

Underregulated Supplements

May 2022, Volume 24, Number 5: E343-451

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CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

Should Clinicians Ever Recommend Supplements to Patients Trying to Lose Weight?

Melinda M. Manore, PhD, RDN and Megan Patton-Lopez, PhD, RDN

Abstract

Helping patients lose weight can mitigate their risk of chronic disease and improve their quality of life. Over-the-counter dietary supplements for weight loss, however, are not reviewed or approved for safety or efficacy, nor does evidence support their clinical use. This commentary on a case suggests 3 reasons why clinicians cannot ethically recommend these supplements to patients: these products' safety and efficacy are unknown, ingredient lists might not be complete, and advertising could be misleading. This article reviews facts clinicians should know regarding over-the-counter weight loss products and explains how they can support, educate, and promote culturally and individually sensitive weight-management strategies.

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Case

Ms S is a 42-year-old Latina woman with a body mass index (BMI) of 30.2 kg/m² and a long history of dieting for weight loss. She gained weight with her 2 pregnancies and is now heavier by 56 pounds, 10 of which she gained during the COVID-19 pandemic. As an administrative assistant, she sits most of the day and has no planned physical activity. Her mother, who has a BMI of 37 kg/m², was diagnosed with type 2 diabetes at age 50 and has experienced a mild stroke. Ms S takes no prescription medications but has risk factors for chronic disease: fasting blood glucose (110 mg/dL), lipids (total cholesterol of 220 mg/dL and low-density lipoprotein cholesterol of 100 mg/dL), and blood pressure (138/89 mmHg). Ms S has made an appointment to address her weight gain and ways to improve her health without taking medications. Her overall goal is not to have the same health issues as her mother. A friend has recommended that Ms S consider taking a fat-burning weight loss supplement.

Ms S has tried many diets over the years, but they have not worked with her family's lifestyle; she has 2 active teenage boys who play sports and a husband who is a construction manager. She loves to cook and prepares many traditional dishes learned from her mother, who emigrated from Mexico. When she does not have time to cook, the

family orders takeout food (3 to 4 times per week). Coming to see a physician for weight loss help has been difficult, since she is not sure a physician will understand her weight struggles.

Commentary

Ms S's case highlights the difficulty many women face in managing weight gain with pregnancy and juggling the stress of work, home, and family. Although extensive research emphasizes that lifestyle changes are required for successful weight loss,^{1,2} each year millions of consumers turn to unproven over-the-counter weight loss supplements to "quick start" their weight loss attempts, hoping this time things will be different.^{3,4} Below, we discuss the safety and efficacy of over-the-counter weight loss supplements and suggest ways clinicians can discuss weight loss with patients like Ms S.

Weight Loss Supplements

Efficacy. In 2019, Americans spent more than \$2 billion on over-the-counter weight loss supplements.⁴ The US Food and Drug Administration (FDA) does not review or approve nonprescription, over-the-counter dietary supplements for safety or efficacy and does not require certification of substance purity on labels, although it does require listing of all ingredients.^{5,6} Manufacturers might also add adulterants (eg, sibutramine, fenfluramine, laxatives, and diuretics) to produce weight loss, which is illegal, and these adulterants pose significant safety concerns.^{7,8,9} Finally, research reviews of over-the-counter weight loss supplements show that the products have little efficacy and pose potentially serious risk of harm.^{5,10,11} Clinical studies for weight loss supplements typically include only 1 or 2 ingredients in a trial, lack a control group, are not double-blinded, and require lifestyle changes.⁵

The American Medical Association *Code of Medical Ethics* states that the physician shall "use sound medical judgment on patients' behalf, and to advocate for their patients' welfare."¹² Thus, a physician **cannot ethically recommend** an over-the-counter weight loss supplement since the safety and efficacy of the actual ingredients are not known, as might be the entirety of the ingredients. Sharing these concerns with patients will help them understand and appreciate why their clinician is not recommending the supplement they want to use.

Mechanisms and common ingredients. Weight loss supplements typically rely on 4 general mechanisms: (1) blocking carbohydrate or fat absorption, (2) increasing metabolism and "fat burn" (eg, through caffeine, green tea, or carnitine), (3) changing body composition (eg, through conjugated linoleic acid or chromium), or (4) suppressing appetite (eg, through soluble fibers or chili pepper).^{7,13} Ms S's multi-ingredient supplement is marketed as increasing metabolism (caffeine, green tea, cayenne pepper)^{7,13,14} and improving fat oxidation (carnitine).^{7,15} Below is a quick overview of common over-the-counter weight loss supplement ingredients.

- *Caffeine.* The amount of caffeine might not be listed on the label and could range from 150-500 mg per serving or more. Caffeine intake that does not exceed 400 mg/day is not associated with dangerous, negative side effects, but higher intake increases risk of insomnia, irritability, heart palpitations, and anxiety.¹³
- *Green tea extract.* Catechins are the active ingredient in green tea.⁷ All adverse effects reported for green tea are from the use of extracts and not beverages.⁷

The European Food Safety Authority concluded that catechin intake of less than 800 mg/day does not cause increased transaminase activity associated with liver toxicity.¹⁶ However, products are not required to list the total catechin content on the label.

- *Carnitine*. Carnitine has been extensively studied and is generally considered safe, but there is no evidence that it produces clinically significant weight loss.^{13,15}
- *Cayenne pepper extract*. Capsaicin is the primary active ingredient in hot peppers and is hypothesized to support weight loss through increasing energy expenditure and lipid oxidation while reducing appetite.¹⁴ Capsaicin is not a magic bullet for weight loss, however, and its long-term impact is small.^{14,17,18}

Discussing Weight Loss With Patients

Addressing weight loss supplement use with a patient can be tricky. On one hand, quick dismissal can be interpreted as judgmental. On the other, a patient who feels pressured by a friend to use a supplement might need a reason *not* to use that supplement. These questions can help clinicians discuss supplement use with patients like Ms S, with a goal of directing them toward weight management approaches that are safe and culturally appropriate.

1. Why do you want to use this weight loss dietary supplement?
2. How much does it cost?
3. How frequently do you plan to take it and at which dose?
4. What are the **health risks**?

Once a patient understands why a supplement cannot be clinically recommended, the clinician should discuss past weight loss attempts, challenges and **barriers to healthy eating** and physical activity, and available social support for making lifestyle changes.

Finally, weight management discussions can be difficult if the health care practitioner is also overweight.¹⁹ Clinicians should consider their approach to this dilemma should it arise (eg, sharing their own struggles with positive lifestyle changes). Clinicians should also be aware that some overweight patients might assume that a thin clinician will not understand their struggles. Assure patients that they are not alone and that help and support are available.

Recommending a Weight Loss Program

Weight loss and management are challenging in our current environment of readily available energy-dense foods and a sedentary lifestyle. Telling the patient to “eat less and exercise more” does not work.^{20,21,22} Ms S will only be successful if she believes she can follow the approach agreed on, has support in setting achievable goals, and has a realistic plan to reach those goals.

Clinicians should discuss the **impact of excess weight** on health with patients like Ms S before a best weight loss approach is determined. For overweight and obese adults, even a weight loss of 5% to 7% can decrease major chronic disease risk factors.^{1,23} For example, the Diabetes Prevention Program showed that a 7% decrease in body weight reduced the risk of conversion from impaired glucose tolerance to type 2 diabetes by 58%.²⁴ The Finnish National Diabetes Prevention Program also showed a 69% risk reduction for type 2 diabetes with a 5% reduction in body weight.^{25,26} The American Heart Association, the American College of Cardiology, and the Obesity Society²⁷ have

outlined guidelines for the management of obesity in adults for the reduction of chronic disease risk.

There is no magic diet for weight loss. Almost any diet that reduces energy intake will produce weight loss if followed.¹ Explaining dynamic energy balance and the many factors that contribute to one's body weight will help reduce patients' guilt about past weight loss failures.²⁸ Research shows that extreme weight loss approaches do not work for most patients²⁹ and can slow metabolic rate, which makes it even harder to keep the weight off.^{30,31} Clinicians should emphasize moderate, achievable weight loss and health goals and the importance of lifelong healthy lifestyle changes over quick, dramatic weight loss.

There are a number of successful, evidence-based lifestyle approaches focused on diet quality, energy intake, physical activity, and behavior therapy that reduce weight and chronic disease risk factors.^{1,24,26,27} These programs typically include group or individual sessions for at least 6 months, are led by trained interventionists, and address diet, physical activity, and behavior modification.^{1,21} Clinicians should remind their patients like Ms S that lifestyle change can be difficult and requires time and support from family and friends.^{21,27} Research shows that social support is an important predictor of improved diet and increased physical activity.^{32,33} Successful weight loss maintainers report that, in addition to maintaining a healthy diet and physical activity, body weight monitoring is key to keeping off excess weight.^{1,34} Bray and Ryan¹ provide a comprehensive review of these programs and various diets for weight loss. Clinicians should be ready to provide referrals if their facility does not offer a comprehensive weight loss and management program.

Determinants of Healthy Body Weight

It is essential to provide culturally and individually appropriate support and guidance regarding weight loss. Among Latina women, cultural, social, and economic factors play an important role in attitudes, beliefs, and behaviors associated with body weight, dietary habits, and physical activity.³⁵ For example, the cultural importance of obligation to one's family and family relationships (familism), which is relevant in Latinx cultures,³⁶ is associated with less successful weight management among Mexican American women.³⁷ Thus, in counseling Latina women, clinicians should consider the role of family responsibilities and integrate strategies that work toward the patient's achieving 2 goals: weight loss and fulfilling family needs.³⁸ Access to stores carrying healthy foods³⁹ and to neighborhood parks⁴⁰ improve nutrition and physical activity, respectively. Unfortunately, many neighborhoods **lack access to these resources**, which makes meeting diet and physical activity recommendations challenging. Connecting patients to appropriate resources will improve their weight management success.³²

Conclusion

Lifestyle changes that result in weight loss can be difficult to implement and maintain, but success can be achieved if patients take part in evidence-based programs that provide appropriate support and education. These programs need to address the social and cultural beliefs concerning weight loss, body size, and family dynamics and barriers that prevent healthy weight loss and maintenance. Finally, over-the-counter weight loss supplements marketed to consumers are not regulated by the FDA for safety or efficacy, and research does not support their use. Thus, it is not ethical to recommend them to patients.

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Melinda M. Manore, PhD, RDN is an emeritus professor of nutrition in the School of Biological and Population Sciences at Oregon State University in Corvallis. She is the author of more than 150 scientific publications, book chapters, reviews, and textbooks and has mentored more than 40 nutrition and exercise graduate students. Her research and teaching focus on energy balance in active and sedentary individuals, chronic disease prevention, dietary and energy expenditure assessment, and sport nutrition.

Megan Patton-Lopez, PhD, RDN is an associate professor at Western Oregon University in Monmouth. Her research and practice focus on promoting healthy eating and active living among children and families through culturally affirming and equitable public health programs and policies. Past projects include childhood obesity prevention among school-age Latino youth, food security and community nutrition assessment among Latino mothers in rural Oregon, and increasing health care access among Latino farmworkers.

Editor's Note

The case to which this commentary is a response was developed by the editorial staff.

Citation

AMA J Ethics. 2022;24(5):E345-352.

DOI

10.1001/amajethics.2022.345.

Conflict of Interest Disclosure

The author(s) had no conflicts of interest to disclose.

The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

Should Clinicians Prescribe Non-FDA Regulated Dietary Supplements When Caring for Children With Hypovitaminosis D?

Ethan A. Mezoff, MD, Hannah Hays, MD, and Ala Shaikhkhalil, MD

Abstract

Hypovitaminosis D is a prevalent micronutrient deficiency that can be severe and hard to treat in children with short bowel syndrome, a condition treated with substantial bowel resection. Surgically altered bowel anatomy then results in iatrogenic digestion and absorption limitations that require short- and long-term management and follow-up. Care of children with hypovitaminosis D standardly includes prescription dietary micronutrient supplementation, sometimes in irregularly high doses. This commentary responds to a pediatric case of vitamin D toxicity and suggests micronutrient-prescribing risk mitigation strategies in light of the absence of regulatory oversight of over-the-counter dietary supplements, inadequate insurance coverage, and easily available commercial retail products.

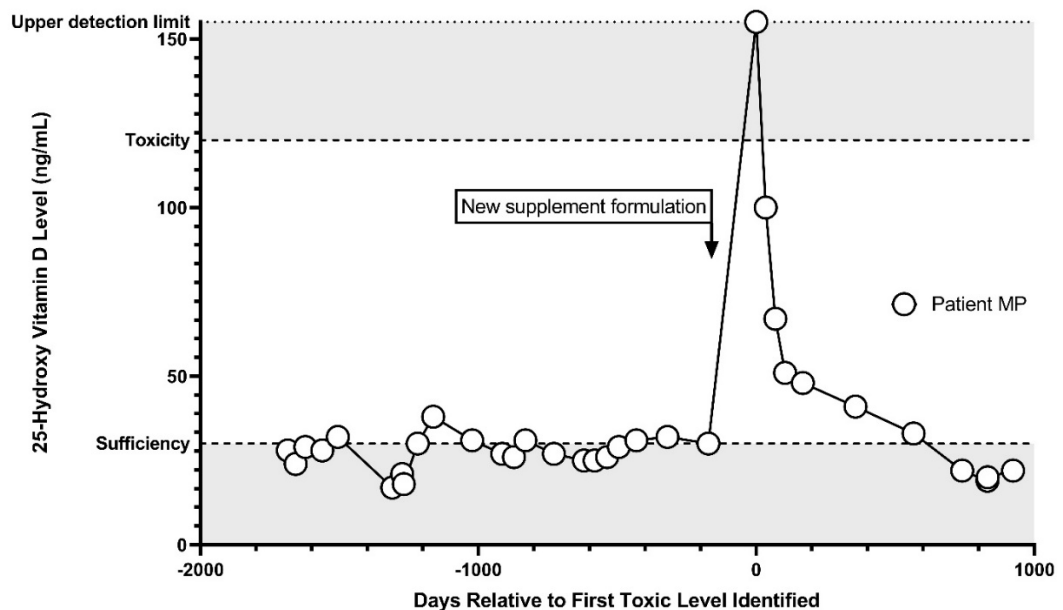
Case

MP is a teenage girl with short bowel syndrome (SBS) related to gastroschisis, initially leaving her with approximately 10 centimeters of small bowel in continuity with her descending colon. Following multiple autologous intestinal reconstructive surgeries performed to address clinically relevant bowel dilation, her small bowel length was measured at 73 centimeters. Her clinical course has been complicated by intestinal failure-associated liver disease, recurrent small bowel bacterial overgrowth, limited vascular access related to thrombosis that requires anticoagulation, and multiple central line-associated bloodstream infections prior to central line removal. She achieved enteral autonomy with line removal at age 10 years.

MP was found to have a toxic 25-hydroxy vitamin D level in August of her ninth year. At 4 years of age, she began a series of upward ergocalciferol titrations in response to insufficient vitamin D levels through December of her seventh year, when she began receiving ergocalciferol at a dose of 24 000 international units (IU) daily administered through her gastrostomy tube. Subsequent repeated insufficient vitamin D levels prompted a transition to cholecalciferol 50 000 IU administered daily through her gastrostomy tube. However, her vitamin D levels were largely insufficient with this dose, with values ranging from 25 to 32 ng/mL over the next year-and-a-half. In early summer of MP's ninth year, her mother transitioned from purchasing her cholecalciferol from a

local pharmacy to purchasing it from a large e-commerce platform due to insurance coverage barriers that lead to a high out-of-pocket cost. Following this transition, MP's 25-hydroxy vitamin D level rose beyond the upper limit of detection, from 30 ng/mL to greater than 155 ng/mL (see Figure). MP's serum calcium was normal (9.2 mg/dL). Supplementation was discontinued and monthly vitamin D levels were obtained. Vitamin D supplementation was resumed, with cholecalciferol 10 000 IU administered twice daily and purchased through a local pharmacy.

Figure. MP's 25-Hydroxy Vitamin D Levels



Commentary

Pediatric intestinal failure (IF) occurs when bowel digestive and absorptive function is insufficient to meet the demands of a growing body. Pediatric SBS is a heterogenous disorder resulting from extensive small bowel resection in the setting of primary bowel pathologies such as necrotizing enterocolitis and gastroschisis. Pediatric SBS is the most common cause of IF. The remnant bowel undergoes a process of physiologic adaptation over a period of years, increasing gut function and permitting the achievement of enteral autonomy in most patients, although the loss of key areas of the gut can be felt through the remainder of the child's life. Hypovitaminosis D is a prevalent micronutrient deficiency that can be severe and hard to treat in children with SBS.

Vitamin D Deficiency in SBS

Micronutrient deficiency is common in IF, including deficiencies of fat-soluble vitamins, copper, and iron.^{1,2,3} These deficiencies risk metabolic bone disease, infection, anemia, thrombosis, demyelinating disease, growth failure, and more.^{4,5,6,7,8} Programs that care for children with SBS typically monitor vitamin and mineral levels.⁹ Vitamin D inadequacy is among the most common findings, with a prevalence of 20% to 42% during the months-to-years-long process of weaning from parenteral nutrition and of 30% to 68% after achievement of enteral autonomy.^{1,2,10}

Vitamin D, a fat-soluble vitamin also referred to as calciferol, primarily promotes calcium absorption from the gut and facilitates bone mineralization for growth and strength.

Vitamin D deficiency is associated with metabolic bone diseases such as rickets and osteomalacia, signs and symptoms of which include delayed growth, delayed acquisition of motor skills, bony pain, and muscular weakness.¹¹ Vitamin D has additional roles in many organ systems, and hypovitaminosis D increases risk of many diseases.¹²

The achievement of nutritional sufficiency in patients with SBS through enteral supplementation is challenging due to malabsorption, decreased intestinal mass, and incomplete or absent coverage of supplementation costs. Thus, the high prevalence of hypovitaminosis D in patients with SBS supports the need for a systematic approach to supplementation, often employing doses higher than those used in other populations.¹³ Vitamin D supplementation can be in the form of ergocalciferol (D2) or cholecalciferol (D3). Supplements can be prescribed or obtained over the counter (OTC), with estimates of out-of-pocket costs ranging from \$12 to \$70 per month or more depending on dose and preparation (eg, liquid).^{14,15} Heightened testing needs are also costly.¹⁶

In 2020, the Intestinal Rehabilitation and Nutrition Support Center at Nationwide Children's Hospital cared for 165 patients with SBS. Of these, 142 (86%) were supplemented with vitamin D with a median dose of 10 000 IU per day, with a range of 200 IU to 100 000 IU per day (E. A. Mezoff, MD, and R. Lee, unpublished data, 2020). Of note, the recommended dietary allowance (RDA) for vitamin D in children is 600 IU per day.¹⁷

Toxicity of vitamin D leads to hypercalcemia and imbalance in the regulation of bone metabolism. Hypercalcemia can cause symptoms of toxicity that span the neurological, gastrointestinal, and renal systems.¹⁸ In this case, a child developed vitamin D toxicity in the context of a complex medical condition in which high doses were needed. While the need for such high doses of vitamin D is rare, the ethical and practical challenges of prescribing vitamin D and other unregulated dietary supplements (DS) apply to many patient populations.

Inconsistent Access to Vitamin D

Despite the essential physiologic function of vitamin D and the deleterious side effects of vitamin D deficiency, most vitamin D preparations are sold as OTC DS. Insurance companies frequently restrict access due to OTC status.¹⁹ Inconsistent insurance coverage of OTC vitamin D and out-of-pocket costs of these preparations raise health equity concerns. As described in the case, MP transitioned from a product purchased at the local pharmacy to one purchased from an e-commerce platform due to insurance coverage barriers that lead to a high out-of-pocket cost. Unfortunately, DS purchased on large e-commerce platforms may be unreliable, as manufacturers may seek to cut costs. An additional issue that arises in this example is that the local **pharmacy cannot be contacted** to verify adherence, as can be done when a DS is prescribed and dispensed from a pharmacy.²⁰

Absence of or Limited Regulation of Vitamin D Supplementation

In addition to concerns about toxicity, as in our case (MP fortunately remained asymptomatic), ineffective treatment that leads to persistent deficiency also poses an important risk to patients. Many DS contain micronutrients for which RDAs have not been determined, which can further complicate the issue of supplementation in the clinical and research setting.

Because manufacturing processes can be inconsistent, these products can contain quantities of ingredients in amounts not listed on the label. This inconsistency can lead to either over- or underdosing the desired supplement, which in turn can lead to poor clinical outcomes for patients. In the United States, deficits in **regulatory and labeling laws** also compromise the effectiveness and safety of these preparations.^{21,22} In the case of vitamin D, for example, a widely available preparation has a dose of 50 000 IU (which is 12 500% of the RDA).¹⁶ At the other extreme, in one study of echinacea products, 10% of samples contained no echinacea, and only 43% met the quality standard described by the label, suggesting that most echinacea products did not contain the claimed ingredient content.²³

In addition, there are numerous reports of contamination and adulteration of DS with heavy metals and pharmaceutical compounds.²⁴ For example, the US Food and Drug Administration has reported hundreds of adulterated sexual enhancement supplements.²⁵ There has been some focus on improved regulation, including labeling requirements, mandatory adverse event reporting, and proposals for increased integrity of the manufacturing process.^{24,26,27} Nevertheless, the existing regulations are too narrow in scope, often ignored, and difficult to police. With 72% of adults and 50% of children using DS,²⁸ clinicians must be aware of the potential risks involved with DS use, either when prescribed or obtained OTC.

Recommendations for Patient Education on Supplementation

To mitigate health risks due to inconsistent manufacturing processes, clinicians should **guide patients** to choose DS that are verified by the United States Pharmacopeia (USP). The USP Convention is a 200-year-old nonprofit organization that promotes safety of drugs, foods, and DS by establishing standards for quality and purity, auditing manufacturing facilities, and performing quality control testing.²⁹ The USP verified mark ensures that a product contains the ingredients listed on the label in the declared potency and amounts and does not contain harmful levels of contaminants.³⁰ A study that evaluated the potency of different vitamin D preparations found that the manufacturer that had USP verification had “generally more accurate and less variable” content of vitamin D, whereas the remaining manufacturers’ products had highly variable content, with potency of all OTC products ranging from 9% to 146% of the amount of vitamin D listed on the label.³¹ Unfortunately, only a very small percentage of DS use the USP seal, and other verification seals exist and can confuse consumers.^{23,29}

Data indicate that 15% of people take pharmaceuticals and DS concurrently and that potential adverse interactions occur in 40% of users.^{32,33} Due to the risk of DS contamination and adulteration, inconsistent DS manufacturing processes, and the absence of pharmacokinetic data, these interactions can present a diagnostic challenge. Clinicians should be aware that the highest risk occurs in patients taking drugs with a narrow therapeutic window, such as digoxin and warfarin.²⁴ Additionally, St John’s wort and ephedra are commonly involved in DS-drug interactions.^{26,34}

A 2006 survey found that 38% of acute care facilities do not have a formal policy on DS use and that most allow DS if they are ordered by an “authorized prescriber.”³⁵ Clinicians tasked with recommending or continuing DS use—or who have concerns regarding toxicity, adverse effects, or drug interactions—should have an open conversation with their patients about these products and their goals for use (see Table) and consider consulting with a medical toxicologist or regional poison center.

Table. Questions to Guide Discussion of Unregulated Products

Category	Questions
Origin	Who recommended the supplement?
	Why is that person's advice trusted?
Rationale	What is supplementation trying to achieve
	Is the preference for regulated or unregulated supplements, and why?
	What does regulation mean?
Options	What are the options (eg, preparation and/or formulation, dosing route, concentration) and how are they regulated?
	Are there medical reasons to narrow the options?
	What are the costs of options and what is good value?
	Where can the options be obtained?
	Is the source trusted?
Goal	How will we know the supplement is effective?
	How will we know the supplement is safe?
	Are there drug or disease state interactions?

Conclusion

There are challenges in prescribing vitamin D and other dietary supplements, particularly for children. The OTC status of products, large number of products and suppliers, lack of oversight, and potentially inconsistent patient adherence and caregiver administration are all risk factors for harm in the form of toxicity or persistent deficiencies. Clinicians should explore patients' knowledge, evaluate their adherence, and advocate for their patients with insurance companies to maximize effectiveness and minimize health inequities.

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Ethan A. Mezoff, MD is an assistant professor of clinical pediatrics at the Ohio State University College of Medicine, a pediatric gastroenterologist, and a member of the Center for Intestinal Rehabilitation and Nutrition Support at Nationwide Children's Hospital in Columbus, Ohio. He has published numerous primary articles and reviews on intestinal rehabilitation.

Hannah Hays, MD is an assistant professor of emergency medicine and pediatrics at the Ohio State University College of Medicine, the associate medical director of the Central Ohio Poison Center, and a medical toxicologist at Nationwide Children's Hospital in Columbus, Ohio.

Ala Shaikhkhalil, MD is an attending pediatric gastroenterologist and a physician nutrition specialist at Nationwide Children's Hospital and an assistant professor of clinical pediatrics at the Ohio State University College of Medicine in Columbus, Ohio. Her research focuses on nutrition education in medical training, gastrointestinal and nutritional manifestations of cystic fibrosis, and the role of zinc in growth and body composition of extremely preterm infants.

Editor's Note

The case to which this commentary is a response was developed by the editorial staff.

Citation

AMA J Ethics. 2022;24(5):E353-360.

DOI

10.1001/amajethics.2022.353.

Conflict of Interest Disclosure

The author(s) had no conflicts of interest to disclose.

The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.



AMA Journal of Ethics®

May 2022, Volume 24, Number 5: E361-367

CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

How Should Clinicians Respond to Patient Interest in Dietary Supplements to Treat Serious Chronic Illness?

Valerie Clinard, PharmD, APh and Jennifer D. Smith, PharmD, BCACP, BC-ADM, CDCES

Abstract

The Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey data reveal that consumption of over-the-counter vitamins, minerals, and herbals is widespread. Many clinicians, however, lack critical information about their patients' use of dietary supplements. Particularly clinically relevant are supplement ingredients' interactions with prescription medications, supplements' questionable effectiveness in treating serious conditions, and their potential for causing harm. This article considers how clinicians might address dietary supplements' safety, efficacy, and appropriate use with patients.

The American Medical Association designates this journal-based CME activity for a maximum of 1 AMA PRA Category 1 Credit™ available through the AMA Ed Hub™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Case

Mr R visits Dr G to follow up on his type 2 diabetes after initiating basal insulin, mealtime insulin, empagliflozin, and metformin. Mr R explains that his metformin prescription expired, so he's only taking empagliflozin, and that he prefers not to restart insulin because it gives him "brain fog." Due to past pancreatitis, Mr R is not a candidate for glucagon-like peptide-1 receptor agonist treatment. Mr R states that he'd like to control his diabetes by modifying his diet, and he also expresses interest in taking a blood sugar control product he found at a nutrition store, which is labeled as containing cinnamon, chromium, bitter melon extract, gymnema, zinc, and a B-complex. Mr R's most recent hemoglobin A1C is 8.6% (diabetic range) and his renal and liver function test results are normal. Dr G wonders how to respond to Mr R.

Commentary

Mr R's case is not atypical in the management of chronic disease states. In practice, patients report using dietary supplements for a variety of reasons, including cultural or traditional family beliefs, conviction that dietary supplements promote a healthier way of living, or the belief that dietary supplements are a safer, more natural way of healing diseases than pharmaceutical agents. However, "safer" and "more natural" cannot be

validated when comparing dietary supplements to prescription medications. Dietary supplements are regulated under the general umbrella of foods, not drugs.¹ The Dietary Supplement Health and Education Act (DSHEA) of 1994 defines a dietary supplement as a product taken with the intent to supplement the diet and as including one or more of the following ingredients: vitamins, minerals, herbs or other botanicals, amino acids, or other substances.¹ Since herbal supplements are considered dietary supplements that contain one or more herbs,² the term *dietary supplement* in this article will include herbal supplements.

Based on the most recent Centers for Disease Control and Prevention National Health and Nutrition Examination Survey data, approximately 58% of the surveyed US adult population (aged 20 years and older) reported using a dietary supplement in the past month.³ The use of dietary supplements increased with age; the survey report noted that almost 25% of those surveyed over the age of 60 took 4 or more supplements.³ The most common dietary supplements reported included multivitamin-mineral supplements, vitamin D, and omega-3 fatty acid supplements.³ For many clinicians, [conversation about supplements](#) might seem easy when patients report taking a multivitamin, calcium supplement, or vitamin D, for each of which there is sufficient data to demonstrate improved overall health or disease management. Conversation becomes more difficult when clinicians are uncertain or skeptical of available scientific data about safety, efficacy, and regulatory oversight of supplements containing herbal ingredients.

Regulation of Dietary Supplements

Practitioners might mistrust dietary supplements due to perceived insufficient regulation of these agents. Unlike drugs, dietary supplements are not approved by the US Food and Drug Administration (FDA) for safety and efficacy. In fact, dietary supplements with ingredients sold in the United States before October 15, 1994, do not require FDA review for safety prior to marketing because these ingredients are presumed safe based on previous use in humans.¹ For a new supplement or ingredient not marketed prior to October 15, 1994, the FDA must be *notified* by the manufacturer of the intent to market the product and provide information on how it determined that the product is safe for human use.¹

Moreover, unlike prescription medications, dietary supplements cannot be labeled or marketed with claims of treating, diagnosing, preventing, or curing a disease.¹ However, dietary supplements can be labeled with a health, nutrient content, or structure/function claim. For these claims, the DSHEA requires a “disclaimer” that the FDA has not evaluated this claim. Once a dietary supplement is available on the market, the FDA only restricts the use of or removes the product after it has been proven that the product is unsafe or misbranded (ie, labeled falsely or in misleading way).¹ At no point in the process does the FDA address product efficacy. The FDA does expect manufacturers of dietary supplements to use current good manufacturing practice (CGMP) and guarantee the identity, purity, strength, and composition of their product,¹ but it does not require standardization to ensure batch-to-batch consistency of the product. However, there is a loophole in that CGMP regulations require only the total amount of a proprietary blend to be stated on the label, with ingredients of the blend listed in order of predominance by weight.⁴ This labeling requirement allows manufacturers to change the actual amount of each ingredient in the blend without that information being conveyed to the consumer or FDA. Potentially this could be both a safety and efficacy concern.

Discussing Supplements With Patients

Advising patients about supplement use. To compile a complete medication list for each patient, practitioners should ask about use of prescription medications, over-the-counter medications, vitamins and minerals, and herbal supplements at each visit. Some patients will readily disclose the use of dietary supplements, but others might be more reluctant to provide this information. There are 3 common reasons patients do not disclose the use of complementary and alternative medicine to practitioners: (1) the practitioner did not ask, (2) a belief that the practitioner did not need to know, and (3) past or potential discouragement of use by practitioners.⁵ Thus, practitioners' first step should be to inquire about past, current, or potential use of dietary supplements. Shared decision making is key in **advising patients** on use of these products.

Efficacy. If a patient is using or intends to use a dietary supplement, the next step is to determine if the product is potentially effective and if the product is safe for this patient. For some products, sufficient data on efficacy exists for specific indications; however, this is not true of all products or all indications. This assessment can be time-consuming, particularly when a patient takes multiple supplements with multiple ingredients. Clinicians might consider referring patients to pharmacists to evaluate the safety and efficacy of dietary supplements in more complex cases or when there are multiple ingredients that need consideration.

When evaluating a product such as Mr R's for efficacy, clinicians should consider the intended purpose of the product and extant data supporting that purpose. Although the FDA does not require efficacy data, there are resources available to guide practitioners on potentially effective agents for the intended use. The Natural Medicines Comprehensive Database⁶ (available by subscription) is an excellent resource for reviewing available information on effectiveness of dietary supplements. Based on this resource, all the ingredients in Mr R's product have some data supporting their glucose-lowering effects (see Table); thus, it *might be* effective. The practitioner should also ensure that the amount per serving (dose) of ingredients used in the product and the doses taken are within the recommended range and advise against products that contain a proprietary blend when the dose of each ingredient in the proprietary blend is not available, as it becomes difficult to assess if the product contains a therapeutic, excessive, or insufficient dose of each ingredient.

Table. Evaluation of Dietary Ingredients in Mr R's Product^a

Ingredient	Effectiveness for type 2 diabetes	Safety	Common or significant antidiabetes drug-supplement interactions
Cinnamon	Possibly effective: mixed evidence of effectiveness in improving glycemic control; best evidence from cassia cinnamon (120 mg to 6 g daily for 4-18 weeks)	Likely safe when consumed in amounts commonly found in foods, but causes hepatotoxicity in large doses	Possible additive effects with antidiabetes drugs

Chromium	Possibly effective; might improve glycemic control	Likely safe when used orally in appropriate amounts short-term (up to 1000 mcg daily for 6 months), but 3 reports of kidney damage (picolinate form) and at least 3 cases of hepatotoxicity	Potential for hypoglycemia with antidiabetes drugs
Bitter melon extract	Insufficient reliable evidence; might improve glycemic control	Possibly safe as a powdered agent (0.5-12 g daily for up to 16 weeks). Insufficient data on long-term use and should be avoided in patients with G6PD deficiency	Increased risk of hypoglycemia with antidiabetes drugs
Gymnema	Insufficient reliable evidence; might improve glycemic control in combination with other glucose-lowering agents	Possibly safe when used orally and appropriately (200 mg 2 times daily for up to 20 months)	Possible increased risk of hypoglycemia with antidiabetes drugs
Zinc	Possibly effective; might improve glycemic control	Likely safe when used orally and appropriately (no more than 40 mg daily)	Not applicable

^a Adapted from Natural Medicines.⁶

Safety. To address safety, practitioners must consider if there is a potential drug-supplement or disease-supplement interaction. Patients considered at increased risk of interactions include those with chronic diseases who take multiple medications, elderly patients, pediatric patients, pregnant women, patients with poor nutritional status, and patients with poor overall health.⁷ Several resources can aid in determining the safety of dietary supplements.^{6,8,9,10} As illustrated in the Table, the Natural Medicines database provides information on the safety of supplements, including for specific disease states or conditions and in interactions with medications.⁶ The National Institutes of Health (NIH) Office of Dietary Supplements Fact Sheets website provides basic information about dietary supplements and their ingredients and is written for consumers as well as practitioners.⁸ It also provides up-to-date information on emerging topics, such as ingredients touted for the treatment or prevention of COVID-19. Based on the available resources, Mr R's product appears to be safe other than the risk of hypoglycemia when combined with other glucose-lowering agents (see Table).

Purity. With multiple dietary supplements available to consumers, consideration should be given to the purity of the product. The FDA maintains a list of tainted products marketed as dietary supplements that might result in dangerous drug interactions, have undeclared ingredients, or contain dangerous drug levels.⁹ Although manufacturers

have been advised by the FDA of safety concerns, some of these products are still widely available through online marketplaces and social media. The most commonly available tainted products contain phosphodiesterase type 5 inhibitors, steroids, or sibutramine.⁹ Additionally, the FDA does provide a list of products, the ingredients of which it is further investigating.¹⁰ Being on the list does not mean that the product has been found unsafe but rather that further investigation is taking place. Lastly, as mentioned previously, in the absence of required standardization to ensure batch-to-batch consistency, the variability in the *actual* amount per serving of ingredients in a supplement can make accurate dosing difficult.

One way to promote confidence in the purity and manufacturing processes of dietary supplements is to look for the USP (United States Pharmacopeia) or ConsumerLab label. USP and ConsumerLab are independent organizations that voluntarily evaluate the quality of medications and dietary supplements.^{11,12} These independent third parties conduct a careful testing and auditing process using science-based quality standards, including federally recognized standards of quality, purity, potency, performance, consistency, and CGMP.

Conclusion

Mr R's desire to use a dietary supplement for glycemic control is not unusual. Overall, as noted above, the ingredients in his product have data supporting the intended purpose and appear safe. However, it would be prudent to discuss with Mr R that, while there is evidence that a glucose-lowering effect might be possible with this product, it likely cannot replace all of his diabetes medications. This is an example of shared decision making. If the dietary supplement proves effective, Mr R will feel he has found a product he is willing to take that effectively lowers his glucose levels and does not have established safety concerns. Conversely, if the dietary supplement proves ineffective, the practitioner should discuss the initiation of traditional medications for glycemic control.

Overall, when a patient is using or has intentions to use a dietary supplement in place of a prescribed agent, practitioners should approach this decision from the standpoint of the safety and efficacy of the agent. If the product appears safe and has some data supporting its efficacy for the intended use, practitioners should support the patient's decision to trial the agent for a specified time period. If the agent's safety or efficacy is unknown, practitioners should discuss these concerns with the patient and consider if there might be an appropriate dietary supplement alternative for the intended purpose. They should also provide resources to their patients, such as the NIH Office of Dietary Supplements fact sheets. Collaborating with a **pharmacist** might serve as the best approach to collecting and verifying information on safety and efficacy of dietary supplements, particularly when there are time constraints in providing optimal patient care or in complex cases.

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Valerie Clinard, PharmD, APh is an associate dean in the Office of Experiential Education and Professional Development and a professor of clinical pharmacy at the University of California, San Francisco School of Pharmacy. A member of the Haile T. Debas Academy of Medical Educators, she has worked in academia, community pharmacy, and transitions of care and has interests in immunizations, medication reconciliation, and nonprescription therapeutics.

Jennifer D. Smith, PharmD, BCACP, BC-ADM, CDCES is a clinical pharmacy specialist in the US Department of Veterans Affairs. She has worked in academia, community pharmacy, and in a federally qualified health center and has interests in endocrinology and nonprescription therapeutics.

Editor's Note

The case to which this commentary is a response was developed by the editorial staff.

Citation

AMA J Ethics. 2022;24(5):E361-367.

DOI

10.1001/amajethics.2022.361.

Conflict of Interest Disclosure

The author(s) had no conflicts of interest to disclose.

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AMA Journal of Ethics®

May 2022, Volume 24, Number 5: E368-375

CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

How Does Cognitive Bias Affect Conversations With Patients About Dietary Supplements?

Ila M. Harris, PharmD, Christine C. Danner, PhD, and David J. Satin, MD

Abstract

Many patients use dietary supplements but do not inform their clinicians. Some allopathic clinicians' conscious and unconscious cognitive and emotional biases against complementary and alternative medicine can affect whether patients disclose details about dietary supplement use, the quality of communication during clinical encounters, and the information clinicians draw upon to make decisions and recommendations. This article describes 6 cognitive biases that can influence patient-clinician communication and shared decision making about dietary supplements and suggests 6 ways to mitigate biases' negative effects on patient-clinician relationships.

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Case

ST is a 52-year-old patient visiting an interdisciplinary family medicine clinic due to more frequent migraine headaches, now occurring about 4 times monthly. She has resisted taking allopathic preventative medications and wants to know more about feverfew, a plant long used in many traditions to prevent headaches for which ST found evidence of safety in the allopathic clinical literature.¹ A physician, psychologist, and clinical pharmacist consult with ST and aim to discuss the possible benefits of starting propranolol, topiramate, or divalproex instead. One asks ST, "Are you taking feverfew right now? What prompted you to do so?" ST responds and then listens and asks questions about the allopathic medications but says no more about other dietary supplements she's reviewed and hoped to discuss. ST leaves the appointment with a prescription for propranolol but does not plan to have it filled.

Commentary

The clinical team in ST's case steered the conversation from feverfew toward allopathic medicine. This common reaction might reflect the team members' negative **emotional and cognitive biases** against dietary supplements. Conscious and unconscious biases in clinical decision making can result in suboptimal case management.^{2,3,4,5,6,7} Although conscious, willful bias can be egregious, we restrict discussion to unconscious negative

cognitive bias, hereafter referred to as bias. There are many ways bias can negatively affect clinical communication and outcomes (eg, missed diagnosis, assuming a common rather than uncommon diagnosis is correct). Since clinicians in the United States have little, if any, training in dietary supplements' roles in complementary and alternative medicine (CAM), they might be biased against supplements and CAM, even when trying to be open-minded. Almost 60% of adults in the United States use dietary supplements, with higher use among women and individuals aged 60 and older.⁸ Like ST, nearly half of adults with migraines or severe headaches use CAM, which is associated with decreased mental distress.^{9,10}

This commentary describes 6 cognitive biases—visceral, ascertainment, overconfidence, omission, confirmation, and feedback sanction—that can influence patient-clinician communication and shared decision making about dietary supplements. It also suggests 6 tools—insight and awareness cultivation, emotional regulation, metacognition, feedback, task simplification, and time pressure minimization—to help mitigate biases' negative effects on patient-clinician communication and relationships.

Six Cognitive Biases

In our experience, 6 kinds of bias tend to influence clinical approaches to dietary supplements (see Table 1).

Table 1. Types of Cognitive Bias in Medicine

Visceral	<ul style="list-style-type: none"> • “Excessive emotional involvement of the clinician” in a relationship with a patient³ • “Affective sources of error” influence clinical decision making²
Ascertainment	<ul style="list-style-type: none"> • Clinician’s “thinking is shaped by prior expectation”² • Distortion in measuring a phenomenon’s rate of occurrence due to bias in the way information is collected³
Overconfidence	<ul style="list-style-type: none"> • Overestimation of knowledge, limited identification of knowledge gaps³ • Decisions based on incomplete knowledge, information, or intuition; placing faith in opinion rather than evidence²
Omission	<ul style="list-style-type: none"> • A “tendency towards inaction”^{2,3} based on intention to avoid harm¹ • Follows from idea that events deemed part of “natural” disease progression are more clinically and ethically acceptable than events attributable to clinicians’ actions^{2,3}
Confirmation	<ul style="list-style-type: none"> • Consciously or unconsciously noticing evidence in support of a decision at the expense of definitive evidence to the contrary^{2,3} • Misinterpreting what a patient says and remembering events as one “wish[ed] they had happened”³
Feedback sanction	<ul style="list-style-type: none"> • Apparent absence of immediate or obvious consequences of clinician’s actions or decisions leads to an erroneous belief that there were none²

Visceral bias. Visceral bias occurs when positive or negative feelings influence decision making. Possibly due to visceral bias, many allopathic clinicians have negative attitudes toward CAM.^{11,12} Rather than acknowledging that such an attitude is a product of their training, allopathic indoctrination, or current professional environment, some clinicians respond viscerally to what they perceive as a negative stimulus (eg, the patient or the supplement). Perhaps unsurprisingly, patients often do not reveal their use of or interest in dietary supplements to clinicians.¹³ Visceral bias can activate expression of additional biases, negatively influencing conversations with patients, as occurred with ST, who will not be filling the propranolol but will likely take feverfew over the counter without saying she plans to do so.

Ascertainment bias. Ascertainment bias occurs when a clinician's thinking is shaped by prior expectations. The fact that women are more likely to use dietary supplements and that women physicians are more likely to recommend them suggests that personal identity and perspective influence practice.¹⁴ When collecting patients' medication histories, allopathic clinicians often do not ask patients what supplements they use and patients often do not report using them,^{13,15} so clinicians can easily develop a skewed view of supplements' roles in patients' care plans and outcomes. In the case, it seems that ST probably will not tell her future allopathic clinicians about the feverfew she plans to take instead of propranolol.

Overconfidence bias. Overconfidence is common⁵ and happens when clinicians overestimate their own knowledge and make decisions based on opinion, intuition, incomplete information, or poorly understood evidence. For example, if a clinician's go-to medication for migraine prophylaxis is propranolol, that clinician might not explore potential therapeutic benefits of feverfew, despite evidence of its efficacy in migraine prevention.¹⁶

Omission bias. Omission bias reflects a tendency toward inaction based on the greater acceptability of negative outcomes that are due to a disease's natural progression rather than a prescribed treatment or other iatrogenic source.^{2,3,4} For example, if one assumes that an action (eg, endorsing ST's interest in and use of feverfew) is more likely to cause an immediate adverse effect than inaction, and if one assumes that inaction would not result in ST feeling worse, then one might feel safer in not endorsing feverfew. Clinicians tend to not blame themselves for a patient's underlying illness but might blame themselves for feverfew's side effects if they endorsed it.

Confirmation bias. Confirmation bias, also described as "tunnel vision,"^{2,4} occurs when clinicians acknowledge evidence supporting a decision but ignore evidence not supporting that decision. Some clinicians prescribing propranolol for migraine prevention would likely review evidence of propranolol's but not feverfew's effectiveness in migraine management, despite evidence of feverfew's effectiveness.¹⁶ Moreover, were ST to take propranolol, a reduction in her migraine frequency would further predispose the clinician to favor propranolol, even if feverfew might have been effective. Confirmation bias feeds overconfidence bias and is supercharged by feedback sanction.

Feedback sanction. Feedback sanction occurs when the apparent absence of immediate consequences leads one to believe there were no significant consequences at all. A form of "ignorance trap," feedback sanction enables the formation and influence of other biases, privileging short-term over long-term assessment of outcomes. This effect can be a source of patient harm, as clinicians remain ignorant of undetected

consequences.² Dietary supplements can activate this bias because patients frequently underreport their use of supplements,^{13,15} and, as a result, clinicians could remain ignorant of the positive or negative consequences of supplement use. Because negative side effects of a supplement can be noted immediately, whereas benefits might become clear over time, feedback sanction is also described as a “time-delay trap.”¹ Together with confirmation bias, it can muddle clinicians’ formation of a more complete picture of supplements’ merits and drawbacks for patients like ST. That is, if feverfew reduces ST’s migraines such that she need not return to clinic, the benefit might remain invisible to the clinician, who, if aware that ST was taking feverfew, would assume that feverfew was ineffective.

Mitigation Strategies

Bias mitigation strategies generally target bias development or block the influence of bias on reasoning.^{2,17} The latter strategy is further divided into strategies that help individual clinicians and those targeting system-wide influences on bias.^{2,17} Several biases can be activated at once, so multiple mitigation strategies might be needed.

Table 2. Mitigation Strategies for Cognitive Biases

Develop insight/ awareness	<ul style="list-style-type: none"> Describe clinical examples of one’s own biases and their effects on relationships, communication, decision making, and outcomes.²
Emotional regulation	<ul style="list-style-type: none"> Strive for positive emotional states to broaden one’s scope of attention and ability to take in new information, which can decrease activation of biases.¹⁷
Metacognition	<ul style="list-style-type: none"> Adopt a reflective approach to solving problems.² Step back and contemplate thinking processes.²
Feedback	<ul style="list-style-type: none"> Recognize decisions’ consequences so that errors can be quickly understood and corrected.²
Make task easier	<ul style="list-style-type: none"> Seek information and tools to reduce task difficulty.²
Minimize time pressures	<ul style="list-style-type: none"> Allow time to make high-quality and complex clinical decisions.²

Develop insight and awareness. Training to combat the negative influence of common biases in clinical practice can help clinicians become aware of how biases manifest and of their obligation to manage biases.^{2,5} Developing insight into their biases about dietary supplements specifically might help clinicians during clinical encounters to facilitate patients’ disclosure of interest in and use of supplements.

Emotional regulation. Biases are more likely to be activated under conditions of emotional stress, sleep deprivation, high cognitive load, and time pressure, each of which are defining features of clinical work environments.¹⁷ Although bias mitigation strategies should also address environmental factors, emotional regulation is a key strategy for individuals and can be cultivated by practicing mindfulness, meditation, exercise, relaxation, and other wellness activities. The benefits of emotional regulation extend beyond bias mitigation to improving overall cognitive function, creativity, problem solving, and relationships and even to illuminating other prejudices.^{18,19,20,21}

Metacognition. Metacognition means thinking about how we think. Self-reflection is necessary to **identify disruptive thoughts** and emotions during decision making. To mitigate negative biases' influence on decision making, clinicians must first notice that they are experiencing disruptive emotions or unhelpful thoughts (eg, "I noticed the urge to roll my eyes when ST told me she wanted to use feverfew for migraine prevention.") Self-reflection reminds us that not believing in something doesn't make it untrue and prompts us to ask, "Why is that?" Metacognition allows clinicians to step back and be open to the possibility of thinking differently.²

Feedback. Feedback is an obvious solution to feedback sanction as a source of bias, yet it has broader effects. For example, it could be valuable to learn that ST's use of feverfew reduced her migraine frequency by, say, 50%. Although delayed, because positive results take months to manifest, this feedback provides an opportunity for learning but does not guarantee it. Ideally, feedback is best combined with other strategies like metacognition.² If the clinicians in the case, for example, reconsider their initial resistance to feverfew, they might be able to better open a conversation with ST and perhaps learn something important about her experience of her illness.

Make tasks easier and minimize time pressures. Many clinicians' limited knowledge of, or experience with, dietary supplements can be exacerbated by the fact that doing more research takes time that can be hard to find.²² Yet remaining willfully ignorant supports omission bias and unconsciously feeds confirmation bias. Making research tasks easier (eg, sharing them with **colleagues in pharmacy**) can help clinicians gain knowledge and experience, cultivate new point-of-care references, or identify decision support tools.^{23,24} Having evidence-based references on supplements, such as Natural Medicines™, readily available—ideally linked directly from an electronic health record—would meet this criterion. References many clinicians use every day, such as Micromedex®, include information on supplements (eg, feverfew, butterbur, riboflavin, coenzyme Q10) that have efficacy for migraine prophylaxis.²⁴ With these tools at their disposal, ST's clinicians might have been able to quickly look up evidence about feverfew for migraine prophylaxis during her visit. ST could have left with the clinicians' endorsement, or at least better understanding, of feverfew instead of a prescription for propranolol that she's unlikely to use.

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Ila M. Harris, PharmD is a clinical pharmacist and professor in the Department of Family Medicine and Community Health in the Medical School and an adjunct professor in the Department of Pharmaceutical Care and Health Systems in the College of Pharmacy at the University of Minnesota in Minneapolis. Her clinical and scholarly interests include comprehensive medication management, education of medical and pharmacy learners, and use of dietary supplements.

Christine C. Danner, PhD is a clinical psychologist and the director of behavioral health for the Woodwinds Hospital Family Medicine Residency Program in St Paul, Minnesota. She is also an assistant professor in the Department of Family Medicine and Community Health at the University of Minnesota Medical School. Her academic and clinical interests include refugee health, chronic pain management, health behavior change, and physician communication skills.

David J. Satin, MD is an assistant professor and physician in the Department of Family Medicine and Community Health at the University of Minnesota Medical School, where he directs the core medical arts and social science curriculum. With research interests spanning the field of health systems science, he has written on quality improvement, public health, behavioral economics, shared decision making, and bioethics.

Editor's Note

The case to which this commentary is a response was developed by the editorial staff.

Citation

AMA J Ethics. 2022;24(5):E368-375.

DOI

10.1001/amajethics.2022.368.

Conflict of Interest Disclosure

The author(s) had no conflicts of interest to disclose.

The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

Do You Know How to Assess Risks Posed by Over-the-Counter Vitamin A Supplements?

Dina H. Zamil, Emily K. Burns, Ariadna Perez-Sanchez, MD, and Rajani Katta, MD

Abstract

Dietary supplements are regulated as foods by the US Food and Drug Administration (FDA) and, despite their potentially harmful effects, are not subject to labeling rules that apply to prescription medications. This commentary responds to a case about vitamin A supplement safety. The commentary compares regulation of vitamin A-derivative prescription medications, such as isotretinoin, to regulation of high-dose vitamin A supplements, illuminating both products' potential for causing birth defects. Label analysis is key to educating patients about risks of vitamin A-containing supplements. The commentary also suggests the need for more FDA oversight of the dietary supplement industry.

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Case

A 24-year-old woman asks a dermatologist about an acne supplement she purchased online. An advertisement for this product suggests that other products only cleanse the skin's surface, while this one is designed to prevent repeated breakouts of acne by making the immune system stronger. The product's label recommends 2 servings daily and specifies vitamin A content per serving as 1150% of the recommended dietary allowance of vitamin A in micrograms (mcg) of retinyl palmitate and beta-carotene. The dermatologist is concerned that this dose of vitamin A could be teratogenic, since isotretinoin is a vitamin A derivative requiring rigorous monitoring, especially to prevent birth defects. The patient asks, "Is this product safe?"

Commentary

The US Food and Drug Administration (FDA) defines a dietary supplement as a product taken by mouth that contains vitamins, minerals, herbs, botanicals, amino acids, and other ingredients intended to supplement a diet.¹ Acne is common among young adults, and several dietary supplements available online—including some containing high doses of vitamin A—claim to help treat it.² While vitamin A is an essential nutrient, high-dose

vitamin A dietary supplements can harm patients, given their teratogenic potential.^{2,3} These supplements are widely available, have confusing labels, and lack the equivalent of a category X warning label,^{2,4} so physicians should help patients understand these products' risks.

Regulatory Differences

Potentially teratogenic prescription medications must include a package insert with pregnancy warning categories D or X, which indicate evidence of fetal risk. The FDA requires patients taking prescription isotretinoin (a category X derivative of vitamin A) who could become pregnant to comply with requirements of the iPLEDGE Program, which involves monthly pregnancy tests and multiple forms of birth control.^{5,6,7} To emphasize this warning, isotretinoin packaging must prominently display multiple warnings against use during pregnancy.⁵

Dietary supplements are not subject to the same labeling and compliance standards that the FDA requires for prescription medications like isotretinoin,^{8,9} which is a source of serious **clinical and ethical concern** for clinicians caring for patients consuming vitamin A dietary supplements available without a prescription. Unlike prescription drugs that must be proven safe and effective to receive FDA approval for sale in the US market, dietary supplements do not require FDA approval and are easy to buy and widely consumed.⁴ The FDA may remove products from the market, but only if they are determined to be unsafe, adulterated, or mislabeled (ie, as treatment, prevention, or cure).¹⁰

Vitamin A Safety

Consumers taking large doses of vitamin A are subject to the same risks of harm as patients taking prescription isotretinoin,^{3,5,7} yet over-the-counter (OTC) vitamin A supplement labels are not required by the FDA to indicate risk of birth defects.^{2,4}

Assessing risk from amount. One study found that, among acne products available online with potentially teratogenic doses of vitamin A, 2 products lacked a warning about these potential harms and 2 products recommended only to **consult a physician** prior to use if pregnant.² Supplement labels are required by the FDA to convey how much vitamin A a product contains. This is important, since one large study found that the ratio of the prevalence of cranial neural crest defects in babies born to women who took more than 10 000 international units (IUs) of preformed vitamin A daily during pregnancy to that of babies whose mothers took 5000 IUs or less was 4.8, indicating higher odds of such birth defects in babies born to women taking high doses of vitamin A during pregnancy, 1 in 57 of whom had a baby with a cranial neural crest defect.³ These results are based on the numbers of IUs, while supplement labels typically display other units of measurement and thus require conversion to assess risk of harm.

Assessing risk from form. In addition to the number of IUs, the source, or form, of vitamin A is needed on a supplement's label. Dietary or supplemental sources of vitamin A provide either preformed vitamin A (ie, retinol and retinyl esters) or vitamin A precursors (ie, provitamin A carotenoids, including beta-carotene).¹¹ Labeling the percentage of preformed vitamin A and vitamin A precursors in a supplement is important because excess preformed vitamin A can be stored in the body and cause harm.³ The risk of excess vitamin A *precursors*—including risk of teratogenicity in humans—is not known.³ Despite the importance of the form of vitamin A, providing the

percentage of vitamin A supplied as preformed and precursor forms in nutrition labels is voluntary, according to FDA regulations.⁹

Another challenge in interpreting vitamin A dosage is that the units of measure need not be listed on the label. The recommended dietary allowance of vitamin A is currently reported not in IUs but in a measure called retinol activity equivalents (RAEs) by the Food and Nutrition Board,^{8,9,11} and manufacturers are expected to use RAEs to calculate the percent daily value (% DV) on product labels. However, manufacturers are not required by the FDA to list the word *RAE* on supplement labels. Clinicians and consumers tend to assume that manufacturers comply with this labeling regulation but would have to perform calculations to confirm this supposition. If these sources of confusion are neither recognized nor resolved, it's impossible to accurately ascertain how much vitamin A is actually in a consumer's body and therefore impossible to accurately assess that consumer's risk of harm from vitamin A.

Using amount and form to assess safety. In the case, the vitamin A supplement label lists 10 500 mcg per serving from retinol palmitate (preformed vitamin A) and beta-carotene (a precursor) but does not specify whether 10 500 mcg means mcg RAE or mcg of retinol palmitate and beta-carotene. The only hint available on the label is the % DV, which is listed as 1167%. An extremely well-informed and health-literate consumer or a good clinician would try to confirm that the 10 500 mcg indicated on the label means 10 500 mcg RAE. To do this, one would need to know to look for—and find—in the Code of Federal Regulations the reference daily intake (RDI) for vitamin A: for adults and children aged 4 and older, it's 900 mcg RAE.⁹ Multiplying 900 mcg by the DV (11.67) calculated from the % DV on the label, one could indeed confirm that 10 503 mcg RAE is close enough to the 10 500 mcg value indicated on the supplement's label.^{8,9} The Table gives IU equivalents in mcg RAE and the teratogenic dose for different sources of vitamin A.

Table. IU Equivalents in mcg RAE and Teratogenic Dose for 3 Sources of Vitamin A^a

	Source of vitamin A		
	Retinol ^b	Supplemental beta-carotene ^c	Dietary beta-carotene ^c
IU equivalent	0.3 mcg RAE	0.3 mcg RAE	0.05 mcg RAE
Risk of toxicity	> 3000 mcg RAE ³	Unknown	Not applicable

Abbreviations: IU, international unit; RAE, retinol activity equivalent.

^a Adapted from Office of Dietary Supplements.¹¹

^b Preformed vitamin A.

^c Vitamin A precursor.

If one knows that a teratogenic dose of vitamin A is greater than 10 000 IU (3000 mcg RAE) of preformed vitamin A,³ then one could question whether and to what extent the product poses risk of harm. A vitamin A supplement that contained 10 500 mcg RAE from preformed vitamin A would contain 35 000 IUs of vitamin A per serving.¹¹ Although this amount is a potentially dangerous dose for people who might be pregnant, especially during early gestation (eg, 7 weeks or earlier),³ responsibility for considering the safety of OTC high-dose vitamin A supplements currently devolves upon consumers and clinicians, not the FDA or manufacturers.

Need for Expanded Oversight

Consumers and clinicians can't know the risks posed by vitamin A supplements if they don't know or can't learn the amount of vitamin A active in a consumer's body when that supplement is used. Is it reasonable to expect that consumers and clinicians know how to assess risk of a vitamin A dietary supplement? Even assuming it is reasonable, one study found that for 5 of 26 vitamin A-containing acne supplements sold online, the IUs of vitamin A could not be calculated from information listed on the label or there was no specification of the form of vitamin A or the relative proportions of vitamin forms in the supplement.²

Due to vitamin A's teratogenic potential, the FDA should require manufacturers to label amounts of vitamin A in mcg RAE and percentages of vitamin A forms so that consumers and clinicians can quantify vitamin A amounts and assess risk.^{3,4} We recommend that packaging of dietary supplements containing high doses of vitamin A provide pregnancy **warning labels**, that phrases such as "dermatologist formulated, tested, and approved" be clarified as insufficient evidence of a product's safety, and that adverse events from dietary supplemental vitamin A be reported by clinicians or consumers to the FDA's MedWatch program.¹²

In the case, the dermatologist should learn or calculate relevant clinical information about the amount of vitamin A in a dose of the supplement and educate the patient about those amounts' risks. At the policy level, the FDA should expand oversight of dietary supplements with teratogenic risk.

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Dina H. Zamil is a second-year medical student at Baylor College of Medicine in Houston, Texas. She graduated from the University of Houston in 2020 with a degree in honors biomedical sciences and minors in medicine and society, chemistry, and Arab studies. Dina is interested in medical humanities, global health, and refugee service, in addition to clinical medicine.

Emily K. Burns is a fourth-year medical student at Baylor College of Medicine in Houston, Texas. She graduated from the University of Texas at Austin in 2018 with a degree in Plan II honors and is interested in pediatric dermatology and medical ethics.

Ariadna Perez-Sanchez, MD is an internal medicine resident physician at the University of Texas Health Science Center at San Antonio. Interested in clinical dermatology and infectious diseases, she volunteers with several nonprofit organizations.

Rajani Katta, MD is clinical professor of dermatology at the McGovern Medical School at the University of Texas Health Science Center at Houston and clinical assistant professor of medicine at the Baylor College of Medicine. She has written and lectured extensively on medical education, allergic contact dermatitis, and diet and dermatology. She also serves on the Media Expert Team of the American Academy of Dermatology.

Citation

AMA J Ethics. 2022;24(5):E376-381.

DOI

10.1001/amajethics.2022.376.

Conflict of Interest Disclosure

Dr Katta is a member of the advisory board of Vichy Laboratories. The other authors had no conflicts of interest to disclose.

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AMA Journal of Ethics®

May 2022, Volume 24, Number 5: E382-389

MEDICAL EDUCATION: PEER-REVIEWED ARTICLE

What Should Clinicians Know About Dietary Supplement Quality?

Marissa Chaet Brykman, JD, Virginia Streusand Goldman, PhD, Nandakumara Sarma, PhD, RPh, Hellen A. Oketch-Rabah, PhD, MSc, Deborah Biswas, JD, and Gabriel I. Giancaspro, PhD

Abstract

Increase in dietary supplement use in the United States suggests a great need for clinicians to be aware of the range of supplements' quality parameters. Regulatory requirements exist, but specific quality parameters for each ingredient are not set by regulators. This article considers how clinicians can evaluate dietary supplement product quality, assess manufacturers' adherence to public quality standards, and encourage use of verification and certification programs.

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What Matters About Supplements' Quality

The dietary supplement industry in the United States has grown from approximately 4000 products in 1994 to between 50 000 and 80 000 products in fiscal year 2021,¹ with about 80% of US adults reporting that they take dietary supplements, according to a 2021 consumer survey.² These increases in the number of products and in consumer usage underscore the importance of clinicians understanding potential quality concerns about products represented as dietary supplements, given that the US Food and Drug Administration (FDA) does not regulate supplements as rigorously as drugs. The quality of products can be compromised by impurities, contaminants, or misidentified or substituted ingredients. Products containing drugs such as sildenafil (an active ingredient in certain erectile dysfunction drugs) or drug analogs, which are compounds whose structure and function are similar to active pharmaceutical ingredients, might also be illegally marketed as dietary supplements.

Assuming a recommendation to use a supplement is clinically indicated and evidence based, is it reasonable to expect clinicians to cultivate knowledge about which brands contain what they say they contain, recommend specific brands, and lead lab-testing efforts of what patients buy and ingest? It's important for practitioners not only to understand the quality differences, such as in purity or strength, but also to be able to apply this understanding in practice with patients. This article describes tools and

resources that clinicians can use to differentiate among products, consider select features of product quality using publicly available information, and inform patients about safe uses of dietary supplements.

Public Standards

In the United States, dietary supplements must include at least one “dietary ingredient.”³ Dietary ingredients include vitamins, minerals, herbs or other botanicals, amino acids, and dietary substances used to supplement the diet.³ The Dietary Supplement Health and Education Act (DSHEA) of 1994, which amended the Federal Food, Drug, and Cosmetic Act of 1938, sets forth the primary framework for how dietary supplements are regulated as a category of food. Under this framework, there are overarching requirements for manufacturers to ensure the quality and safety of dietary supplement products. These include a premarket notification requirement for certain new dietary ingredients, but FDA review of such notifications is not comparable to the preapproval process for drugs.⁴ Moreover, unlike the framework for drugs, conformance to a *United States Pharmacopeia-National Formulary (USP-NF)* public quality standard is voluntary for all dietary supplements. Under US law, a dietary supplement shall be deemed violative if it is represented (eg, on the product’s labeling) as conforming to a standard in the *USP-NF* but fails to so conform.⁵ This situation potentially creates a disincentive for manufacturers to claim that their dietary ingredient or supplement meets a public quality standard, such as one contained in the *USP-NF*, because the product could be deemed misbranded if it does not actually conform to the standard.

Under the DSHEA, dietary supplement manufacturers must follow current good manufacturing practice (CGMP) requirements that are intended to ensure the quality of dietary supplements. The CGMP requirements⁶ state that manufacturers must establish—for each component and for each finished dietary supplement product—specifications for identity, purity, strength, composition, and limits on contamination to ensure quality.⁷ The regulations require that manufacturers set limits for contaminants that may adulterate their products—such as microbes, microbial toxins, elemental contaminants (eg, lead, arsenic, mercury, and cadmium), and residual solvents—based on toxicological considerations. The regulations also require that appropriate tests be conducted to ensure that specifications are met and that the tests and methods used are appropriate and scientifically valid.⁸

However, the CGMP regulations do not include language specifying the tests and methods to be used or how to determine whether the tests and methods used are appropriate and scientifically valid. Accordingly, manufacturers have the flexibility to determine what tests and methods they use, including analytical methods and acceptance criteria, unless the FDA deems them inappropriate or scientifically invalid after the products have been introduced on the market (eg, if FDA discovers a problem during a routine facility inspection). Dietary supplement products manufactured from the same ingredients by different manufacturers thus could vary in quality since the manufacturers use different specifications and different tests and methods to determine whether those specifications are met. Dietary supplements that do not meet specifications as required by CGMP regulations are considered violative⁹; however, the FDA can generally only make such a determination after the products are on the market, and dietary supplement products on the market are not routinely tested by the FDA to determine whether product specifications are met.

Overall, the characteristics of the current regulatory framework for dietary supplements allow variability in quality specifications for comparable products and thus can contribute to a lack of consistency and transparency in product quality.

Contamination and Misidentification

Dietary supplements can contain impurities and contaminants in excess of levels considered acceptable for human use and can contain misidentified or substituted ingredients. The consequences of quality assurance failures can range from no noticeable or measurable effects to harms of varying severity (eg, from heavy metals in a product that can damage internal organs or increase risk of cancer¹⁰). Manufacturers' adherence to public quality standards can help address these quality concerns and help ensure dietary supplements' consistency and quality.

*Impurities and contaminants.*¹¹ Since dietary supplements are typically taken chronically, exposure to impurities and contaminants can be insidious over time. One study of 138 dietary supplements—including alfalfa, echinacea, garlic, ginger, ginkgo, St John's wort, and several vitamins and minerals—found microbial contamination ranging from low levels to higher levels.¹² Furthermore, antibiotic-resistant bacteria have been detected at low levels in various products (eg, those containing garlic, onion, and turmeric).^{13,14} A fatal case has also been reported of stomach-intestine mucormycosis in a premature infant following the infant's ingestion of a dietary product contaminated with a *Rhizopus* species (mold).¹⁵

Ingredient misidentification or substitution. Public standards can help manufacturers set appropriate specifications for identity that would enable a misidentification or substitution to be detected. Accidental substitution of ingredients can occur when ingredients with similar common names or close morphological characteristics are misidentified. For example, American black cohosh (*Actaea racemosa*) is often replaced by other Asian *Actaea* species, which can lead to liver toxicity.¹⁶ Intentional substitution of an inferior ingredient can occur when the authentic ingredient is expensive or in short supply. In some cases, the adulterants are potential allergens, such as contamination of grape seed extract with peanut skin extract.¹⁷ A recent analysis of ginseng products globally found that different species of ginseng or different parts of the ginseng plant were substituted in 24% of dietary supplements.¹⁸ Examples of economically motivated adulteration are the addition of ubiquitous flavonoids to ginkgo extract¹⁹ and the addition of dyes to bilberry extracts.²⁰ These examples of adulteration can be detected using appropriate analytical methods, such as those included in public standards.²¹

Appropriate analytical test methods are also important for preventing substitution of nonbotanical ingredients. In a recent illustrative case, a certificate of analysis was provided by a supplier positively identifying the product as L-citrulline, but it was found that affected batches actually contained N-acetyl-leucine.²² According to the certificates, the manufacturer had used a nonspecific titration-based method for testing. A more discriminating method, such as one based on high-performance liquid chromatography (HPLC), as described in the *USP-NF* dietary ingredient monograph for L-citrulline, could have been used to discriminate L-citrulline from other closely related amino acids—namely, N-acetyl-leucine and arginine. However, use of such a method is not specifically required under the CGMP regulations for dietary supplements.

Products purporting to be dietary supplements. Another major concern is products marketed as dietary supplements that do not meet the statutory definition of a dietary

supplement, often because the product contains an approved drug or drug analog(s) or does not include any dietary ingredients. In recent years, potentially harmful substances have been found in products promoted to enhance weight loss, sexual function, and athletic performance, including bodybuilding.²³ Specifically, certain dietary supplement products tested by the FDA have been found to contain the drugs sildenafil or sibutramine or to contain steroids or other potentially hazardous substances.²⁴ Adverse consequences of ingesting these products include cardiac symptoms, such as palpitations, chest pain, or tachycardia,²⁵ and other reported adverse events.^{26,27,28} The USP has published public standards on techniques that can be used to detect some of the undeclared substances that may be found in products marketed as dietary supplements.²⁹

When clinicians consider dietary supplement quality, they should be aware that not all products marketed as dietary supplements meet the legal definition of a dietary supplement.³ The FDA maintains a list of tainted products marketed as dietary supplements dating back to 2007,³⁰ which, as of December 2021, contained 1087 products. According to the FDA, this list only includes a small fraction of the potentially hazardous products with hidden ingredients marketed to consumers on the internet and in retail establishments.³⁰

Resources for Clinicians

It is important for clinicians to ask their patients about dietary supplement intake when discussing current medication usage. Patients often consume dietary supplements without consulting clinicians and frequently do not report dietary supplement intake unless specifically asked.³¹ Asking about supplement use is vital when patients are taking prescription medicines because harmful medication-supplement interactions could occur.³² Additionally, it is important for clinicians to be aware of dietary supplement quality in order to provide appropriate care and identify adverse events. A variety of resources can be used by clinicians to increase their familiarity with dietary supplements and help them differentiate among dietary supplements with regard to quality.

USP-NF public quality standards for dietary supplements. USP publishes its official public quality standards for drugs, excipients, and dietary supplements in the *USP-NF* and publishes food ingredient standards in the *Food Chemicals Codex*. Physical reference standards, which are highly characterized specimens, are used in conjunction with the monograph methods to verify that a product and its ingredients can pass tests indicating their adherence to quality standards. In the *USP-NF*, there are more than 800 dietary supplement-related documentary standards (including standards that apply to ingredients, products, and classes of ingredients or products) and approximately 200 physical reference standards. These standards provide scientifically valid analytical methods and evidence-based acceptance criteria to determine identification, composition, and limits on contaminants for dietary ingredients and dietary supplement products. Clinicians can recommend that patients look for dietary supplements that are marketed as conforming to a public standard, which may be indicated on the label.³³

The *USP Dietary Supplements Compendium (DSC)*, which provides a comprehensive set of quality standards related to dietary supplements, also contains over 100 summary admission evaluations for a variety of dietary ingredients. Admission evaluations are comprehensive literature reviews that present a dietary ingredient's known public health and safety profile, including the ingredient's chemistry, typical intake levels, potential

adulterants or contaminants, clinical trial and toxicological data, and potential adverse interactions.^{34,35} The DSC's admission evaluations can serve as a unique resource for clinicians and retailers to help them evaluate appropriate usage and potential risks of these products for patients or consumers.

Quality verification and certification programs for dietary supplements. Verification and certification programs for dietary supplements and dietary supplement ingredients can be used by manufacturers to help ensure their products' quality. These programs also serve as another tool to help consumers make decisions about dietary supplements and provide additional information for clinicians to consider regarding dietary supplement quality.³⁶ The USP, for example, provides a verification service program for dietary supplements and other products.³⁷ The program involves annual CGMP audits; evaluation of quality procedures with test methods for identity, purity, strength/composition, and contaminants; and product testing for conformance to specifications. Programs are also offered by other organizations.³⁸

Other resources for dietary supplement information. There are many other resources that can provide useful information on dietary supplements for clinicians. The National Institutes of Health Office of Dietary Supplement Programs³⁹ and the FDA's Office of Dietary Supplement Programs⁴⁰ provide informative tools and resources. Many resources are also available from the Dietary Supplements Quality Collaborative, which is a multistakeholder, cross-sector collaborative with a mission "to advance the quality and safety of products marketed as dietary supplements in the United States in the interest of protecting public health."⁴¹

Conclusion

As dietary supplement use increases in today's market, it is imperative to ensure supplements' quality. Clinicians should be aware of quality differences that may affect dietary supplements. By gaining knowledge about resources and tools that help identify quality dietary supplements—for example, meeting public standards and use of verification programs—clinicians can help their patients select appropriate products.

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Marissa Chaet Brykman, JD is director of US regulatory policy at United States Pharmacopeia in Rockville, Maryland, supporting its work in dietary supplements and other areas.

Virginia Streusand Goldman, PhD is senior director of the dietary supplements and herbal medicines team at United States Pharmacopeia in Rockville, Maryland.

Nandakumara Sarma, PhD, RPh is director of dietary supplements and herbal medicines at United States Pharmacopeia in Rockville, Maryland. He is a pharmacist with a background and interest in the science of botanical quality.

Hellen A. Oketch-Rabah, PhD, MSc is senior manager and senior toxicologist in the dietary supplements and herbal medicines team at United States Pharmacopeia in Rockville, Maryland, who works in the areas of dietary supplements and herbal medicines nomenclature and safety.

Deborah Biswas, JD is senior counsel at United States Pharmacopeia in Rockville, Maryland, supporting USP's work on standards, including those for dietary supplements and dietary ingredients.

Gabriel I. Giancaspro, PhD is a distinguished scientific fellow, the head of compendial policy, and the former vice president of dietary supplements and herbal medicines at United States Pharmacopeia in Rockville, Maryland.

Citation

AMA J Ethics. 2022;24(5):E382-389.

DOI

10.1001/amajethics.2022.382.

Conflict of Interest Disclosure

All the authors are employees of the United States Pharmacopeial Convention.

The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.



AMA Journal of Ethics®

May 2022, Volume 24, Number 5: E390-395

MEDICAL EDUCATION: PEER-REVIEWED ARTICLE

Is My Patient Taking an Unsafe Dietary Supplement?

Ilisa B. G. Bernstein, PharmD, JD and Karin L. Bolte, JD

Abstract

Dietary supplements do not require premarket approval by the US Food and Drug Administration (FDA), yet they can have side effects; interact with medications, food, or other supplements; or be unsafe, so it is important for clinicians to discuss dietary supplement use with patients. This article provides an overview of dietary supplement requirements related to safety, manufacturing, labeling, advertising, and adverse event reporting; discusses tainted supplements and the FDA's and Federal Trade Commission's enforcement actions against dietary supplements; and offers recommendations to clinicians on matters of key clinical and ethical importance during clinical encounters.

Helping Clinicians Help Patients

Nearly three-quarters of Americans take dietary supplements¹ as tablets, capsules, powders, softgels, or liquids.² With 80 000 products currently on the market,³ clinicians should help patients safely choose and use these products. This article aims to further that cause; we discuss the US Food and Drug Administration's (FDA's) regulation of dietary supplements and the Federal Trade Commission's (FTC's) oversight of dietary supplement advertising and offer recommendations to help **guide clinicians' discussions** with patients.

Regulating Dietary Supplements

Dietary supplements are regulated under the Dietary Supplement Health and Education Act (DSHEA) of 1994,⁴ which defines a dietary supplement as a non-tobacco product taken by mouth that contains an ingredient intended to supplement the diet. Dietary ingredients in supplements can include vitamins, minerals, herbs, botanicals, amino acids, enzymes, or metabolites.⁵ Many incorrectly assume that dietary supplements are tested by the FDA for safety and effectiveness. While manufacturers must ensure their products are safe and that all labeling claims are substantiated by adequate evidence,⁶ dietary supplements do not require FDA approval before they are marketed.⁶ The FDA can only act against misbranded, unsafe, or adulterated supplements after they are on the market.⁷

Adverse events. Manufacturers must notify the FDA of serious adverse events (SAEs) associated with their supplements.⁸ Clinicians and patients may also report SAEs to the FDA through the agency's Safety Reporting Portal⁹ or by calling 1-800-FDA-1088.¹⁰ In addition to ensuring safety, manufacturers are required to register their production facilities with the FDA¹¹ and to adhere to current good manufacturing practices.¹²

Labeling requirements. The FDA requires dietary supplement labels to include the following:

- A descriptive name of the product stating that it is a "supplement"¹³
- The name and address of the manufacturer, packer, or distributor¹⁴
- A complete list of ingredients¹⁵
- The quantity of each ingredient or the total quantity of all ingredients in a proprietary blend¹⁵

Each dietary supplement must have a "Supplement Facts" panel¹⁶ that includes the following¹⁷:

- Serving size and amount per serving
- Names and quantities of each ingredient for which daily values have been established: total calories, calories from fat, total fat, saturated fat, trans fat, cholesterol, sodium, total carbohydrate, dietary fiber, sugars, protein, vitamin A, vitamin C, calcium, and iron (when present in measurable amounts)
- Dietary ingredients with no daily value must be listed by common name
- Percent daily value (% DV) for each dietary ingredient

Although each ingredient must be listed, the FDA does not regulate serving sizes or nutrient amounts.⁶

Dietary supplement claims. Three types of claims can be made about dietary supplements: health, structure/function, and nutrient content claims. Health claims describe relationships between a nutrient or food substance and reduced risk of a disease or health-related condition. There are 3 ways in which the FDA oversees health claims: (1) by authorizing regulations; (2) through sufficient notification that a health claim is based on an authoritative statement of the National Academy of Sciences or a scientific body of the US government that has responsibilities in nutrition research or public health protection; and (3) by issuing a letter of enforcement discretion for credible, nonmisleading, qualified health claims.¹⁸ Some dietary supplements' packaging might claim that a nutrient or ingredient is intended to affect the body's structure or function. The FDA does not authorize structure/function claims, but the DSHEA requires the supplement label to bear the disclaimer, "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."¹⁹ Nutrient content claims describe a nutrient's "level" beyond amounts listed on a label's "Supplement Facts" panel and must be authorized by the FDA. For example, "high protein," "low fat," or "100% whole grains" are common¹⁸ and must comply with information found in Appendices A and B of the FDA's food labeling guide.²⁰

Adulteration. The FDA bears the burden of proof that a supplement is adulterated.²¹ Under the DSHEA, a dietary supplement is deemed adulterated if any of the following 4 conditions hold:

1. It “presents a significant or unreasonable risk of illness or injury under (i) conditions of use recommended or suggested in labeling, or (ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use.”²²
2. It “is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury.”²³
3. It “pose[s] an imminent hazard to public health or safety.”²⁴
4. It meets a conventional food adulteration standard in the Federal Food, Drug, and Cosmetic Act “under the conditions of use recommended or suggested in the labeling of such dietary supplement.”²⁵

Enforcement. If the FDA finds that a dietary supplement is unsafe, contains false or misleading labeling, or is adulterated, the agency can issue a warning letter or require the product’s removal from the market.²⁶ The FTC may prohibit **false or misleading** dietary supplement advertising as “an unfair or deceptive act or practice.”²⁷ Violations of the FTC Act may result in issuance of an injunction or an administrative cease and desist order.²⁸ Manufacturers making deceptive claims about treatment, cure, prevention, or mitigation of disease can be subject to civil penalty up to \$43 792 per violation and be required to refund consumers or provide other relief.²⁹ Since 2010, the FTC has challenged more than 100 dietary supplement health claims.³⁰ Clinicians and patients can report false and misleading advertising claims at ReportFraud.ftc.gov.³¹

Dietary supplements of particular concern. Tainted supplements containing undeclared ingredients can pose serious risks. To date, the FDA has found over 1060 tainted products marketed as dietary supplements,³² including products for bodybuilding, sexual enhancement, weight loss, arthritis or pain, and insomnia.³³ The FDA has taken action against products sold on the internet that claimed to be, but were not, legally marketed dietary supplements.³⁴ The FDA notes that it is “unable to test and identify all products marketed as dietary supplements on the market that have potentially harmful hidden ingredients” and urges consumer caution.³⁵

Three Upshots

1. *Dietary supplements can have side effects; interact with medications, food, or other supplements; or be unsafe.* These harms result due to the supplement’s being contaminated, tainted with at least one drug ingredient, or containing more than a labeled amount of ingredients.³⁶ For these reasons, clinicians should specifically ask whether patients use dietary supplements, which ones, at which dose(s), and counsel them appropriately.
2. *Clinicians may recommend products tested by independent labs.* The United States Pharmacopeia (USP), ConsumerLab.com, NSF International, and the Natural Products Association, for example, can verify product ingredients and amounts. The USP Verified Mark indicates that a dietary supplement meets its evaluation criteria.³⁷

3. *Counsel patients about claims that seem too good to be true.* Clinicians should counsel patients not to use dietary supplements with exaggerated or unrealistic advertising, such as those claiming to be magical, cure-alls, quick fixes, or scientific breakthroughs.³⁸ Simply put, if a claim seems too good to be true, it probably is!

Most Americans take dietary supplements in some form, and it is important for clinicians to help consumers understand that their safety and efficacy are not established by the FDA. Supplements' quality varies, so clinicians should cultivate adequate knowledge prior to recommending a dietary supplement, specifically ask patients about their use of dietary supplements, and counsel patients appropriately.

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Ilisa B. G. Bernstein, PharmD, JD is senior vice president of pharmacy practice and government affairs at the American Pharmacists Association in Washington, DC. Previously, Dr Bernstein held several senior leadership positions at the US Food and Drug Administration in over 30 years of public service.

Karin L. Bolte, JD is the former director of health policy at the American Pharmacists Association in Washington, DC. She has more than 25 years' experience in health policy and advocacy.

Citation

AMA J Ethics. 2022;24(5):E390-395.

DOI

10.1001/amajethics.2022.390.

Conflict of Interest Disclosure

Karin Bolte represents the American Pharmacists Association on the Dietary Supplements Quality Collaborative that helps promote supplement safety and advance transparency and quality. Dr Bernstein had no conflicts of interest to disclose.

The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.



AMA Journal of Ethics®

May 2022, Volume 24, Number 5: E396-401

HEALTH LAW: PEER-REVIEWED ARTICLE

Does Regulating Dietary Supplements as Food in a World of Social Media Influencers Promote Public Safety?

Joshua J. Klein and Scott J. Schweikart, JD, MBE

Abstract

Social media influencers promote a wide variety of products, including dietary supplements. Dietary supplements are regulated as foods, not drugs, by the US Food and Drug Administration and the Federal Trade Commission. This article details weaknesses in administrative and common law regulatory approaches to addressing some influencers' negligent misrepresentation claims about dietary supplements.

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Paid Influence

Recent years have seen the rise of influencers—“social media personalities paid to leverage their popularity to market products”¹—marketing dietary supplements. These supplements, often created and marketed to stimulate weight loss,² include “vitamins, essential minerals, protein, amino acids, and herbs.”³ Influencers' foray into the realm of dietary supplements has had a significant impact on the marketing industry, as demonstrated by their enormous advertising revenue, with estimates that influencer marketing would reach “\$10-20 billion in 2020, with close to 80% of brands participating.”¹ With regard to the regulation of this industry, the federal government plays a role via both the US Food and Drug Administration (FDA) and the Federal Trade Commission (FTC), which “both serve to protect consumers by ensuring safe, effective products and accurate marketing to consumers.”² However, the regulatory environment for dietary supplements, which has been criticized as being inadequate in the face of hazards,⁴ has serious pitfalls when confronting promotion of these supplements by social media influencers. This article explores the federal regulatory mechanisms in place to govern dietary supplements and proposes strategies for how US law—both administrative regulation and common law—can strengthen the regulation of dietary supplements in the new era of influencers.

FDA and FTC Liaison Agreement

In the United States, the 2 agencies responsible for regulating dietary supplements, the FDA and FTC, are subject to a “liaison agreement” to divide enforcement duties. The

FDA focuses on food and drug safety and accurate labeling, while the FTC is charged with regulating advertising and promotional claims.²

FDA. FDA authority to regulate dietary supplements stems from the Dietary Supplement Health and Education Act (DSHEA) of 1994,^{2,5} passed in direct response to a supplement industry boom.² The act categorizes supplements as food, not drugs, and defines supplements as follows:

The term “dietary supplement” (1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

- (A) a vitamin;
- (B) a mineral;
- (C) an herb or other botanical;
- (D) an amino acid;
- (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).⁵

The DSHEA specifies requirements about dietary supplements’ labeling, including that “manufacturers must have substantiation at the time the claim is made, establishing that the statement is truthful and non-misleading,” and labels must include the phrase, “This product is not intended to diagnose, treat, cure or prevent any disease.”²

A key weakness in the enforcement structure created by the DSHEA is that “manufacturers are not required to submit safety information before marketing ‘dietary supplements.’”⁴ This leaves the FDA, as Stephen Barrett notes, “unable to monitor and regulate thousands of individual products,” and the public “virtually unprotected against supplements and herbs that are unsafe.”⁴ The FDA can act against unsafe supplements only when it “proves the supplement poses an imminent health hazard,”² a high burden, satisfied for the first time in 2004 with the ban on ephedra—a supplement promoted for “weight loss and sports performance enhancement”—due to a number of consumer deaths associated with its use.²

FTC. The FTC is charged with regulating advertising—a broad array of media that may include “print, broadcast, infomercials, catalogues, direct marketing, and Internet promotions”²—of dietary supplements. The FTC analyzes 2 key issues when considering advertising claims: “(1) whether the advertisement is truthful and non-misleading, and (2) whether the advertiser has adequate substantiation for all objective product claims before the advertisement is disseminated.”² Because the FDA does not approve dietary supplements before they are marketed, as it does drugs, “the sole regulation of dietary supplements is post-market regulation in the form of false advertising claims,” and the FTC remains “skeptical of most claims that appear too good to be true and do not receive sufficient scientific substantiation.”² Yet, as Alexandra Roberts notes, the FTC “lacks the resources and perhaps the authority to force industry-wide change,” and because private parties do not “have standing to challenge competitors’ practices based on violations” of FTC regulations,¹ they are left with few regulatory remedies if the FTC is not able to take action.

Social Media

Exacerbating current regulatory limitations is the proliferation of influencer marketing (ie, giving or receiving compensation in exchange for product endorsement via social media),¹ which has made it easier to use false or misleading claims about dietary supplements to promote their purchase and use and to shape consumer trends.

Influencer marketing has exploded over the past several years, increasing in value from \$1.7 billion in 2016 to an estimated \$13.8 billion in 2021.⁶ The monetary value of influencer marketing derives from 3 characteristics: (1) consumers perceive influencers as being authentic, which drives more engagement; (2) **social media posts** can turn engagement directly into sales by providing a link to the product in the post; and (3) the lower cost of influencer marketing compared to traditional advertising allows for more varied advertisements.^{4,7} The practice is so effective that some brands have forgone traditional advertising completely, and, as of 2020, “74% of consumers report relying on social media content when making purchasing decisions.”⁷

However, this method of marketing is difficult to regulate. Under the FTC Act,⁸ the FTC requires the disclosure of a monetary relationship between a brand and the endorser in a manner that is “clear and conspicuous.”⁷ Yet, in an effort to create the illusion of a genuine endorsement, influencers frequently hide the disclosure—typically signified by “#ad” or a mention of “paid partnership”—deep within other hashtags, putting the disclosure after multiple pages or forgoing the disclosure entirely.⁹ This deception often goes unnoticed and may change how a consumer perceives the post, as the average consumer cannot differentiate content that is advertising from content that is not,⁷ opening the door to harmful deception. One study conducted by the University of Glasgow found that of the 9 leading bloggers in the United Kingdom, 8 provided inaccurate health information or “present[ed] opinion as fact.”¹⁰ Some companies using influencer marketing were found to disclose product dangers after presenting multiple images (ie, burying warnings after the entertaining content), and others presented claims in a way that would lead consumers to believe the product was FDA approved when it was not.¹¹ By failing to provide the whole picture, giving misleading information, or not including valid alternatives, influencers risk leading their followers to purchase potentially ineffective or dangerous products.¹¹

Common Law Regulation

Although there are no private rights of action under the FTC Act or DSHEA, common law offers a tool for consumers to reduce false and misleading claims in influencer marketing by holding individual influencers—and not the companies selling the products—liable for negligent misrepresentation. As Natasha Brison et al note, to prevail, a plaintiff typically must show:

(1) that the defendant supplied false information, (2) that the defendant failed to “exercise reasonable care or competence in obtaining or communicating the information,” (3) that the defendant intends for the information to influence the plaintiff and for the plaintiff to rely upon the misrepresentation, and (4) that the plaintiff was damaged as a result of his or her “justifiable reliance on the information.”¹²

The first and third elements of the claim can be met simply by looking to the nature of influencer marketing: the influencer is the person supplying the false information in the advertisement, and advertisements are used to induce consumers to buy a product. Further strengthening this assessment, most brands provide influencers with substantial creative freedom, giving up significant control over what is said in the advertisement.⁷ Control is key in determining that the influencer—not the company—is the proper “defendant” who is actually supplying the false information. Hence, the control given to influencers over advertising may make establishing influencer liability for false or misleading claims easier, and doing so would not be without precedent. Under an FTC action similar to negligent misrepresentation, actor/singer Pat Boone’s control over the advertiser was used as justification for holding him liable for claims made while endorsing the ineffective product Acne-Stat in 1978.¹²

The second element may be more difficult for a plaintiff to sustain in negligent misrepresentation claims. In an action brought by the FTC in 1979, former astronaut Gordon Cooper “was ordered to cease and desist all endorsement activities [for an engine product] unless he relied on competent scientific evidence to substantiate any representation made in the endorsement.”¹² Although not part of a negligence action, the FTC’s order is consistent with the duties of those who supply information when there is a risk of physical harm—as is the case with supplements.¹³ Thus, influencers would not be able to avoid liability by claiming they did not know their statements were false or misleading—failing to take reasonable actions to substantiate the claims is enough.¹² Therefore, a plaintiff could meet the second element by demonstrating that, with reasonable care, a prudent influencer would have discovered the claims made were false or misleading.

Regarding the fourth element of negligent misrepresentation, damages would vary with each case, but they would need to stem from the consumer’s relying on the influencer’s statements when making the purchase and the consumer’s reasonable belief the statements were true.¹² With one exception, for a consumer’s reliance to be reasonable, the false or misleading statement made by the influencer must be an assertion of fact and not merely opinion.¹² The exception to this rule, which allows for statements of opinion, applies “when the statement carries with it the implied assertion that the speaker knows of nothing that would preclude the opinion, and that he or she knows facts that would justify it. This is implied when the speaker is understood to have a special knowledge of the matter which is not available to the plaintiff.”¹³ This exception might not often apply in the context of influencers, as some influencers lack “special knowledge” of the product. However, if a consumer can establish that the influencer made such a false statement and that it was relied upon to their detriment, even an opinion could potentially be used to hold an influencer liable.¹²

Conclusion

Although it is unlikely to be as effective as a change in regulation or enforcement, there is reason to believe that using negligent representation to dissuade influencers from selling potentially ineffective or dangerous supplements would be beneficial for consumers. As influencers begin to face litigation for making **misleading and false claims** to sell dangerous or ineffective products, others will take note and make changes to protect their income.¹⁴ Admittedly, there may be challenges to bringing such suits on a large scale, as doing so may require class-action torts, and many influencers may be bit players. Just as the FTC faces challenges in policing influencers, so difficulties will remain with private litigation. However, if claims come to fruition, it follows that, as influencers move to protect their income, they will be less likely to take on brands with unscrupulous marketing strategies or baseless claims, leading to a decrease of ineffective or dangerous supplements being advertised to consumers on social media.

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Joshua J. Klein is a JD candidate at DePaul University College of Law in Chicago, Illinois, where he is symposium editor for the *DePaul Journal for Social Justice*, public relations chair for OUTLaws, and a health law fellow with the Jaharis Health Law Institute. He earned his BM from Winona State University in Winona, Minnesota, with a focus on saxophone performance.

Scott J. Schweikart, JD, MBE is a senior research associate for the American Medical Association Council on Ethical and Judicial Affairs in Chicago, Illinois, where he is also the legal editor for the *AMA Journal of Ethics*. Previously, he worked as an attorney editor and reference attorney at Thomson Reuters and practiced law in Chicago. Mr Schweikart earned his MBE from the University of Pennsylvania, his JD from Case Western Reserve University, and his BA from Washington University in St Louis. He has research interests in health law, health policy, and bioethics.

Citation

AMA J Ethics. 2022;24(5):E396-401.

DOI

10.1001/amajethics.2022.396.

Conflict of Interest Disclosure

The author(s) had no conflicts of interest to disclose.

The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.



AMA Journal of Ethics®

May 2022, Volume 24, Number 5: E402-409

POLICY FORUM: PEER-REVIEWED ARTICLE

What Should Dietary Supplement Oversight Look Like in the US?

Elizabeth Richardson, MSc, Farzana Akkas, MSc, and Amy B. Cadwallader, PhD

Abstract

Most American adults who use dietary supplements (eg, vitamins, minerals, plant and animal extracts, hormones, and amino acids) ingest them orally. The market for these products has grown rapidly and significantly over the last 25 years, but consumer protection regulations have not kept pace. In the United States, supplements' safety is regulated by the US Food and Drug Administration (FDA), but statutory limitations prevent the FDA from effectively regulating these products, exacerbate public health risk, and have generated numerous calls for reform. This article considers key features of reforms likely to strengthen the FDA's capacity to promote safety and consumer protection.

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Growing Market, Growing Risk

Dietary supplements, which include vitamins, minerals, plant and animal extracts, hormones, and amino acids that are ingested orally, are widely used in the United States, where 4 of 5 adults report having taken one.¹ The market for these products has grown exponentially over the last 25 years—from a \$4 billion industry with 4000 products in 1994 to an industry worth more than \$40 billion with as many as 80 000 products today²—but consumer protection regulations have not kept pace. Although the US Food and Drug Administration (FDA) is charged with ensuring the safety of supplements on the market, the regulatory gap between its legal authority and limited resources creates risks for public health and prevents the agency from effectively regulating these products.^{2,3} In recent years, there have been increasing calls for reform, and several proposals have been advanced that could strengthen oversight and better protect consumers.^{4,5}

Falling Short on Safety

Adverse Events (AEs) associated with dietary supplements are not uncommon. One study found that between 2004 and 2013, the FDA's central reporting system (CFSAN Adverse Event Reporting System, or CAERS) received more than 15 000 reports of health problems linked to supplements, including 339 deaths and nearly 4000 hospitalizations.⁶ However, this is likely an undercount of all supplement-related AEs.

While supplement manufacturers must report serious AEs associated with their products to the FDA, CAERS—like all other passive reporting systems—is hampered by underreporting and incomplete reporting, especially by voluntary reporters like consumers and physicians.^{7,8} Indeed, based on CAERS data, Awortwe et al estimate that the reporting rate for supplement-related AEs in the United States is approximately 2%.⁸ Hundreds of dietary supplements on the market have contained undeclared or banned pharmaceutical ingredients, including some that were the subject of FDA warnings.^{9,10,11} Many products marketed for weight loss, muscle building, or sexual function have contained illegal substances that caused severe AEs, especially among young adults using them more frequently.¹²

Regulatory Gaps

Quality issues in the supply chain also pose safety risks.¹³ FDA inspections of dietary supplement manufacturing facilities continue to reveal noncompliance with federal standards for quality and accurate labeling.¹⁴ Unlike drugs or devices, the FDA does not regulate the efficacy of dietary supplements. And while supplement products cannot be marketed to treat or prevent disease—claims can only describe how a particular nutrient or dietary ingredient affects the structure or function of the body—manufacturers are not required to submit evidence to the agency that substantiates the claims they make about their products.¹⁵ Even if they were to do so, the evidence supporting the use of dietary supplements is mixed. While there is relatively robust evidence to support use of some supplements (eg, folic acid in early pregnancy to avoid birth defects¹⁶), the evidence is minimal or even nonexistent for many products.^{17,18,19}

Under the Dietary Supplement Health and Education Act (DSHEA)—the 1994 law that established the current regulatory framework for dietary supplements—the FDA generally does not conduct premarket review of dietary supplements, and manufacturers are not required to provide the agency with basic information about their products, including names or ingredients, before selling them.²⁰ This leaves the agency with no clear view of what’s on the market at any given time. The FDA instead largely relies on postmarket surveillance methods to monitor the safety of these products (AE monitoring, inspections, internet searches), and can only restrict their use or mandate a recall if it can prove that a product or ingredient is unsafe.^{21,22} However, bans or recalls can consume significant time and resources; it took the FDA 7 years of litigation, which went all the way to US Supreme Court, to ban the use of the amphetamine derivative 1,3-dimethylamylamine, and 7 years to ban ephedra, an ingredient associated with increased risk of stroke and death.^{23,24} Additionally, because the FDA does not have mandatory recall authority over drugs as it does over supplements, it is unclear whether the agency can mandate a recall of supplement products tainted with active pharmaceutical ingredients. These products currently fall into a regulatory gray zone.²⁵

Meanwhile, unsafe supplements continue to reach consumers through a legal loophole that allows manufacturers or distributors to “self-affirm” the safety of dietary ingredients through the generally recognized as safe (GRAS) exemption for food products.²⁶ This exemption allows them to circumvent the FDA’s new dietary ingredient notification (NDIN) pathway—the agency’s premarket review process for supplements that contain novel dietary ingredients.²⁷ The FDA estimated in September 2016 that it had received over 900 premarket NDINs since the process was finalized in 1997—far below the agency’s expectation.^{28,29} Unless the FDA finalizes the NDIN guidance to better capture products intended for a GRAS designation or unless Congress addresses this loophole

through legislation, manufacturers will continue to pursue the less burdensome—and less rigorous—GRAS exemption.

Finally, the COVID-19 pandemic has exacerbated existing problems in the supplement market. During the first year of the pandemic (March 2020 to March 2021), the FDA issued at least 65 warning letters to supplement companies marketing their products to treat or prevent COVID-19—20% more than it issued to supplement producers for making disease claims in 2019.^{30,31} Nevertheless, this figure likely represents only a fraction of the illegal marketing activity that has taken place since the secretary of the US Department of Health and Human Services declared a public health emergency on January 31, 2020.³² FDA facility inspections also decreased significantly in 2020 due to lockdown provisions and social distancing requirements, with unknown impacts on the quality and safety of supplements on the market.³³

Roles of Clinicians

Clinicians, including physicians and pharmacists, play important roles in ensuring that patients use quality supplements and know about risks associated with some dietary supplements. When reviewing medications with patients, they should include dietary supplements and discuss any potential drug-supplement interactions based on the products patients are using or considering. Risk-based **patient counseling** should include discussion of the variable quality of dietary supplements, the presence of un reputable products in the marketplace, and information on which products are commonly adulterated. It is critical for clinicians to report suspected AEs related to dietary supplements and to consider dietary supplements as sources of unexplained AEs.

More broadly, professional associations like the American Medical Association are taking steps to increase patient, health care practitioner, and retailer awareness of resources that can help patients select quality supplements; invest in educational efforts to increase label literacy; and encourage physicians to engage in risk-based conversations with patients about their use of dietary supplements.³⁴

Reform

Public health, health care, and patient and consumer advocacy organizations have long called for reform of the DSHEA framework. A range of proposals aimed at strengthening FDA oversight of supplement products have been put forward, some of which have been included in bills currently under consideration in Congress.^{35,36} These proposals include:

- *Mandatory product listing.* This proposal would require supplement manufacturers to provide basic information to the FDA about the products they sell, including the ingredients those products contain and a copy of the label. Supported by Congress (specifically, the House Appropriations Committee), the FDA, and 95% of American adults,^{1,37,38} this transparency measure would provide the agency with a comprehensive view of the products on the market. Some sectors of the industry also support this measure. Moreover, some advocates for supplement safety call for additional safeguards that could be integrated into the listing system, such as quick response codes for easy identification, to further boost transparency and help the FDA and retailers recall harmful products more quickly and thoroughly.³⁹

- *Clarified mandatory recall authority.* This proposal would allow the FDA to recall supplements tainted with active pharmaceutical ingredients, just as it can for supplements contaminated by other potentially harmful ingredients.
- *Standards.* Experts have suggested that efforts are needed by both the FDA and industry to increase manufacturer awareness of current good manufacturing practice (CGMP) regulations and quality standards, including quality control specifications for the identity, purity, strength, and composition of finished dietary supplements, as well as their ingredients.³⁹ Wider use of the public standards developed by the United States Pharmacopeial Convention or by other bodies, along with following CGMP, has been recommended for dietary supplements.^{39,40}
- *Premarket review of labeling and claims.* Some have proposed that supplement labels be subject to a premarket review process, wherein manufacturers would be required to submit all label information to the FDA before marketing products to ensure regulatory compliance.³⁹ Under current law, the FDA can only act after it finds that supplement manufacturers have made illegal claims about their products or violated product labeling regulations.
- *NDIN pathway reform.* Proposals to strengthen the NDIN pathway include a statutory change to clarify that manufacturers cannot rely on the GRAS exemption to establish ingredient safety but must comply with the NDIN process, as well as the adoption of a “master file” concept that would protect manufacturers’ proprietary safety or manufacturing data.
- *Adequate funding for FDA oversight.* Industry, health care, and public health groups have called for increased funding for the FDA office that directs the agency’s policy efforts related to supplement regulation. Its current budget is roughly \$10.8 million, a tiny fraction of the \$40 billion industry it oversees.⁴¹

Conclusion

Congress is currently considering legislation that would provide the FDA with better and clearer authority to regulate dietary supplement products and protect public health. Outside of these reforms, however, health care practitioners should regularly engage their patients in conversations about supplement safety to ensure that they make more informed decisions about their consumption of these products.

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Elizabeth Richardson, MSc directs the Health Care Products Project at the Pew Charitable Trusts in Washington, DC. The project focuses on strengthening and improving medical product regulation to safeguard patients and consumers. Prior to joining Pew, Richardson worked at the Robert J. Margolis, MD, Center for Health Policy, the Brookings Institution, and the Urban Institute, focusing on a range of health policy topics. Richardson holds a bachelor's degree in anthropology and French from Wake Forest University and a master's degree in global health and public policy from the University of Edinburgh.

Farzana Akkas, MSc is a senior associate at the Pew Charitable Trusts, where she conducts research and policy analysis on a broad range of topics to inform the strategic needs of the Health Care Products Project. Prior to joining Pew, Akkas worked at the National Center for Health Research, focusing on FDA regulation of medical products. Akkas holds a bachelor's degree in biomedical science from Kingston University London and a master's degree in health promotion and public health from Brunel University, London.

Amy B. Cadwallader, PhD is the director of regulatory and public policy development for the US Pharmacopoeia. Previously, she was the director of science and drug policy at the American Medical Association (AMA) and assistant secretary to the AMA Council on Science and Public Health. She has also worked at the World Anti-Doping Agency-accredited Laboratorio Antidoping FMSI in Rome and served as an adjunct faculty member at John Cabot University and as a senior scientist and dietary supplement expert at Aegis Sciences Corporation. Dr Cadwallader received a PhD in pharmacology and analytical toxicology from the University of Utah, an MS in biology/forensic science from Virginia Commonwealth University, and a BS in chemistry and in biochemistry and molecular biology from Dickinson College.

Citation

AMA J Ethics. 2022;24(5):E402-409.

DOI

10.1001/amajethics.2022.402.

Conflict of Interest Disclosure

The author(s) had no conflicts of interest to disclose.

The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.



AMA Journal of Ethics®

May 2022, Volume 24, Number 5: E410-418

POLICY FORUM: PEER-REVIEWED ARTICLE

Which Features of Dietary Supplement Industry, Product Trends, and Regulation Deserve Physicians' Attention?

Amy B. Cadwallader, PhD and AMA Council on Science and Public Health

Abstract

Patients expect that dietary supplements they purchase—and physicians expect that dietary supplements they recommend—are safe, accurately labeled, quality products. Since many dietary supplements, especially vitamins and minerals, are key parts of evidence-based interventions for patients with many conditions, illegal, fraudulent, adulterated, or improperly labeled products should be regarded as sources of clinical and ethical concern. Adverse events (AEs) can occur and, when they do, relevant data should be carefully collected and analyzed. This article considers how many physicians' and patients' confusion about dietary supplement regulation can undermine quality caregiving and responses to AEs. This article also summarizes a recent American Medical Association Council on Science and Public Health report on dietary supplement supply and marketing practices and on physicians' roles in guiding patients when dietary supplement use is clinically indicated.

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Market Growth

The dietary supplement industry grew from approximately 4000 products in 1994 to as many as 90 000 in 2017, according to estimates.^{1,2} Surveys indicate that more than half of US adults consume dietary supplement products.^{3,4} The economic value of the industry is projected to reach nearly \$60 billion in the United States—and nearly \$200 billion worldwide—by 2025.^{5,6} As the industry grows and more individuals use dietary supplements, a renewed focus on the risks associated with these products and the **regulatory processes** involved in bringing them to market is warranted.

Regulation

The Federal Food, Drug, and Cosmetic (FD&C) Act defines a dietary supplement as a product, taken orally, containing a dietary ingredient intended to supplement the diet.⁷ Dietary supplements come in many forms—including tablets, capsules, powders, energy bars, and liquids—and are available for purchase over the counter in stores and via the internet. Dietary supplements are only intended to supplement the diet; they are not

therapeutic medications and are not intended to treat, diagnose, mitigate, prevent, or cure diseases. Dietary supplements are regulated by the US Food and Drug Administration (FDA) differently from “conventional” foods and drugs.⁸ Drugs go through a rigorous **FDA approval process** before entering the market; drugs are considered unsafe until evidence shows they are safe. Dietary supplements do not undergo this approval process and are considered safe until proven unsafe.

The FDA regulates the processing, manufacturing, labeling, and packaging of dietary supplements through the Dietary Supplement Health and Education Act (DSHEA), enacted as an amendment to the FD&C Act in 1994.⁹ Dietary supplement companies are responsible for having evidence that their products are safe and for ensuring that the label claims are truthful and not misleading. The FDA is responsible for taking action against any adulterated or misbranded dietary supplement product only after it reaches the market and a violation is found. The FDA pursues enforcement actions on dietary supplement products for safety issues, manufacturing violations, and improper marketing or misbranding, including the use of prohibited disease claims.^{8,10} While structure/function claims, which describe the effect a substance has on bodily structures or functions (eg, “helps improve memory”), are permitted, disease claims—or claims that a product can diagnose, cure, mitigate, treat, or prevent disease (eg, “reduces the pain and stiffness associated with arthritis”)—are prohibited on dietary supplement labels and require FDA approval and evidence to be used on labels of approved drug products.

The FDA recently announced efforts to strengthen the regulation of dietary supplements by modernizing and reforming their oversight.¹¹ A recent survey conducted by the Pew Charitable Trusts found that most American adults believe the FDA should do more to ensure dietary supplements’ safety, and experts support stricter regulation and reform of the DSHEA.^{12,13,14} Reform proponents support mandatory product listing that includes safety provisions^{15,16}; the Supplement OWL[®] is also a resource that can be improved.¹⁷

Supply Chain Opacity and Poor Quality

Beyond oversight by the FDA and related agencies, the dietary supplement industry can, and should, play an active and influential role in addressing dietary supplement quality and compliance. The FDA inspected 656 dietary supplement production facilities in fiscal year 2017 and found violations in more than half of them, the most common violation being the failure to establish “purity, strength, or composition of their final product.”¹⁵ Although many companies adequately self-regulate, it is well documented that unethical individuals and companies continue to manufacture and distribute low-quality, adulterated, or misbranded products labeled as dietary supplements.^{18,19,20,21}

The supply chain link between manufacture and distribution of dietary supplements can involve multiple ingredient suppliers, brokers, and domestic and international contract manufacturers. Supply chain complexity can obscure tracking of ingredients’ lineages and identities of parties involved in producing a single supplement. Supply chain complexity and lack of transparency also exists for drugs and is a topic of policy debate,^{22,23} but it is beyond this article’s scope.

With large increases in the number of manufacturers and a subsequent rise in the number and kinds of safety concerns, several companies have engaged independent product certification companies to provide additional security and risk minimization for consumers relying on dietary supplements. For example, companies offer verification

and **certification services** to test whether products contain labeled dose(s) of active ingredient(s) and do not contain microbes, toxins (eg, heavy metals), or substances banned by athletic organizations.^{24,25,26,27,28}

Trends

Not all dietary supplements lack evidence of efficacy. Many products considered dietary supplements are an important part of patient health care, including products to treat vitamin and mineral deficiencies and supplementation during pregnancy. However, as the American Medical Association (AMA) notes: “many products that have medical benefits are commonly overused among the general population in an attempt to improve or maintain health and use in these ways provides little benefit” or even create risks.²⁹ For example, vitamin C is an essential vitamin, antioxidant, and required building block that the human body cannot synthesize. However, ingesting more than the recommended daily allowance of 75 to 90 mg for adults, which is often achieved through diet, may not add additional benefit and can cause unpleasant symptoms such as diarrhea, nausea, abdominal pain, and other gastrointestinal disturbances.³⁰ More generally, studies have noted that dietary supplement use was not associated with mortality benefits in a nationally representative sample of US adults; that supplement use itself does not have direct health benefits; and, in some cases, that excess intake might increase harmful effects, including cancer and mortality.^{24,31} Nevertheless, a recent study found that the majority of patients in the United States are overly optimistic about the results they can achieve through supplementation.³² Physicians would seem to be less optimistic, as only approximately a quarter of dietary supplements are used by adults on the recommendation of their physician.³³

Adulteration

An AMA report describes 2 types of adulteration:

Adulteration of dietary supplements is usually either economic adulteration, when a less expensive ingredient is used in place of a more expensive ingredient listed on the label, or pharmaceutical adulteration, when an active pharmaceutical is included in a product and not listed on the label. Adding to the complexity and safety risks associated with adulteration, pharmaceutical adulteration includes the use of not only FDA-approved drugs, or drugs formerly approved by the FDA and withdrawn, but also drugs used in other countries (and never FDA-approved) and experimental drugs minimally or never tested in humans.²⁹

Based on a literature review,^{20,21,34,35,36,37,38} the AMA report concluded:

Dietary supplements are associated with an estimated 23,000 emergency department visits each year, and many of these visits are due to products that are adulterated with pharmaceutical drugs. The most commonly pharmaceutically adulterated dietary supplements are those marketed as weight loss, sexual enhancement, or sports supplements.²⁹

Responding to Adverse Events

Postmarket surveillance is a key part of identifying safety problems with dietary supplement products. The FD&C Act defines a dietary supplement adverse event (AE) as “any health-related event associated with the use of a dietary supplement that is adverse” (eg, headache, abdominal pain, allergic reaction, rash, or dizziness or lightheadedness).⁷ A serious AE is defined as an AE that “(A) results in—(i) death; (ii) a life-threatening experience; (iii) inpatient hospitalization; (iv) a persistent or significant disability or incapacity or; (v) a congenital anomaly or birth defect; or (B) requires, based on a reasonable medical judgement, a medical or surgical intervention to prevent an outcome described under subparagraph (A).”⁷

Concomitant use of dietary supplements and prescribed medications is common and can result in life-threatening AEs, hospitalizations, and fatalities.³⁹ During the year 2017 to 2018, 57.6% of US adults aged 20 and over reported using a dietary supplement in the past 30 days,⁴⁰ as compared to 69% of US adults aged 40 to 79 who reported using at least one prescription drug and 22% who reported using at least 5 prescription drugs in the past 30 days during the year 2015 to 2016.⁴¹ Additionally, more than two-thirds of older adults concurrently use prescription medications with over-the-counter medications or dietary supplements.⁴² Suspected supplement-related AEs should be reported to the FDA using the Safety Reporting Portal.^{24,43} Reporting by physicians is voluntary but is strongly recommended; the FDA gives extra credence to physician reports, and the voluntary system of passive surveillance is the only opportunity the FDA has to detect harmful dietary supplements.

Although some high-quality studies demonstrate dietary supplements' health benefits, several others show evidence of harm.⁴⁴ Some dietary supplements are known to cause clinically important interactions with drugs.³⁹ Additionally, some dietary supplements have the potential to interfere with laboratory results.⁴⁵ The US Government Accountability Office estimates that a small fraction of the estimated 50 000 AEs each year from dietary supplements are reported to the FDA. Underreporting and the poor quality of information in the few reports submitted make it nearly impossible for the FDA to find and remove supplements that are dangerous.^{46,47}

Patient-Physician Interaction

Physicians or their office staff should include discussion of dietary supplements when reviewing medications with all patients. Risk-based counseling of patients should include discussion of the variable quality of dietary supplements, the **presence of unreputable products** in the marketplace, and which products are commonly adulterated. Physicians should also make an effort to evaluate any potential drug-supplement or supplement-disease interactions based on the products patients are using or considering. Risk-based and open conversation with patients is crucial in minimizing and appropriately identifying interactions.

When counseling patients about dietary supplements, it should be noted that supplementation is not a substitute for a healthful and balanced diet and, in most cases, provides little benefit. Targeted supplementation may be warranted for high-risk populations for whom nutritional requirements may not be met through diet alone, including people at certain life stages and those with specific risk factors.²⁴

Resources exist for patients and physicians who are seeking more information about products, product ingredients, or products with reported violations. The United States Pharmacopeia provides a list of products it has independently verified for quality²⁶; NSF International has a listing of products that are NSF Certified for Sport^{®27}; and the US Anti-Doping Agency hosts a resource for dietary supplement safety education and awareness, Supplement 411.⁴⁸ Other, more comprehensive resources exist but may require a paid subscription. An example is the Natural Medicines database, which claims to contain over 1200 monographs on natural ingredients, including vitamins, herbs, minerals, nonherbal supplements, naturally sourced chemical compounds, and foods; the monographs include information on a variety of topics, including interactions, for both health care professionals and patients.⁴⁹

AMA Policy and Activities

In light of reported information and evidence, the AMA recently updated its already comprehensive policy related to dietary supplements to call for the following²⁹:

- Enhanced FDA resources and enforcement
- Continued research on efficacy, safety, and long-term effects of dietary supplements
- Modernization of DSHEA, including standards for identity, strength, purity, packaging, and labeling and mandating that product listings include safeguards
- Education to improve physicians' capacity to talk with patients about supplements' risks
- “[I]ncrease[d] patient, health care practitioner, and retailer awareness of resources to help patients select quality supplements”
- Education to support label literacy

Conclusion

A safe dietary supplement marketplace will require supply chain transparency and will involve robust AE, drug interaction, and tainted product reporting. Industry self-regulation is insufficient and ineffective for public health protection and patient safety, since unethical individuals and companies manufacture and distribute adulterated, misbranded, and improperly labeled products that pose significant risks. As the dietary supplement industry continues to grow and patients continue to use dietary supplements, revision and modernization of the DSHEA and FDA and Federal Trade Commission oversight of the industry are necessary. Professional and lay education is also needed to help physicians and patients understand this industry and the risks posed by dietary supplements.

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Amy B. Cadwallader, PhD is the director of regulatory and public policy development for the US Pharmacopoeia. Previously, she was the director of science and drug policy at the American Medical Association (AMA) and assistant secretary to the AMA Council on Science and Public Health. She has also worked at the World Anti-Doping Agency-accredited Laboratorio Antidoping FMSI in Rome and served as an adjunct faculty member at John Cabot University and as a senior scientist and dietary supplement expert at Aegis Sciences Corporation. Dr Cadwallader received a PhD in pharmacology and analytical toxicology from the University of Utah, an MS in biology/forensic science from Virginia Commonwealth University, and a BS in chemistry and in biochemistry and molecular biology from Dickinson College.

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public, and the private sector. Additionally, CSAPH proposes activities that might be undertaken by the AMA as major scientific projects in medicine and public health.

Citation

AMA J Ethics. 2022;24(5):E410-418.

DOI

10.1001/amajethics.2022.410.

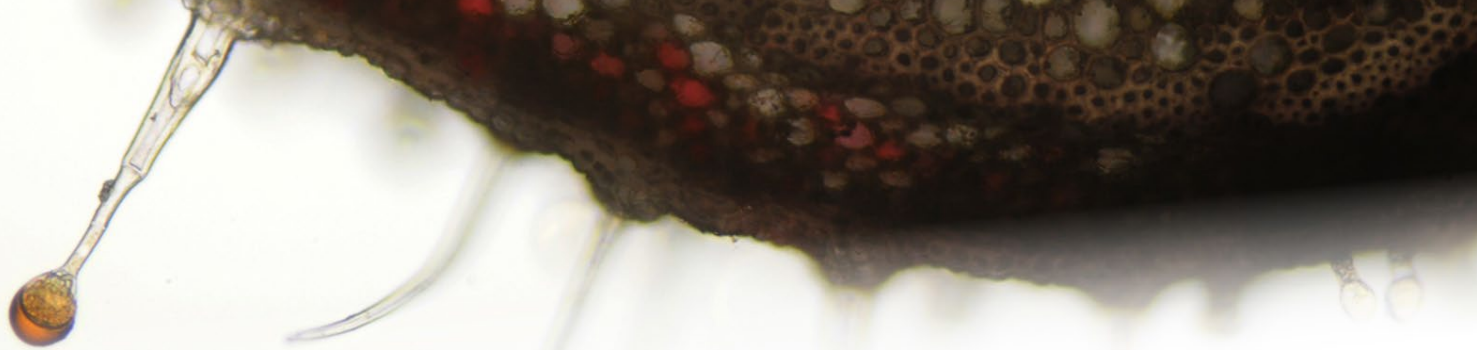
Acknowledgements

American Medical Association Council on Science and Public Health members who contributed to the development of this article include the following: John T. Carlo, MD; Noel N. Deep, MD; Alexander Ding, MD, MS; Kira A. Geraci-Ciardullo, MD, MPH; Laura Halpin, MD, PhD; Dayna Isaacs; Mary LaPlante, MD; Michael M. Miller, MD; Tamaan Obsourne-Roberts, MD; Padmini Ranasinghe, MD, MPH; Corliss Varnum, MD; and David J. Welsh, MD.

Conflict of Interest Disclosure

The author(s) had no conflicts of interest to disclose.

The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.



AMA Journal of Ethics®

May 2022, Volume 24, Number 5: E419-436

HISTORY OF MEDICINE

How Long Have Supplements Promised to Make Us Slim, Sexy, and Virile?

Jorie Braunold, MLIS

Abstract

The American Medical Association's Historic Health Fraud and Alternative Medicine Collection provides a glimpse into the origins of America's cosmetic and supplement industry and the advertising practices that sustain it.

Supplements in the Industrial Age

Turn on the television, open Instagram, sit at a bus stop, and you will be bombarded with messages that your looks could and should be improved upon—if you just buy stuff. Individuals' and companies' claims to secrets of success in weight loss, flawless skin, or lifelong virility are not new. Ancient Egyptians used makeup as we know it,¹ and scientists have documented face and body paint use during the middle Pleistocene, about 130 000 years ago.² Since the Industrial Age, consumers have created a market for enhancement products. Increased rates of literacy and technology advances³ led to a boom in newspaper and magazine sales, and both media were filled with advertisements for patent medicines, including supplements.⁴

From 1906 to 1975, the best resource the public had for evaluating claims about supplements was the Bureau of Investigation of the American Medical Association (AMA).⁵ Individuals curious about weight loss pills or beauty creams could write to the AMA's chemical laboratory to request information or relay horror stories about the ill effects of their use of such products. When the AMA investigated, it reported fraudsters to the Better Business Bureau or the US Food and Drug Administration (FDA). Due to high demand for its services, however the AMA's lab was pressed to prioritize investigation of supposed cures for cancer and diphtheria. Some beauty, diet, and virility products' effectiveness claims were so outrageous that the lab often responded to inquiries about them by stating that any company or physician making such clearly false promises should be reported to state authorities. But state medical licensure as we know it today didn't exist until the late 19th century.⁶

Advertisements for supplements were directed to consumers in newspapers, letters, pamphlets, celebrity endorsements, and on billboards. For 69 years, the AMA's Bureau of Investigation collected these products' packaging and advertisements, establishing what is known today as the Historical Health Fraud and Alternative Medicine Collection

of the AMA Archives. Some of its most interesting items are categorized by “ailment” and are described herein.

Before and After Fat Foe

In the late 19th and early 20th century, America underwent a cultural shift in body image. Between Hollywood and the advertising industry, a desire to have a lean physique became *de rigueur*.⁷ While obesity and “overindulgence” were problems for both men and women,⁸ advertisements for **weight loss supplements** in the early to mid-20th century tended to feature images of women’s bodies, in particular.

This early example of “anti-obesity” advertising represents women’s bodies, despite use of the gender-neutral term *fat folks*.

Figure 1. Fat-Foe Obesity Herb Tea Ad, 1912

**SIP YOUR
FAT AWAY**

**START
REDUCING TODAY**
with
FAT FOE

**INCLUDING
OBESIT
HERB TEA**
*which brings
JOY TO
FAT FOLKS*

Price \$1.00

Weight loss tea is still commonly available today, although we have known for at least 100 years that weight loss attributed to tea is minimal.⁹

Figure 2. Charm Tea Package, 1933



Re-duce-oids were more harmful than teas, with side effects ranging from serious to fatal.

Figure 3. Re-duce-oids Ad, 1929



Although Re-duce-oids were for both men and women, the packaging represents 2 lean women's bodies' silhouettes.

Figure 4. Re-duce-oids Package, 1936



Re-duce-oid pills included a thyroid extract and potassium iodide, a commonly used medication for hyperthyroidism, and were especially dangerous for persons with diabetes, goiter, or coronary diseases, each of which is commonly comorbid with obesity.¹⁰

The ingredients used in Re-duce-oids were atypical for the time, since most reducing tonics were simply laxatives, suggesting why the 1920s and 1930s were known as the “golden age of purgation.”¹¹

Figure 5. Bonkora Ad, 1933

Appearance Benefited by Normal Weight

Most stout people reduce for the sake of appearance.

Certainly a trim, daintily covered figure, is far more attractive than heavy neck and shoulders, large hips and thighs, and thick ankles.

But you should consider your health, too. Excessively stout people are prone to more diseases than those not burdened with excessive fat.

Excess fat crowds the great vital organs, particularly the heart.

Insurance companies, which have the best possible doctors to advise them, are constantly warning their policy-holders against overweight.

Don't take chances with excess fat. For appearance sake—for increased popularity and for your health's sake, take steps to get rid of this fat at once.

No Fatiguing Exercises

We don't advocate strenuous exercise for stout persons.

Mild exercise is desirable, if it is not carried to the point of excess.

Walking is an excellent form of exercise. Swimming is good exercise, also good for general health. Tennis is good exercise if you do not carry it to excess. Golf is healthful. If the weather and other conditions are favorable take exercise in the open air.

But do these things for enjoyment—don't overdo them as a duty.

If You Wish Further Information or Advice Write Us

We have tried to make this circular as clear as possible. However, if there is any further information you desire, please don't hesitate to write us. We will be glad to answer. But be sure to address your letter to the proper department.

Address:

Has Your Fat Made You Look Older Than Your Age?

Fat is associated in people's minds with age. If two women are about the same age and about the same appearance as regards facial lines and complexion, the stouter one will often be judged to be older than the thinner one.

We all like the figure that makes us look as young as our age.

This is possible by following the treatment if excess weight is due to indiscretion in diet or lack of exercise. When strenuous, overdone, health-breaking exercises are avoided. When, instead of weakening yourself by insufficient diets, you eat plenty of the kind of energy-producing vegetables we have suggested. When you keep the system free from wastes by proper elimination, for which Bonkora is designed.

Eat—don't be hungry. Exercise in moderation. Follow the Bonkora Treatment faithfully. And keep it up!

Start Today. The Sooner You Begin, the Sooner You May Have the Beneficial Effects

Start the Bonkora Treatment Today. Keep it up faithfully. Don't be discouraged if you don't see results the first week.

Some people respond more quickly than others. In some cases beneficial results may be noticed in a day or two. In others, it may take several days before results are really noticeable, but when once they start, the reduction should be steady.

Bonkora contains no drugs which speed up the heart action or accelerate the vital organs unduly.

But, in spite of that, don't try to rush the treatment too rapidly, by overdosing or overdoing. Follow the directions.

If you lose a couple of pounds a week it is healthier than losing a pound a day. Moderate reduction allows the body and skin to adjust themselves to the new condition, and tends to prevent the weakness that may result from drastic change in diet or starvation diet and heavy dosing.

FREE—A Jar of New Beauty Cream

Read about Bon Sontay, the new kind of beauty cream in enclosed circular. One of these circulars is enclosed with every box of Bonkora, with coupon attached. After you have taken six bottles of Bonkora, send us the 6 coupons. Write us a letter telling your experience with Bonkora.

Tell us how much you weigh at that time and how much you weighed before starting the treatment.

In return for your kindness, we will send you FREE a FULL SIZE Jar of Bon Sontay Cream.

Bonkora usually sells at \$1.00 a bottle. 3 bottles for \$2.75. 6 bottles for \$5.00.

Bon Kora

TRADE MARK REG.

TREATMENT

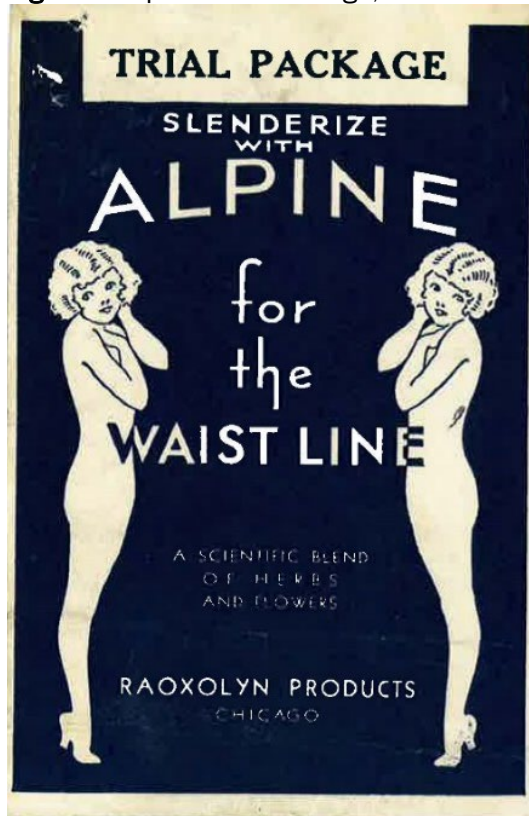


6% ALCOHOL

The Complete BonKora Treatment Consists of an Eliminant with Rational Method for Correcting Causes of Excess Weight Due to Indiscretion of Diet and Lack of Exercise

FULL DIRECTIONS INSIDE

Figure 6. Alpine Trial Package, 1934



In 1941, the Federal Trade Commission successfully issued a cease-and-desist order to stop Re-duce-oids manufacturers from disseminating misinformation.¹² Three years earlier in 1938, passage of the Food, Drug and Cosmetic Act enabled the US government oversight of some supplements,⁷ forcing many companies out of business. Demand continued apace, however, and new products entered the market.

In the 1950s, a variety of new supplements entered the market, including phenylpropanolamine, which was the primary ingredient in both Du-Dol and RX-120.

Figure 7. Du-Dol Ad, 1957

DON'T DELAY! SUPPLIES LIMITED! SEND NOW!

.....

ANDERSON PHARMACAL CORP., 400 East Fordham Rd., New York 58, New York

Please rush my DU-DOL by return mail. If I am not completely satisfied in every way, I may return the unused portion and you will refund my purchase price immediately, no questions asked.

I have checked the size I want below.

Rush regular size supply at once. When my package arrives, I will pay postman only \$3.00 plus C.O.D. postage and handling.

Rush big double supply at once. When my double package arrives, I will pay postman only \$5.00 (I save \$1.00) plus C.O.D. postage and handling.

(PLEASE PRINT CLEARLY)

NAME _____

ADDRESS _____

CITY _____ ZONE _____ STATE _____

P.S. SAVE MORE! Postage rates have just gone up. Send cash, check or money order. For \$3 or \$5 and we pay all postage and handling charges.

Figure 8. RX-120 Ad, 1958

NOW...YOU CAN WEAR REVEALING BATHING SUITS, SHORTS, EVENING GOWNS!



BEFORE

Case #3478. Ann Cusmano, only 21 but she looks 20 years older! Here she weighs 225 pounds! A wallflower because of this ugly fat! What a tragedy!



**HAVE A SLENDER,
GLAMOROUS FIGURE
IN TIME FOR YOUR
SUMMER WARDROBE!**

Yes, now you can trim down those unattractive pounds and inches all over your body just in time for the summer months ahead! You can take off 9 pounds in 10 days, 18 pounds in 20 days, 27 pounds in 30 days... lose up to 49 pounds in 8 weeks or we'll pay you \$14.00. You'll be able to wear revealing bathing suits, slacks, shorts, evening gowns in time for the glorious fun-filled days ahead... even before the Summer months start! All without special diets, regimens, dietary supplements, habit-forming drugs, exercise, calorie counting, massage, hungry moments... with new amazingly safe RX-120.



AFTER

It's the same girl! She took off 90 pounds with RX-120. Now she wears a size 11... instead of 22½. She's lovely... she has a young, glamorous figure! The whole world looks different!

WILSON-WILLIAMS, Inc., 114 East 32 Street, New York 16, N. Y.

SEP 17 1958
30 8444

Laboratory reports confirmed by 1958 that, taken in amounts allowed over the counter, phenylpropanolamine did not promote weight loss.¹³ By 1962, 20 court actions had been filed alleging false advertising for products containing phenylpropanolamine.¹⁴ This nasal decongestant and appetite suppressant was removed from over-the-counter sales in 2005.

Beauty Products and Cosmetics

Most beauty products and cosmetics were, and still are, applied topically. But demand for products promising clear, unblemished skin led some manufacturers to **promote dietary supplements** for this purpose, too, regardless of whether they worked.

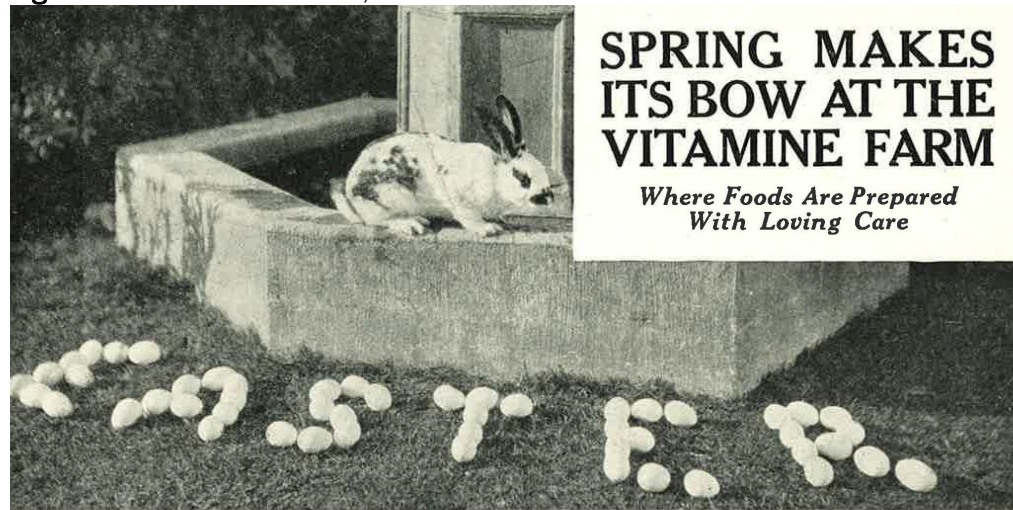
Beecham's pills claimed to cure acne. In addition to claiming to cure acne, Beecham's pills also claimed to cure cold chills, "lowness of spirits," stomach pain, wounds, and headaches. Scientists in England found that the pills contained aloe, ginger, and powdered soap.¹⁵

Figure 9. Beecham's Pills Ad, circa 1909



The Vitamine Farm, based in Geneva, Illinois, also promised a cure for a variety of ills with mineral salts and other ingredients printed in advertisements.

Figure 10. Vitamine Farm Ad, circa 1932



SPRING MAKES ITS BOW AT THE VITAMINE FARM

Where Foods Are Prepared With Loving Care

We Raise In Our Gardens Twelve Parts Of Your Body Chemistry

THOSE TWELVE MINERAL SALTS WHICH KEEP YOU ALIVE WHEN YOU LIVE

CALCIUM—The executive, strong, enduring chemical, which gives us will, long life and red blood.

SILICON—The joy maker, the optimist, speed artist, hair growing chemical which brightens eyesight and complexion, and immunizes against tuberculosis.

30 Capsules\$1.00

FLUORIN—The youth preserver, the protector against infections, bone disease, and fear.

30 Capsules\$1.00

POTASSIUM—The healer, pain reliever, enthusiast, athlete, and the preventive of constipation and growths.

30 Capsules\$1.00

SODIUM—The alkalinizer, the digestive chemical, the good nature and clear brain chemical which prevents catarrh, deafness, hardening processes, moodiness, and enables the body to take up iron.

30 Capsules\$1.00

CHLORIN—The laundryman of the body which expels waste matter, and keeps joints and tendons supple. Prevents pyorrhoea, excessive fat, and auto intoxication.

30 Capsules\$1.00

IODINE—The great gland regulator, which gives mental energy, originality, pep and confidence, and which prevents goitre, insanity through auto intoxication, and nervous breakdowns. Prevents baldness.

30 Capsules\$1.00

MANGANESE—The chemical of poise, strong nerves and good judgment, which coordinates thoughts, gives elasticity, and quick recuperative ability.

30 Capsules\$1.00

MAGNESIUM—The cool, alkaline, refreshing, and sleep promoting chemical, which is a laxative, complexion aid, and preventive of wrinkles from restlessness and anxiety.

30 Capsules\$1.00

IRON—The master chemical which keeps the life force in harmony in the body, gives warmth, magnetism, mental endurance, and creative ability, success, ambition, and vitality.

30 Capsules\$1.00

SULPHUR—The beautifier, the inspirer, the maker of glossy hair, which makes it difficult for disease to enter the body, which promotes bile secretions, throwing out bodily impurities, and which enables the liver to take up the 16 chemical elements.

30 Capsules\$1.00

PHOSPHORUS—The life chemical which is consumed with every thought. Prevents neurasthenia, and enables other elements to create bone, brain and red blood cells. Prevents fatigue. Needed badly by all types who do any kind of mental or indoor work.

30 Capsules\$1.00

Every one of these chemicals is derived from foods, and foods alone. Drugless medicines of great power are they. They are absolutely pure, absolutely clean, and everyone is grown under our own supervision. No preservatives or adulterants of any kind are added. The foods are dehydrated, powdered and put into dainty capsules so that no matter where you are you may have your twelve life-giving chemicals.

Each order is prepared individually, and fresh, at the time of the order. No wholesale stocks to deteriorate. Order your foods five days in advance of your needs, allowing us time to prepare your individual order. Our foods are prepared with loving care. The vibration of 100% wishes for your health is put into every little capsule.

"You love every one of these capsules, don't you," said a visitor to the Vitamine Farm. "The whole place reflects it."

THE VITAMINE FARM, GENEVA, ILLINOIS

“Diseases of Men”

While weight loss and beauty products were aimed more at women than men, anything related to sex was nearly always geared to men. Impotence, virility, and venereal diseases were regarded as “diseases of men” that were “more sensitive” issues, requiring discretion. Physicians’ and manufacturers’ products targeting men were advertised in what were called *street guides*.

In the late 19th to mid-20th century, men could expect to come upon pocket-sized street guides, containing information about local baseball games, bus routes, health advice, a directory of men’s health specialists, and advertisements for tonics, creams, and capsules.¹⁶ Impotence or lack of sex drive were described euphemistically and as “abnormal conditions.”

Figure 11. Set of 3 Street Guides for Men, 1922 to 1937

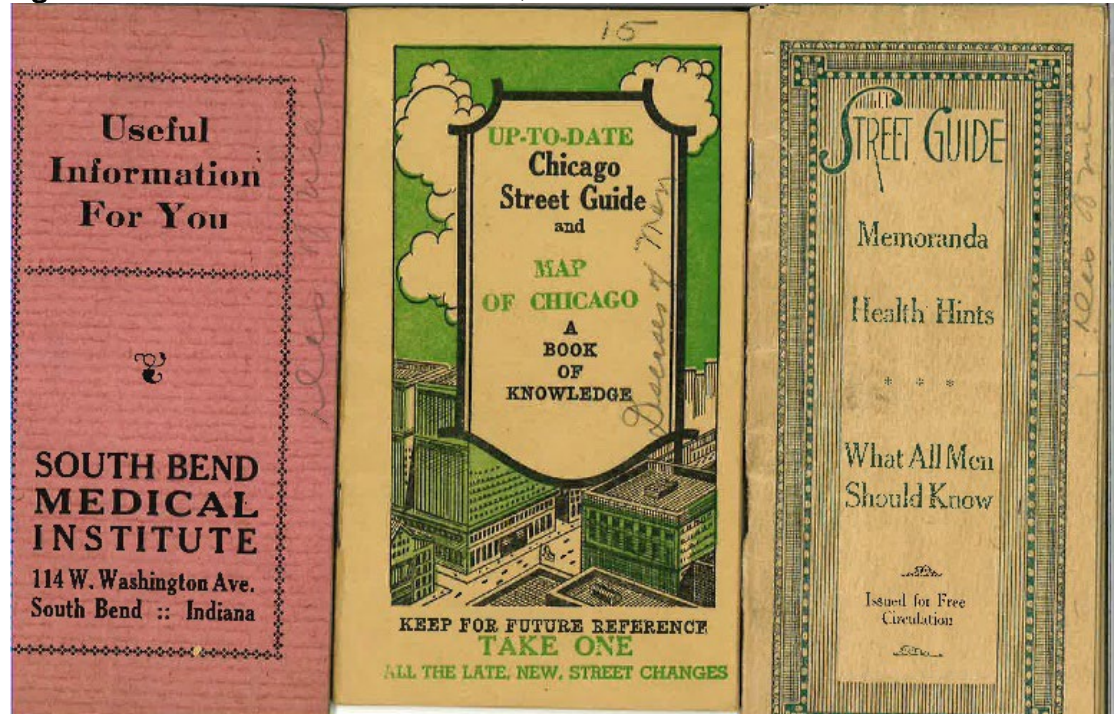
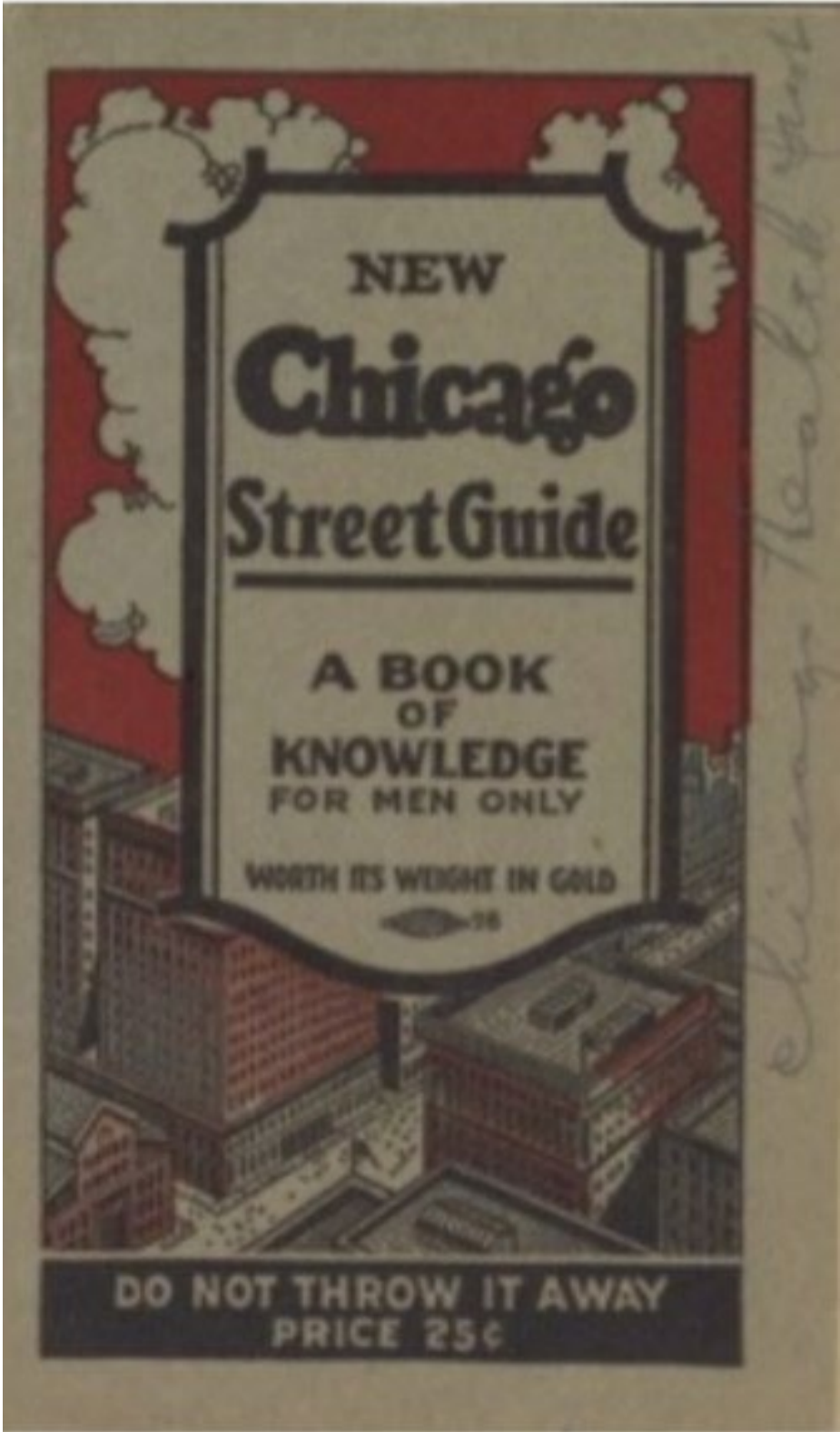


Figure 12: New Chicago Street Guide, 1928



The Erie Medical Company advertised that its product, in which the main ingredient was hemoglobin of bullock's blood, would transform men suffering "sexual weakness" into men as "strong as an ox."¹⁷

Figure 13: Erie Medical Company Ad, 1911

Haemoglobin of Bullock's Blood

Now available to all who seek, in renewal of perfect health and normal vigor, to regain the lost zest of life, and the glow of enthusiasm which should last longer than mere youthfulness.

How Haemoglobin Tinges Life Anew with "The Gold of Vigor."

This Haemoglobin compound restores to the blood the red life-giving elements of organic phosphorus, iron, etc., which the generative glands, lymphatic glands, nerves and brain tissues require. By increasing or rejuvenating the activity of these glands, making them secrete normally, and the nerve and brain tissues act with healthy vigor, a great change is worked in the general physical and mental condition.

The haemoglobin of bullock's blood is now being treated by a process which obtains the full value of its remarkable building and sustaining forces.

This powerful extract has a decided effect upon the glandular system, due to the ready absorption of the iron, organic phosphorus, etc.

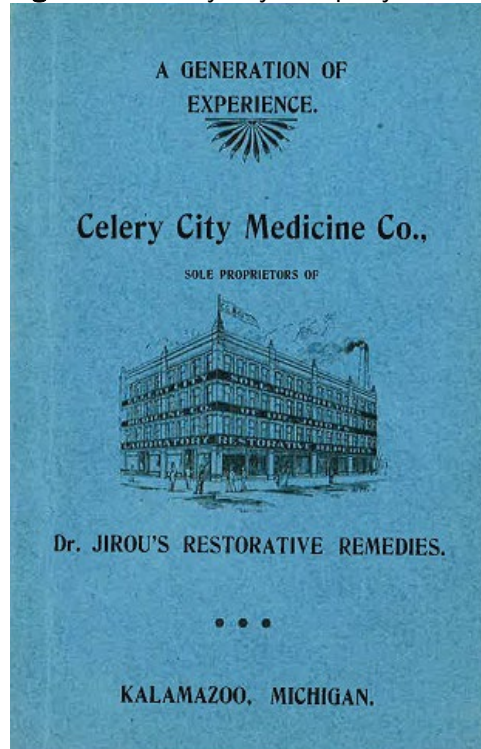
In sexual weakness it has been tested in many cases without the patient's knowledge, he being told that it was administered for his general broken health. These patients have reported to the doctor the happiest effects upon the debilitated sexual condition, which came as a surprise to them.

It has been found that frequently the wasted exterior genital glands of the male begin to fill out and become firm and healthful after a few days.

Women showing all the evidences of the "change of life"—cessation of the menses, shrinkage of the bust, hot flashes and

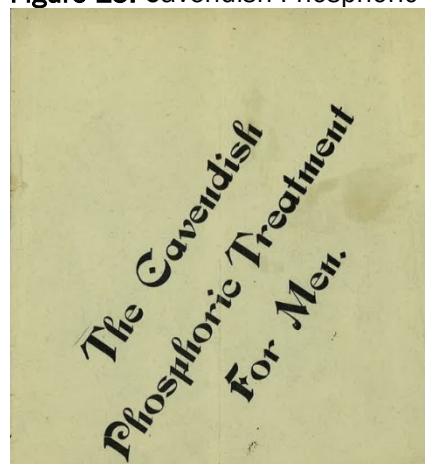
Celery City Company's Dr Jirou marketed its "Famous French Prescriptions for sexual weakness, impotency, and small, shrunken organs,"¹⁸ as tablets containing leaves of coca (primary ingredient in cocaine), nux vomica (with strychnine and brucine, both poisonous), aphrodisiacal herbs and chemical compounds, and phosphorous (more common than bullock's blood, but less common than glandular therapy, which is discussed below).

Figure 14. Celery City Company Famous French Prescriptions, 1915



The Cavendish Phosphoric Treatment offered another phosphorous-based product. Ironically, high serum phosphorous levels are now known to cause erectile dysfunction in some cases.¹⁹

Figure 15. Cavendish Phosphoric Treatment, 1886



The Cumberland Chemical Company created a nostrum it called Sextonique, which promised to “rectify vital weakness” and Tonique Tablets to supplement the tonic 3 times per day.

Figure 16. Cumberland Chemical Company Pamphlet, 1926

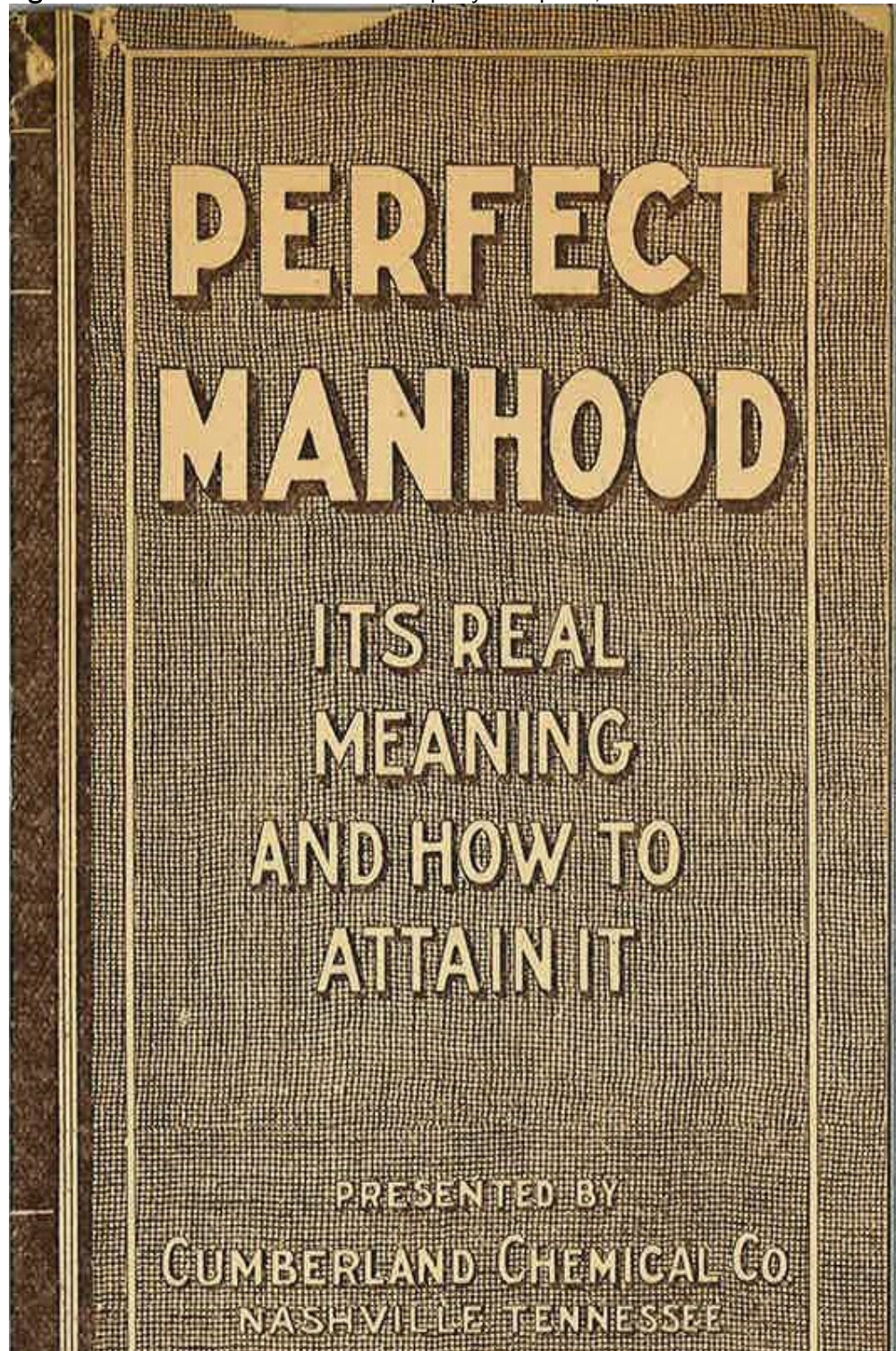


Figure 17. Cumberland Chemical Company Ad, 1925

A DIRECT CHALLENGE TO IMITATORS

A FEW STATEMENTS OF FACTS TO PROVE THAT "SEXTONIQUE" IS THE ORIGINAL AND GENUINE "SEX-TONIC"

The wonderful results reported by users of the genuine C. C. C. SEXTONIQUE treatment in thousands of cases is so well known that many persons and firms have attempted to make money out of our reputation of years standing, by offering various imitations and substitutes to the public, claiming that their preparations "are the original and genuine Sex-Tonic for vital weakness."

Several such imitators have sprung up over the country; many of them have deliberately copied our booklets, circulars, etc. Six or eight such firms have started in business right here in Nashville—now only one or two remain, as their existence is generally short-lived. In order to warn the public against such imitators, we wish to state the actual facts clearly, which are

MATTERS OF RECORD

- 1st. The Cumberland Chemical Company is the exclusive owner of the trademarks "SEXTONIQUE" and "Sex-Tonic". "Sex-Tonic" is a registered trade-mark, granted by the U. S. Government under registration No. 39,249. Any person or firm using the names "Sex-Tonic" or "Sextonique" is guilty of an infringement, and liable to prosecution.
- 2nd. Any person or firm claiming that their preparation is the original and genuine "Sex-Tonic" is guilty of a deliberate falsehood. The GENUINE "SEXTONIQUE" or "SEX-TONIQUE" can be obtained only from the Cumberland Chemical Co., and the name SEXTONIQUE has been in constant use by this company for over ten years. (Most of these imitators have been in business only a short time.)
- 3rd. Any person or firm using or copying our copyrighted literature is guilty of an infringement upon our rights, granted under the copyright laws by the Government, and is liable to prosecution.
- 4th. Every testimonial published by us is a genuine, signed letter, written by actual users of SEXTONIQUE and C. C. C. treatments; any person or firm using these testimonials to advertise other preparations, is guilty of wilful misrepresentation.

We publish the above clear statements, in order that we may protect our patrons and the general public, as well as ourselves, against the claims of imitators who are infringing upon our trade-marks and copyrights.

The Cumberland Chemical Company is a reliable, financially sound business institution, having been in business for many years, and backs up each treatment sold with a Positive Agreement to Refund every cent paid, in the event any treatment sold does not give complete satisfaction to the purchaser.

Cumberland Chemical Company
NASHVILLE, TENN., U. S. A.

THERE IS ONLY ONE ORIGINAL AND GENUINE "SEXTONIQUE"

DO NOT ORDER A SUBSTITUTE OR IMITATION IF YOU WANT TO BE ASSURED OF SATISFACTION AND FAIR TREATMENT.

COPYRIGHT 1925

According to the AMA's own Morris Fishbein, no method of treating illness in the 1920s was more popular than glandular therapy.²⁰ Used for weight loss, impotence, and treating other ills, Goldglan glandular tonic was "recommended for the man who doesn't realize that he is not paying his wife the attention he formerly did" and was said to contain thyroid, anterior pituitary, and orchitic substances.²¹ Similar products are still sold today for erectile dysfunction, although as early as 1924, the AMA reported that there was not sufficient evidence to make these claims for glandular therapy.²²

Figure 18. Goldglan Packaging, 1928



Conclusion

Despite some public backlash against the diet and beauty culture of the 21st century,²³ weight loss and other products tempt many of us to attend our deepest insecurities. And despite FDA authority, unregulated supplements remain widely available and advertised. Items gathered in the AMA's [collection of quack](#) beauty, weight loss, and virility products suggest the persistent appeal of enhancement and a century-old (at least) history of profiteering on insecurity.

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Jorie Braunold, MLIS is the archivist for the American Medical Association in Chicago, Illinois. She has an MLIS in library and information sciences with a focus on archives from Dominican University.

Citation

AMA J Ethics. 2022;24(5):E419-436.

DOI

10.1001/amajethics.2022.419.

Acknowledgements

All images courtesy of the American Medical Association Archives.

Conflict of Interest Disclosure

The author(s) had no conflicts of interest to disclose.

The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.



AMA Journal of Ethics®

May 2022, Volume 24, Number 5: E437-442

VIEWPOINT: PEER-REVIEWED ARTICLE

Reimagining Roles of Dietary Supplements in Psychiatric Care

Katherine Wu, MD and Erik Messamore, MD, PhD

Abstract

Despite impressive pharmaceutical advances, mental illness remains a leading cause of suffering and disability. Although some dietary supplements appear to respond to some needs not met by prescription medications, several obstacles prevent their study or use. This article proposes government-supported review and safety monitoring of supplements' use in caring for patients with mental illness.

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Appeal of Supplements

Dietary supplements are regulated more like foods than pharmaceuticals under the Dietary Supplement Health and Education Act (DSHEA) of 1994.¹ Consequently, a number of companies have aggressively marketed their dietary supplements, often highlighting products' "natural" ingredients and implying vague yet appealing health benefits, such as "mood support." Although commercially successful, such marketing tactics invite skepticism, and some clinicians hesitate to consider dietary supplements in care plans.

Nevertheless, some dietary supplement ingredients do have credible scientific support as therapeutics. Acetyl-L-carnitine, for example, has been the subject of 12 randomized controlled trials and has been shown to significantly reduce depressive symptoms in older adults.² In addition, omega-3 fatty acids have shown benefit in populations at high risk of developing schizophrenia.^{3,4,5} These are important findings, given data from 1990 to 2015 suggesting that an increase in conventional pharmaceutical therapies did not decrease the prevalence and symptoms of mood and anxiety disorders in 4 English-speaking countries.⁶

The limitations of conventional pharmaceuticals create a dilemma for patients and clinicians. It would be ideal to subject promising dietary supplements to the types of clinical trials that would definitively assess their potential value. Yet there is little financial incentive to perform extensive (and expensive) definitive research on their therapeutic potential. We first discuss obstacles to supplement research and then

propose government-supported review and safety monitoring of supplements' use to promote the greater good and minimize suffering.

Obstacles to Research

Regulatory requirements. Under existing regulations of the US Food and Drug Administration (FDA), manufacturers are not required to supply the FDA with evidence of the safety and efficacy of a dietary supplement for treatment of any disease, as they are for pharmaceuticals. Within the ClinicalTrials.gov database, as of August 24, 2021, a search for the terms “acetyl-L-carnitine” and “depression” generated 3 results, while a search for “escitalopram” (a serotonin reuptake inhibitor) and “depression” generated 238 results.⁷ Fewer researchers are invested in studying the efficacy and safety profiles of supplements without this infrastructure. Furthermore, the DSHEA effectively proclaimed that supplements do not need to be registered or approved by the FDA for production and sale.¹

The DSHEA also has downstream effects. Lack of FDA registration or review is a disincentive for clinicians to consider dietary supplements in treating patients. Many prescribers look to the FDA for **guidance on safe treatment** and thus are wary and skeptical of the benefits of “off-label” interventions like dietary supplements. Without authoritative regulation, many supplements will be regarded by clinicians as unregulated and outside their scope of practice. Clinicians might feel uneasy about assessing the risks and benefits of dietary supplements without FDA review and approval, which, for drugs, often requires clear delineation of indications and risks.

Lack of incentives. It is uncommon for insurance companies to cover dietary supplements unless there is extensive scientific evidence of proven health benefits (eg, folic acid for prenatal care, calcium and vitamin D for osteoporosis).⁸ Pharmaceutical companies and researchers are not incentivized to prove the efficacy of dietary supplements due to limitations of patent law.⁹ Intellectual property rights are granted to pharmaceutical companies to hold a temporary monopoly on innovative drugs, which enables the company to **set prices high enough** to recover development costs, fund future research, and ensure the business survival of the company.⁹ The nature of dietary supplements, however, makes it difficult to label any composition as a true innovative discovery and for companies to gain intellectual property rights. A discovery within the supplement industry entails (1) isolation of an active ingredient from an already known food to create a supplement with a previously unknown beneficial effect or (2) production of a health-promoting supplement with a novel combination of active and/or inert ingredients in a previously unknown manner.¹⁰ The rarity of innovative discovery discourages manufacturers from conducting trials, and some studies of dietary supplements' ingredients are limited to case reports or small clinical trials typically conducted by independent research groups with limited funding.

More research should be directed toward elucidating the small amount of already existing data on supplements' adverse effects. Some ingredients, for example, can affect cytochrome P450 enzymes activity in the liver and alter serum levels of other pharmaceuticals, which in turn can affect the action of drugs with a narrow therapeutic index (blood thinners, for example).¹¹ Excessive intake of some nutrients, especially those in fortified foods, in conjunction with intake of nutraceuticals, may lead to toxic blood levels of bioactive ingredients—vitamins A and D, for instance.¹¹ Greater knowledge of supplements would promote well-informed prescribing practices.

Gaining Knowledge

Although large, systematic clinical trials on dietary supplements may be lacking, clinicians can gather knowledge about them from other sources. Case reports, retrospective or prospective trials, and open-label trials can provide some clues about the possible efficacy and risks of such products. Even a collection of case reports on a particular supplement might convince some clinicians to accept that use of that supplement is associated with particular side effects or health benefits. For example, the cessation of side effects once supplement use stops would support an association between the side effects and use of that supplement. Case reports and small studies, unlike trials sponsored by large institutions and companies, involve fewer significant conflicts of interest that can influence study design. Cases can also provide insights that might be lost or overlooked in randomized controlled trials.^{12,13,14} The Office of Dietary Supplements at the National Institutes of Health currently compiles fact sheets on dietary supplements and disseminates information about cases and small studies.^{15,16} When large-scale clinical trial data are lacking, it is still possible to evaluate a supplement.

Need for Review and Data

In what follows, we argue that establishing a review entity and prescribers' database would promote the greater good (ie, utility¹⁷) and minimize suffering. For dietary supplements with a stock of convincing evidence, a reviewing body could help achieve these goals by "certifying" widely available and low-cost dietary supplements to treat psychiatric ailments. A reviewing body with governmental authority would thus support the scientific legitimacy of companies' claims about dietary supplements that have been certified. Such a reviewing body would help consumers understand how dietary supplements can be used to improve mental health and how to make informed choices about dietary supplements. It would also provide patients a sense of security in knowing which dietary supplements were recognized by the group and for which supplements the benefits outweighed the risks in patient cases.

Germany has established such infrastructure to approve dietary supplements for medical use.¹⁸ German Commission E, a surveillance body that was founded in 1978, has helped supplements become integrated into conventional medicine. The commission is tasked with banning risky supplements from the market and compiling information on approved supplements into monographs for the public. By giving supplements official recognition like conventional treatments for psychiatric disorders, Germany has expanded the utility of dietary supplements for its citizens. Most notably, herbal supplements make up 30% of all pharmaceutical sales in Germany, more than half of which are paid for by health insurance.¹⁸ The system, however, is far from perfect, with critics lamenting that the monographs of herbal drugs lack scientific evidence to back claims.¹⁹

Other models for expanding the utility of supplements exist besides reviewing bodies. For example, a governmental agency could be empowered to create a "certified supplement" program following the model of the US Department of Agriculture's National Organic Program,²⁰ which sets standards for production and labeling of products. A third avenue would be for private third-party entities to set standards for the composition and production methods of supplements. In this model, natural product or supplement manufacturers would submit to inspection to receive third-party accreditation (like the Joint Commission model for hospital quality assurance²¹). Our ideal accreditation system would likely assume the third-party model of the Joint

Commission, which would have greater flexibility to change procedures and staff in comparison to government organizations. However, it was only 14 years after the Joint Commission's inception in 1951 that the government recognized that its accreditation practices met Medicare Conditions of Participation.²² Unlike a nonprofit organization such as the Joint Commission, a governmental reviewing body would have the recognized legitimacy even with early implementation. Finally, we would like dietary supplements to be of similar status to pharmaceuticals, in that manufacturers are required to provide evidence of a drug's safety and effectiveness to the FDA for approval. A governmental reviewing body would transfer the goal of adducing high-quality evidence from clinical and academic settings to the dietary supplement industry.

Conclusion

Current regulations for approval and marketing of pharmaceuticals in the United States exclude dietary supplements, thereby removing financial incentives for manufacturers to conduct the large, randomized controlled trials required for approval of pharmaceuticals. This paper has discussed regulatory changes that could assist patients and clinicians in making personalized health care decisions about the potential benefits and risks of dietary supplements as part of treatment. Despite breathtaking developments in psychopharmacology over the last 60 years, mental illness remains a leading cause of disability.²³ Considering this substantial unmet need, it is important for clinicians to consider all reasonable options when caring for patients and for policymakers likewise when reviewing regulations. Evidence-based psychotherapies are broadly underutilized,² and existing data suggest that some dietary supplements are potentially useful and relatively safe.^{2,3,4,5,24,25,26,27}

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Katherine Wu, MD is an intern physician at OhioHealth Riverside Methodist Hospital in Columbus, Ohio, who will go on to pursue a psychiatry residency at the University of Virginia. Her career interests include women's mental health, intergenerational trauma, and consultation-liaison psychiatry.

Erik Messamore, MD, PhD is an associate professor in the Department of Psychiatry at Northeast Ohio Medical University in Rootstown, Ohio, and serves as medical director of the department's Best Practices in Schizophrenia Treatment Center.

Citation

AMA J Ethics. 2022;24(5):E437-442.

DOI

10.1001/amajethics.2022.437.

Conflict of Interest Disclosure

The author(s) had no conflicts of interest to disclose.

The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.



AMA Journal of Ethics®

May 2022, Volume 24, Number 5: E443-451

VIEWPOINT: PEER-REVIEWED ARTICLE

Seven Points for Athletes to Consider Before Using a Dietary Supplement

Amy B. Cadwallader, PhD

Abstract

Performance-enhancing drugs (PEDs) have been used by athletes for as long as sporting competitions have existed. To protect the health and safety of athletes and promote fair play, banned substance lists were developed that include several classes of PEDs. Evidence shows that a majority of athletes use dietary supplement products to aid their training and support their health. Evidence also indicates that use of some dietary supplements carries a risk because the products may contain banned PEDs. Consumers and athletes should weigh a number of considerations before purchasing and consuming dietary supplements to protect their health, reputation, and the spirit of fair competition.

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Why Performance-Enhancing Drug Use Matters

Performance-enhancing drugs (PEDs) have been used by athletes for decades, even centuries. To promote fair play—an issue precipitated by the death of an athlete—the International Olympic Committee (IOC) in 1967 banned the use of PEDs, established a new Medical Commission, and created a list of banned substances.¹ Mandatory testing of all athletes began at the 1968 Olympic Games, and drug-testing programs were initiated all over the world in the following years to further promote fair play and to safeguard the health and safety of athletes.²

In 1999, the World Anti-Doping Agency (WADA) was formed to promote and coordinate the fight against doping in sport internationally. An IOC initiative, WADA was founded with the support and participation of intergovernmental organizations, governments, public authorities, and other public and private bodies fighting against doping in sports.³

How a Substance Is Banned

WADA is considered the international standard and one of the most respected organizations for identifying prohibited substances and methods. Each year, WADA updates its Prohibited List to provide a comprehensive list of banned substances.⁴ WADA considers 3 criteria when reviewing substances for inclusion on the Prohibited

List, and any substance included on the list must fulfill at least 2 of the following criteria⁵:

1. Substance has the potential to—or is proven to—**enhance sport performance**.
2. Evidence exists of a potential or actual health risk to an athlete.
3. Use violates the spirit of sport as described in the World Anti-Doping Code.

Classes of substances on banned substance lists include anabolic-androgenic steroids, peptide hormones, growth factors, erythropoiesis stimulators, hormone modulators, stimulants, diuretics, masking agents, and more.² Although WADA sets the international standard, each sport organization creates its own list based on the substances that put athletes at risk or might be used to provide an unfair advantage. Banned substance lists maintained by international, national, professional, amateur, and student sport organizations are now commonplace and updated yearly. The consequences of athletes being caught with a banned substance in their body include sanctions on eligibility for athletic participation, reputational damage, and stripping of prizes and medals, in addition to potential **health risks** or death.

Associations Between Dietary Supplements and Banned Substances

Data indicate that between 40% and 70% of athletes use dietary supplements and that between 10% and 15% of supplements may contain prohibited substances.⁶ While many dietary supplement manufacturing companies make every effort to produce quality products, it is well documented that unethical individuals and companies continue to engage in the manufacturing and distribution of intentionally adulterated or misbranded products labeled as dietary supplements.^{7,8,9,10,11} The most commonly adulterated dietary supplements are those marketed as weight loss, sexual enhancement, or sports supplements.^{9,10,12,13,14,15,16,17} From January 1, 2004 through December 19, 2012, 51% of class I drug recalls in the United States were for dietary supplements as opposed to pharmaceuticals,¹⁷ and copious reports detail the detection of contaminants in dietary supplements.^{2,18,19,20,21}

Contamination of dietary supplements marketed to athletes is often due to pharmaceutical adulteration, which occurs when an active pharmaceutical is included in a product and not listed on the label.¹⁰ Pharmaceutical adulteration includes drugs formerly approved by the US Food and Drug Administration (FDA) and withdrawn, drugs used in other countries and never FDA-approved experimental drugs that were minimally or never tested in humans, veterinary drugs, and other novel compounds.^{22,23,24,25} Additionally, some compounds are intentionally designed and manufactured to avoid regulations and evade standard detection and identification; most of these compounds are added to dietary supplements without efficacy, safety, or toxicity assessments.²⁶

A former chair of the National Collegiate Athletic Association drug-testing committee noted in an interview that most college students who report a positive drug test do so because of substances, including steroids, found in over-the-counter dietary supplements.²⁷ However, when looking at shelves and aisles in stores and through pages of products on the internet, how can consumers and athletes learn which ones might contain banned substances or their markers?

Seven Considerations

With this background in mind, the following considerations should be weighed by all consumers and athletes before purchasing and consuming dietary supplements.

Be educated about applicable banned substance lists. All athletes should know if there is a banned substance list for their sporting organization and what substances are included on it, as many ingredients in dietary supplements appear on banned substance lists.² Minimally, any athlete should have a trusted sports medical professional to consult when thinking about using a dietary supplement.

Be aware of strict liability and understand that athletes use any products at their own risk. Most sports organizations hold athletes to a policy of strict liability, meaning that athletes are solely responsible for the substances in their body, what they consume, and for any subsequent consequences if metabolites or markers of banned substances are found in a biofluid—regardless of whether they intentionally or inadvertently ingested a prohibited substance (eg, in a contaminated dietary supplement).²⁸ Regardless of intent, athletes who take nutritional supplements risk damaging consequences.²⁹ The provision of strict liability is a common feature of the drug-testing programs of many sports organizations.²

Understand that supplement regulations differ from food and drug regulations. Consumers, including athletes, often assume that dietary supplements are subject to the same (or similar) regulations as over-the-counter or prescription medications; this is not true. Dietary supplements are not reviewed premarket and are not held to the same evidentiary standards of safety or efficacy as medications to be sold to consumers. Medications go through a rigorous FDA approval process before entering the market; drugs are considered unsafe until proven otherwise. Dietary supplements do not undergo this approval process and are instead considered safe until contrary evidence is provided. However, through the Dietary Supplement Health and Education Act of 1994, the FDA regulates the processing, manufacturing, labeling, and packaging of dietary supplements.³⁰ This act requires companies to ensure that their products are safe and that the **label claims are truthful** and not misleading before they are brought to market. The FDA is responsible for taking action against any adulterated or misbranded dietary supplement product only after it reaches the market and a violation is found.^{31,32}

Always be skeptical—if a claim on a label sounds too good to be true, it probably is. Claims such as *Helps you use oxygen more efficiently*, *Make 10 lbs of muscle in a week*, *Incinerate fat*, and *Get immediate results in energy, size, and strength* are red flags. Although a claim might sound enticing to athletes looking for a competitive edge, extreme caution is warranted. Advertisement of awards won does not mean a product is safe; in fact, such advertising might suggest a product contains a banned substance.^{33,34}

Read the ingredients list and know what each ingredient is. Consumers, especially athletes, should read the entire list of ingredients, understand what each ingredient is, and be aware of the amount of each ingredient contained in a serving. New ingredients continue to appear in products, yet few or no peer-reviewed publications assess compounds' pharmacology, toxicology, and safety. Compounds could be banned substances or produce markers of banned substances.^{34,35} Some ingredients can cause serious adverse events or be deadly.^{36,37,38,39}

Stimulants are a common contaminant in dietary supplements.^{11,40} The *bodybuilding.com* 2012 supplement of the year was found to contain a methamphetamine analog,³⁴ and once including this particular drug in products fell out of favor, another dangerous and banned stimulant became popular.⁴¹ Instances of

contamination with prescription diuretics have also been documented,^{42,43,44} and estrogenic compounds, anabolic agents—including anabolic-androgenic steroids—are frequently encountered in products marketed to athletes.^{45,46,47,48,49,50,51} Adulterants are even found in dietary supplements for erectile dysfunction.^{19,52}

Look for third-party confirmation of the ingredients list from a trusted source. Often, labels are intentionally confusing. Products have included false seals of approval noting “banned substance free” while at the same time listing a substance banned by most sport organizations among the ingredients. In light of such tactics, third-party certification of product ingredients from a reputable and trusted source may be helpful. With the large increase in dietary supplement manufacturers and the subsequent rise in dietary supplement safety concerns, several companies have started independent product certification services to provide an additional level of security and risk minimization for consumers and athletes.^{53,54,55,56,57}

Unfortunately, it can often be a daunting challenge to collect and evaluate all the information required to develop a strong sense of confidence in a supplement brand and its products, which is a reason why third-party certification is a desirable option for supplement companies. Third-party certification programs are designed to help protect the rights and health of consumers and drug-tested athletes by providing some assurance that certified products are free of the prohibited substances for which they are tested. No certification program can assure that a product is entirely free of prohibited substances because it is not possible to test for all prohibited substances. However, supplement companies that commit to third-party certification have done everything feasible to assure consumers that their certified products present minimal risk of inadvertent doping. In addition to product certification, consumers can also usually place trust in well-established companies with no previous issues with product contamination, a good record with the FDA, and a commitment to scientific integrity regarding claim substantiation.

Additionally, understand what certification entails, as not all certifications are of equal quality or content. Many companies test products to verify they contain the labeled dose(s) of the active ingredient(s), while some companies test to confirm that products do not contain microbes, heavy metals, or other toxins, and others test for a comprehensive list of substances that are banned by athletic organizations.^{53,54,55,56,57}

Protect your health and reputation. Be sure to check with your physician or sports health professional before consuming or incorporating any dietary supplement into your routine. Do not take any supplement purchased from a store, online, or given to you by a friend or relative without first discussing it with a medical professional who has your best interests in mind.

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Amy B. Cadwallader, PhD is the director of regulatory and public policy development for the US Pharmacopoeia. Previously, she was the director of science and drug policy at the American Medical Association (AMA) and assistant secretary to the AMA Council on Science and Public Health. She has also worked at the World Anti-Doping Agency-accredited Laboratorio Antidoping FMSI in Rome and served as an adjunct faculty member at John Cabot University and as a senior scientist and dietary supplement expert at Aegis Sciences Corporation. Dr Cadwallader received a PhD in pharmacology and analytical toxicology from the University of Utah, an MS in biology/forensic science from Virginia Commonwealth University, and a BS in chemistry and in biochemistry and molecular biology from Dickinson College.

Citation

AMA J Ethics. 2022;24(5):E443-451.

DOI

10.1001/amajethics.2022.443.

Conflict of Interest Disclosure

The author(s) had no conflicts of interest to disclose.

The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

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