Why Do Supplements Often Flunk Clinical Trials?

BY ERIK L. GOLDMAN

There seems to be a predictable pattern in nutritional supplement research: Epidemiologic or observational studies suggest that a particular nutrient or botanical might prevent or ameliorate a common chronic disorder, preclinical work describes a plausible physiologic mechanism, and small clinical studies give encouraging findings.

Then the National Institutes of Health or another major research establishment funds a large-scale "definitive trial," and the data come up equivocal at best, negative at worst.

Over the last year or two, several disappointing nutritional/botanical studies have been reported. For example, vitamins C and E failed to reduce cardiovascular disease risk in the Physicians' Health Study II (JAMA 2008;300:2123-33); selenium and vitamin E did not lower prostate cancer risk in the SELECT trial (JAMA 2009;301:39-51); and ginkgo biloba did not prevent dementia or Alzheimer's disease in the elderly in the GEM trial (JAMA 2008;300:2253-62).

So why do big trials often return negative results when preliminary work looks positive? Is the epidemiology wrong to begin with, or were the trials improperly conducted? Are researchers and trial designs biased against natural products? Are the pilot trials biased in favor?

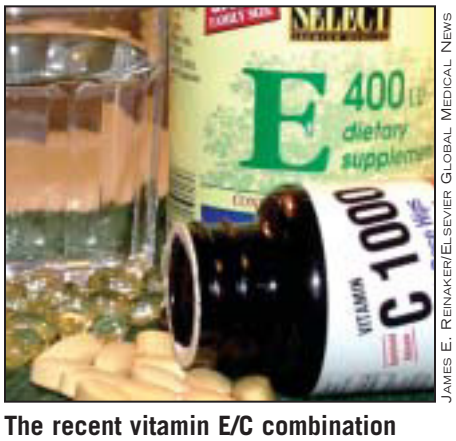
"Some people in the supplements world take umbrage at randomized, controlled trials. But it is not impossible to do good RCTs with nutrients, and it doesn't mean that negative results are wrong," Paul M. Coates, Ph.D., director of the Office of Dietary Supplements (ODS) at the National Institutes of Health, said in an interview. "The RCT worked pretty well to document the impact of folic acid in preventing neural tube defects. No one seems to question the study design when the data are positive."

Still, he acknowledged that the wave of negative studies does raise suspicion that researchers are not asking the right questions, or that epidemiologic signals engender unrealistic expectations.

"Epidemiological and observational studies cannot give cause-and-effect proof. They do provide clues about where to look. If the signals are strong enough, those clues should be followed and tested," said Dr. Coates, whose job is to set the agenda for NIH-funded nutraceutical research.

Public interest in nutrition, botanicals, and dietary supplements is strong, as is physicians' need for scientific guidance, Dr. Coats said at meeting sponsored by the Scripps Center for Integrative Medicine.

Solid evidence-based recommendations for dietary supplements are rare. Dr. Coates said one of his primary responsibilities is to look closely at those unknowns and establish priorities based on public health needs. This process, for better or worse, is driven by epidemiology.



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The recent vitamin E/C combination trial had its roots in population studies looking at heart disease risk in people with high versus low levels of serum markers of various vitamins, he explained. This led to trials designed around two of the possibly relevant nutrients. "We have to recognize that once we move to an intervention design, we cannot include everything that might be relevant," he said.

In the widely anticipated SELECT trial, the impetus for studying selenium in prostate cancer came from an earlier selenium study that did not have prostate effects as a primary outcome. The observation that the mineral might reduce

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risk was a "by the way" finding that might have been misleading, according to Dr. Coates.

Part of the problem in designing supplement trials is that researchers and the public often expect nutrients or botanicals to behave like drugs, with big, discrete, and easily detected benefits in a broad range of people. But nutrients and botanicals are not pharmaceuticals, and Dr. Coates said that he thinks expectations may be unrealistic.

Generally speaking, few people in the United States have frank nutrient deficiencies (such as scurvy, rickets, or beriberi), so supplementation seldom results in dramatic effects.

Using vitamin C as an example, he said that although many people fail to get optimal amounts, few have scurvy. "If you give a lot of vitamin C to people who are more or less replete, you may not see much effect. The net effect was basically zero in the Physicians' Health Study II. It's going to be hard to see a strong signal because the effect size [on heart disease] is probably small to begin with, and the level of 'noise' is high."

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Nutrients exert subtle, nonspecific effects on multiple physiologic pathways, rather than strong effects on a relatively small number of pathways, which is how pharmaceuticals work, Jeffrey Bland, Ph.D., said at the conference. But many of the large-scale NIH-funded trials are premised on single-pathway thinking.

Future NIH trials should make greater use of the emerging science of nutrigenomics, which looks at how various nutrients and combinations of nutrients influence gene expression, suggested Dr. Bland, cofounder of the Institute for Functional Medicine, based in Gig Harbor, Wash. The larger trials would also be more clinically applicable if they controlled for or reported on variables like participants' diets, oxidative stress status, and genetic predispositions for various metabolic states.

Beyond the domain of averting frank deficiencies, the effect of any given nutrient is largely determined by individual factors, such as how well someone digests and absorbs the nutrients, what nutrient-depleting or nutrient-blocking drugs are in a person's system, and individual capacities to metabolize particular nutrients, Dr. Bland continued. Nutrition is definitely not a one-size-fits-all proposition, he stressed.

High-profile government-funded studies understandably carry a lot of weight with physicians, said Dr. Mary Hardy, medical director of the Center for Integrative Oncology at the University of California, Los Angeles. But all too often, "we just run with the top-line findings, and miss secondary but important signals." Although the SELECT study did not show the hoped-for prostate protective benefit, it did show there were no major selenium-associated adverse effects after 6 years' of continuous use, she pointed out, which is reassuring for anyone taking this mineral for other purposes.

Currently, the ODS is working with the federal Agency for Healthcare Research and Quality (AHRQ) and AHRQ's Evidence-Based Practice Centers to conduct a series of meta-analyses and systematic reviews, Dr. Coates said. Of the role of the ODS, Dr. Coates said, "We set the questions, and then we walk away. The Evidence-Based Practice Centers do the actual reviews."

Future reviews will look at chromium and insulin sensitivity; omega-3s for cardiovascular disease prevention; the effects of soy, B vitamins, and antioxidant phytochemicals on neurodegenerative diseases; and the health effects of vitamin D. Some of these reviews were mandated by Congress. Completed reports can be found at www.ahrq.gov/clinic/epcindex.htm. The goal is "to review the totality of evidence for any health effect" from the supplement in question, Dr. Coates said.

Negative studies are a fact of life in science, he added. Although it may seem like supplements are being treated unfairly, the reality is that a lot of pharmaceutical studies are negative, too.

"Most things don't work all the time. In the case of St. John's wort, there was a study a few years ago showing that it doesn't work well in mild to moderate depression. That simply puts it in the company of most antidepressant drugs, which don't work 50% of the time." ■