




# Do You Know the Red Flags for Nutritional Supplements?

More people take nutritional supplements now than ever before. But, are they safe for everyone to use? **By Stuart Richer, O.D., Ph.D.**

Americans spent \$22 billion on nutritional supplements in 2006—a fraction of the nearly \$300 billion dollars spent on prescription and over-the-counter (OTC) pharmaceuticals.<sup>1</sup> Today, more patients take a plethora of vitamins, minerals and herbs for systemic purposes. Optometrists should know and understand exactly how these “nutraceuticals” interact with conventional systemic pharmaceuticals.

So, we ask: Just how safe are these supplements, and what are the associated “red flags,” or potential complications?

Since primary care optometry requires an understanding of current treatment practices, both when it comes to ocular health and systemic health as it relates to the eyes, such nutraceuticals deserve our study and perhaps our concern. Furthermore, therapeutic treatment of chronic ocular disease may be a

major element of both patient care and revenue for the eye care practice of the future.<sup>1,2</sup>

Patients are increasingly looking to use alternative or complementary methods of medication to facilitate the body’s natural healing response. Such patients want natural, effective, less expensive and less risky treatments when possible. Since the Food and Drug Administration (FDA) tends to approve drugs more quickly than before, many once-approved drugs, such as Vioxx (rofecoxib, Merck), have now been withdrawn based upon subsequent and more extensive safety testing. Could the same be true for supplements?

## Supplements in Practice

In many instances, dietary supplements produce the same biological effects as prescription and OTC drugs without associated side effects. Some examples of natural supplementation: Ginger instead of

nonsteroidal anti-inflammatory drugs (NSAIDs) for inflammation; magnesium instead of calcium channel blockers to decrease inotropic cardiac contractility and improve vascular peripheral resistance; fish oil instead blood thinners; garlic instead of aspirin for cardiovascular disease; and vitamin D instead of biphosphonates for osteoporosis.<sup>3-5</sup> Indeed, eating 20 cherries reduces inflammation much like aspirin or cyclooxygenase-2 inhibiting drugs, without the harmful side effects of gastric bleeding or vitamin depletion. It is interesting to note that the molecules in cherries, anthocyanins, work to reduce inflammation at a dosage one-tenth that of aspirin.<sup>6</sup>

While most Americans have access to affordable, high-quality supplements, this is hardly the case in many third-world countries, according to Bruce Ames, Ph.D., a nutritional biochemist at the University of California Berkeley. “It is

## Some Common, Reversible Nutritional Supplement Side Effects:

- Diarrhea from increased vitamin C.
- Loose stools from magnesium.
- Finger “tingling” from vitamin B<sub>6</sub>.
- Flushing from vitamin B<sub>6</sub>.
- Discoloration of skin from beta-carotene.

a distortion of priorities for much of the world's population to have an inadequate intake of vitamins or minerals—at great cost to health—when a year's supply of a daily multivitamin or mineral pill costs less than a few packs of cigarettes,” he says. “The poor, in general, have the worst diets and have the most to gain from improving their multivitamin and mineral supplementation and diet.”<sup>7</sup>

Here is where optometry could play a vital public health role: Encourage your patients to not only use more nutritional supplements, but also consume increased amounts of fruits and vegetables and essential fatty acids, such as fish, nuts and flax seed.

Even healthy, aging populations require stronger nutritional supplementation for several reasons, such as malabsorption from gastric atrophic hypochlorhydria, vitamin B<sub>12</sub> deficiency from frequent use of acid blockers, less efficient ubiquitin reprocessing and accumulated free radical attack and glycosylation.<sup>8</sup> As we age, we experience more free-radical DNA damage with less efficient repair.

Also, our tissues become increasingly cross-linked and rigid due to carbonyl formation and glycosylation. So, the value of nutritional supplements for elderly individuals is becoming increasingly apparent.

Here are a few published studies concerning the safety of nutritional supplements and their potentially negative interactions with prescription and OTC pharmaceuticals.

## Supplements vs. Drugs

A nutraceutical refers to a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease.<sup>1</sup>

Prescription drugs are approved through the rigorous New Drug Application (NDA) process of the FDA. Dietary supplements, on the other hand, are regulated as foods, and the FDA must determine if a dietary supplement ingredient poses a “significant or unreasonable risk of illness or injury.” Recently, however, research studies involving supplements must also undergo the same FDA Investigational New Drug (IND) application process.

Published statistical data widely suggests that the use of nutritional supplements alone does not yield serious systemic health consequences. However, when we look at the safety of either supplements or pharmaceuticals, we need to consider “absolute numbers.”

For example, taking one aspirin tablet each day may be as risky as being a firefighter. How can this be? Because 50-year-old men who take a daily aspirin (which reduces the chances for a heart attack by 30%), in absolute numbers, run the risk of dying from gastrointestinal bleeding by the equivalent of 10.4 deaths per 100,000 men per year. In comparison, professional firefighters face the risk of 10.6 deaths per 100,000 people per year, compared to 3.9 for all other occupations and 0.4 for office workers.<sup>9</sup>

The most complete and

longstanding data on nutritional supplements comes from the American Association of Poison Control Centers, which reviewed the cumulative effect of 29,000 supplement products from more than 600 manufacturers.<sup>10</sup> Over a 23-year period, there were 230 deaths, approximately 10 per year, caused by supplements in the United States; most of these were caused by ephedra (ephedrine) diet products. Moreover, there was no distinct causal link between these deaths and the use of dietary supplements. The findings of this study are consistent with those of previous studies, which demonstrate that dietary supplements are safer than OTC aspirin and acetaminophen.<sup>11,12</sup>

In February 2007, the *Journal of the American Medical Association* printed a pooled analysis of 68 published studies, which suggested that the American mortality rate was insignificantly affected by antioxidant supplementation of vitamins A, C, E, beta-carotene and selenium.<sup>13</sup> Yet, media headlines said otherwise, noting that a subset of 47 “better-quality” studies showed there were 15,366 deaths among 81,343 subjects who took antioxidants (15.5%) vs. 9,131 deaths among 81,343 subjects who did not take antioxidants (11.2%), for a difference of 4.2% in absolute numbers—not the relative 15.5% figure used by the media.

Additionally, there are numerous problems with meta-analyses besides the use of relative numbers and selective inclusion, such as the possibility that older and sicker people could, for example, take more dietary supplements.

In the Heart Outcomes Prevention Evaluation (HOPE) Study, 19 studies of 135,000 total people reported that 400IU of vitamin E per day increased the relative risk of

dying by 4%.<sup>14</sup> Again, the media sensationalized the story.

What researchers claimed was that high doses of vitamin E increased the risk of heart failure by an absolute 1% risk among people who take three drugs that have the potential to induce heart failure (diuretics, statins and beta blockers). Ultimately, vitamin E was blamed for the problem. Worse yet, the researchers eliminated studies where there were no reported deaths, in addition to two other studies that showed a decreased risk!

## Potentially Adverse Reactions

In 2005, Hanna Bartlett, Ph.D., and Frank Eperjesi, Ph.D., reviewed more serious contraindications and adverse reactions associated with the use of ocular nutritional supplements.<sup>15</sup> They concluded that vitamin A supplements and Acutane (isotretinoin, Roche Laboratories), a vitamin A derivative, should be avoided in women who may become pregnant, and men and women who have liver disease or drink heavily.

Relationships have also been found between vitamin A and reduced bone mineral density. But, this is most likely related to concurrent ubiquitous vitamin D deficiency, since vitamins A and D as fat-soluble vitamins compete for storage allocation in the liver.<sup>16</sup>

So, most multivitamin manufacturers have either reduced the amount of vitamin A in their products or have provided vitamin A in the form of beta-carotene, which converts to vitamin A on an as-needed basis. This systemic process prevents an overdose.

In both the Beta-Carotene and Retinol Efficacy Trial (CARET) and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC), a relationship was found

between beta-carotene and an increased risk for lung cancer in males who smoke.<sup>17,18</sup> This may be related to unbalanced carotenoid intake.

Glucosamine, used by patients with osteoarthritis, has been reported to trigger a rise in blood sugar among healthy adults; yet, two separate studies could not reproduce this effect.<sup>19,20</sup>

Although ginkgo biloba has anti-coagulant and anti-platelet effects, high doses have not been found to be problematic in carefully controlled studies.<sup>21,22</sup>

That said, one should nonetheless have a working knowledge of blood thinning nutrients and pharmaceuticals which, in combination, may pose a risk of bleeding in the body, i.e. hemorrhagic stroke.



**Patients with age-related macular degeneration may experience reduced CoQ10 levels from taking high dosages of statins and/or beta blockers. CoQ10 supplements can reverse this deficiency and may help prevent additional oxidation.**

The common blood thinning agents encountered in optometric practice include:

- Coumadin (warfarin sodium, Bristol-Meyers Squibb) and heparin.
- ASA (aspirin, Bayer), especially full-dose non-enteric coated.
- Vitamin E above 1100IU.

- Fish oil above 2 grams.
- Ginkgo biloba and ginseng.

## Drug/Nutrient Interactions

One of the least considered issues in medicine is the interaction of pharmaceuticals with nutrients. This is something that deserves our attention because the problems are increasing. By age 65, the average American takes four prescription medications.

There were 700,000 emergency room visits for overdoses and allergic reactions in 2005. In the same year, more than 15,000 people died from drug reactions compared with 5,519 people in 1998.<sup>23</sup> Many of these were fatalities linked to generic pain pills, such as oxycodone, fentanyl, morphine and acetaminophen.

In 2005, there were 89,482 serious side effects reported to the FDA—2.5 times the number reported in 1998.<sup>10,23</sup>

More than half of all approved drugs, such as Vioxx and Baycol (cerivastatin, Bayer AG), produce serious side effects not detected prior to FDA approval.<sup>24</sup> Only 3% of prescription medicines have been withdrawn from the American market for safety reasons over the last 20 years.

We now realize that many of these side effects and deaths could have been avoided by compensating for drug-induced nutrient depletion through the use of simple comprehensive multivitamins, minerals and individual nutrients.

Here are a few examples:

- Chronic use of proton pump inhibitors for dyspepsia and gastroesophageal reflux disease (GERD) can induce vitamin B<sub>12</sub> deficiency, which may cause secondary effects on optic nerve function.<sup>25</sup>
- Chronic or high dose

acetaminophen use may induce glutathione deficiency, which accelerates cataract formation and yields myriad effects on ocular tissues.<sup>26</sup>

- Overuse of steroids, such as dexamethasone and prednisolone, can induce deficiencies of vitamins C and D, folic acid, zinc, potassium, magnesium and selenium.<sup>27</sup>

One of the most important emerging optometric issues is coenzyme Q10 (CoQ10) depletion in patients taking high dosages of statins and/or beta blockers, which I have found can worsen age-related macular degeneration. This may be the very reason why the statin drug-AMD studies to date have been equivocal, or, at best, demonstrate a small positive or negative effect. On one hand, statins improve lipid profiles and reduce arteriolar inflammation. On the other hand,

they can, especially in high dose situations, deplete CoQ10 levels in the photoreceptor outer segments.<sup>28</sup>

CoQ10 depletion is of further particular concern for AMD patients with concurrent neurodegenerative diseases, such as Parkinson's Disease, which are associated with further loss of mitochondrial CoQ10 reserves.<sup>29</sup> Aging alone diminishes CoQ10 reserves in all tissues, so chronic use of beta-blocker eye drops by a patient who is already taking oral cardiovascular drugs that may deplete coenzyme Q10 (e.g., statins, oral beta blockers, thiazide diuretics, metformin and glyburide) should be carefully monitored.

Always look for red flags, but do not avoid your responsibility to inform patients of the benefits of

nutritional supplementation with respect to aging, disease and drug-induced nutrient depletion. Staying current in the field of ocular nutrition and carefully reading studies, not just media headlines, serves several purposes.

First, you will help to solve the patient's main problem. Second, you will enhance your understanding of the patient's overall health. Also, you will bring patients back to your office. Finally, the information provided by you is more reliable than the "buzz" from the health-food store clerk. ■

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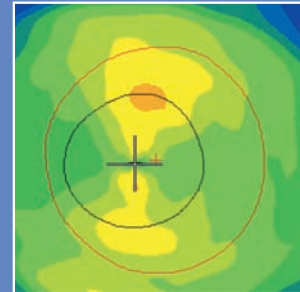
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and Science in North Chicago. Dr Richer is also the research director and a founding member of the Optometric Nutrition Society.

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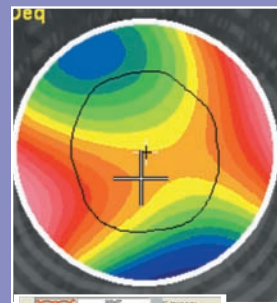
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