and risks of each possible type of product
   c. Choosing to investigate a preparation the patient is considering, even when the name or ingredient is not common or familiar
   d. Discussing the concepts of risk vs. benefit with the patient, confirming and verifying they understand the recommendations to achieve the best outcome
3. Dietary supplement-drug interactions in patients with chronic illness are difficult to identify because:
   a. general information about many supplements is often deficient and is sometimes reported only in case reports highlighting harm or in commercial advertisements.
   b. little may be known about some of the proprietary blends unless an investigation is done to identify each ingredient in the mix.
   c. ingredients in dietary supplements sometimes include substances that are not listed on the label, making the product contaminated or adulterated.
   d. All of the above.
4. According to an FDA-issued special warning to clinicians, when should probiotics containing live bacteria or yeasts be avoided?
   a. In children between 6 and 12 years of age
   b. In healthy adults
   c. When patients of any age have a compromised immune system
   d. All of the above
5. Homeopathic preparations, often mixed with purified water or alcohol, then diluted, may contain which of the following?
   a. Poison ivy
   b. Arsenic varieties
   c. Cobra venom
   d. All of the above
6. Which of the following is a way to successfully research specific ingredients in dietary supplements or homeopathic remedies?
   a. Gather recent newspaper clippings to show patients why they should not have taken the product without discussing it with you.
   b. Use government websites, ask a local pharmacist to assist, and find internet resources to identify more about the special characteristics of the product.
   c. Buy the preparation based on the information on the supplement label.
   d. Find a product in a local store and ask sales staff to clarify any questions.
7. To best serve patients contemplating using homeopathic products or dietary supplements, which of the following is *not* true?
   a. It is helpful for patients to feel their views are heard and accepted.
   b. Providing factual information can be helpful if given in a non-judgmental way.
   c. Offering to help them get more information can be beneficial.
   d. Helping to alert them to hazards or potential harm by scaring them can be very effective.

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