Risks and Benefits of Supplement Use

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Introduction
Dietary supplement sales have experienced an 80% growth during the past decade [1], and sales and use of dietary supplements continue to increase worldwide. For instance, in the United States, dietary supplement sales exceed $20 billion annually, and European sales of over the counter (OTC) herbal medicines alone totaled nearly $5 billion in 2003 [2]. Americans view supplements as beneficial for minor ailments such as colds and influenza, to moderate and more severe diseases such as arthritis, depression, cancer, and AIDS, and the majority (44%) believe that supplements users are “rarely or never” harmed by supplements [1]. However, dietary supplements, like all medications, can be potentially beneficial or dangerous. In the United States, several supplements have been scrutinized for safety issues (eg, ephedra, kava, St. John’s wort), but few have been removed from the market. Several factors can influence the risk to benefit ratio of dietary supplements, including patient-specific factors (eg, age, underlying disease, concomitant prescription or OTC medications), safety and efficacy of the supplements themselves, and quality control. The problem is further confounded by the lack of patients reporting supplement use to their physicians, pharmacists, or other health care providers, and when reported, poor recording of supplement use in medical charts.

Prevalence of Supplement Use and Medication-Supplement Interactions
Approximately 48% of Americans use dietary supplements [1], but this may be as high as 64% in older adults (> 65 years) [3]. Despite the large number of individuals who use dietary supplements, many do not share their supplement intake behaviors with their physicians or pharmacists. One study reported that 30% of regular supplement users do not inform their physician, 44% believe that physicians are biased against supplement use, and 44% believe that their personal physician knows very little about dietary supplements [1]. Collins and Dufresne [4] reported that 70% of patients did not report nonvitamin and nonmineral supplement use to their physicians and pharmacists. Further, two thirds of patients did not offer information on supplement use during preoperative screening [4]. Cohen et al. [3] demonstrated that the majority of dietary supplement use is documented in medical charts less than 50% of the time, and that some supplements (ginger, phytoestrogens, chamomile, aloe vera, and Chinese herbs) had a documentation rate of 0%. The effects of poor communication between physicians and patients regarding dietary supplement use, combined with poor charting by the physicians themselves, can have harmful outcomes due to both known and unknown supplement drug interactions. Recently, Wold et al. [5] analyzed potential medication-supplement interactions in older adults (60–99 years) in the New Mexico Aging Process Study. Over the 6-year study, 89% of subjects reported nonvitamin and nonmineral supplement use, and potential interactions between these supplements and medications increased from 12% to 31% [5]. Potential medication-supplement interactions were found for 10 of 22 supplements surveyed, totaling 142 potential medication-supplement interactions. Nearly 43% percent of medication-supplement interactions involved drugs and supplements with blood-thinning properties [5]. The lack of reporting of dietary supplement use to physicians and pharmacists is not unique to dietary supplements, as many patients under-report OTC medication use unless specifically prompted by their health care provider. Because there is often less research and education available for dietary supplements relative to OTC drugs, this can be even more problematic.

The US Dietary Supplement Health and Education Act
The 1994 US Dietary Supplement Health and Education Act (DSHEA) makes supplement use riskier than ever. In the United States, drug development (from discovery to approval) costs approximately $800 million and takes 10 to 15 years, but supplement manufacturers do not have to withstand these expenses or wait this long to market a dietary supplement. The US DSHEA placed the burden of proof for supplement safety on the federal government. Essentially, dietary supplements can be marketed and sold without proof of safety from well-controlled human
clinical trials as is required for pharmaceutical agents. In the United States, the federal government must accumulate enough convincing evidence to remove a dietary supplement from the market. Recently, ephedra was removed from the market in the United States subsequent to several ephedra-related deaths (due to stroke and myocardial infarction), and several hundred reports of adverse events. Reportedly, 64% of adverse reactions to herbs in the United States were accounted for by ephedra products [6], yet it took the US government several years to remove ephedra from the market. Although the ban on herbal ephedra made it unavailable in stores, synthetic ephedrine continues to be readily available through the internet. Moreover, ephedra was rapidly replaced in the weight loss supplement market by products containing synephrine (contained in citrus aurantium, bitter orange, sour orange, Seville orange), for which little information is available regarding safety and efficacy. Seville orange juice, like grapefruit juice, can increase absorption of calcium channel blockers such as felodipine [7]. Grapefruit juice consumption is contraindicated in patients taking calcium channel blockers because it decreases drug breakdown in the intestines and causes marked increases in blood levels of the drug. Many patients and health care providers are likely unaware that Seville orange-based supplements may pose a risk.

In April of 2005, 1 year after ephedra was banned, a US District Court in Utah determined that the US Food and Drug Administration (FDA) did not prove by a preponderance of the evidence that a 10-mg or less dose of ephedra alkaloids presents a "significant or unreasonable risk of injury." The court determined that supplement manufacturers can sell ephedra alkaloid supplements with a daily dose of less than 10 mg and not have enforcement action taken against them. Despite the lack of rigorous safety testing and proof of efficacy available for many supplements, a recent survey indicates that 49% of supplement users, and 33% of nonusers, believe that supplements are adequately tested [1]. In fact, 57% of regular supplement users believe that manufacturer claims are generally true [1].

Quality Control
The potential dangers of dietary supplements can extend beyond any danger associated with the active components of the supplements. Reportedly, quality control can be poor and product purity can vary widely, leading to huge variability in systemic exposure to active components, as well as exposure to possible contaminants. As an example, Gurley et al. [13] assessed the content of 20 ephedra supplements and found lot to lot variations in ephedra content of 180% and a 20% difference between label claim and actual ephedra alkaloid content. Recently, it was reported that one in five herbal medicine products produced in South Asia and sold in Boston, MA South Asian Grocery stores contain levels of lead, mercury, and arsenic that exceed regulatory standards [14]. Supplement manufacturers are not required to follow "good manufacturing procedures" as are pharmaceutical manufacturers.

Conclusions
Although dietary supplements offer consumers the ability to participate in their own health and well being, steps need to be taken to educate the public and clinicians to prevent misuse and encourage proper use. Better patient education through health care providers and the establishment of good manufacturing procedures for supplement producers will benefit those wishing to take dietary supplements. Currently, supplement users may be exposed to increased risk due to the lack of required good manufacturing procedures, poor communication between patients and health care providers, and the manner in which dietary supplements can be marketed without proof of safety or efficacy derived from large clinical trials.