

# Dietary supplements in the US: pitfalls and safety

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The 1999–2000 National Health and Nutrition Examination Survey revealed that 42% of American adults reported taking a dietary supplement.<sup>1</sup> Owing to the almost ubiquitous presence of dietary supplements, the general public is repeatedly given the, at least implicit, message that dietary supplements will improve elements of their lives, such as strength, energy, endurance, weight and appearance. The public, however, is much less frequently made aware of potential safety concerns.

Ephedra (also known as ma huang), which was marketed for weight loss and enhancing athletic performance, is a classic case study of a harmful dietary supplement that was available for years despite growing safety concerns, and reveals important limitations in the regulations that govern dietary supplements. In 2003, the FDA issued an alert advising consumers to stop using dietary supplements containing ephedra. A final ruling, indicating the danger of these supplements and banning their sale, went into effect in 2004.<sup>2</sup> Safety concerns regarding ephedra had, however, been present for a number of years; hundreds of reports of adverse events were submitted to the FDA before a warning regarding the use of ephedra products was proposed in 1997.

Why did it take so long for ephedra to be banned? The Federal Food, Drug, and Cosmetic Act was only amended in 1994 to establish standards with regard to dietary supplements by the publication of the Dietary Supplement Health and Education Act (DSHEA).<sup>3</sup> There are two key features of the DSHEA that are relevant to product safety: first, manufacturers of dietary supplements do not have to provide the FDA with evidence that a dietary supplement is effective or safe prior to marketing it; and second, once a dietary supplement is on the market, the FDA holds the burden of proof to show that a product is not safe in order to restrict its use or remove it.<sup>3</sup>

Dietary supplements are marketed directly to consumers. Labels might contain one of three

types of claims: a health claim; a structure or function claim; or a nutrient content claim.<sup>4</sup> A health claim for a dietary supplement describes a relationship between a substance and a disease or health-related condition, much as is the case for drugs. The FDA must approve such claims after a review of the scientific evidence. The standard of scientific validity for a health claim includes two requirements: first, that all the publicly available evidence supports the claimed relationship between the substance and the disease; and second, that there is significant scientific agreement among qualified experts that the relationship is valid.<sup>5</sup> In contrast to its requirements for drugs, however, the FDA can allow a qualified health claim for a dietary supplement if the majority of scientific evidence supports the claim, even if it does not reach the standard of significant scientific agreement.

Under the DSHEA, if a dietary supplement has a structure or function claim the label should clearly explain the nature of that claim and the mechanism by which it works.<sup>3</sup> The manufacturer is responsible for ensuring the accuracy and truthfulness of these claims. They do not require approval by the FDA, however, and product labels containing structure or function claims must, therefore, also include a disclaimer.

To a great extent, the general public is unaware of the differences between regulations for drugs and dietary supplements. A 2002 Harris poll revealed that over half of respondents believed that dietary supplements were subject to the same approval processes as drugs, that they required warning labels about potential dangers, and that claims for safety or effectiveness were not allowed unless there was solid scientific evidence to support them.<sup>6</sup>

The various types of adverse events resulting from the use of dietary supplements are well recognized in the literature,<sup>7,8</sup> however, their incidence is very difficult to determine. Dietary supplements, as defined by the DSHEA, include vitamins and minerals, in addition to herbs and other botanicals, amino acids and other

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substances that are used to supplement the diet. Overall, most safety concerns relate to dietary supplements other than vitamins and minerals. Adverse events can be due to toxicity of a supplement, adulteration of a supplement with harmful substances, or interactions between a supplement and a drug. Well-known examples of toxicity include fulminant liver failure, from the use of kava root, and acute cardiac and neurologic events, from the use of ephedra.

The adulteration of dietary supplements can be either intentional or unintentional.<sup>9</sup> Intentional contamination usually occurs when the necessary natural ingredients for the supplement are in short supply or expensive, or when the supplier intends to intensify a specific pharmacologic effect (usually through the addition of a pharmaceutical). Most cases of adulteration are, however, unintentional. Unintentional adulteration can occur at any of several stages in the preparation and packaging of a dietary supplement. The adulterant might exist within the raw material that was used to create the supplement (e.g. a heavy metal), might have been introduced accidentally during harvesting (e.g. a toxic plant), or could be added during the manufacturing process (e.g. microbes). There are no current FDA regulations establishing a mandatory, baseline standard for dietary supplement manufacturing.

One of the major concerns about the safety of dietary supplements is the possibility of interactions between a supplement and a drug, resulting in reduced drug efficacy or an increased risk of adverse events.<sup>10</sup> There is heightened concern for drugs with a narrow therapeutic window such as digoxin and warfarin.<sup>11</sup> It is also possible that an interaction could result in increased levels of a dietary supplement in the body, which might enhance its own potential for toxicity.

As premarketing safety studies of dietary supplements are not required by the FDA, the standard data available before the marketing of a drug are not usually available for dietary supplements. This means that information about how a product is absorbed, metabolized and interacts with drugs is lacking. Systematic postmarketing safety studies are also not

required. Furthermore, the manufacturers and distributors of dietary supplements are not required to disclose to the FDA any reports of adverse event that they receive.

There are several lessons that the practicing physician can take away: first, every patient should be asked about their use of herbal medicines and dietary supplements; second, clinicians should be alert to patients who present with adverse events resulting from supplement use; third, the potential for interaction between dietary supplements and drugs should be considered, especially when prescribing medications with a narrow therapeutic window; fourth, patients should be counseled regarding the potential for adverse events and drug interactions; and, finally, clinicians should support the improved regulation of dietary supplements, to enhance the safety of consumers.

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#### Competing interests

The authors declared they have no competing interests.