

# Adverse Events From Supplements Merit Scrutiny

BY ERIK L. GOLDMAN

Data are lacking on the adverse events that potentially can arise from the millions of people taking nutritional supplements along with pharmaceuticals, but researchers are making some headway in sorting the real causes for concern from the unfounded worries.

Many of the red flags physicians hear about are little more than isolated and unverified case reports that someone has called in to a regulatory agency, according to Philip Gregory, Pharm.D., assistant professor of pharmacy practice at Creighton University's Center for Drug Information and Evidence-Based Practice in Omaha, Neb.

With its limited resources, the Food and Drug Administration investigates a potential adverse event or interaction only if there are multiple reports, clustered in time, that practically scream for attention, he said.

It was only recently that the FDA mandated supplement companies to put adverse event reporting phone numbers on

This fruit contains high levels of synephrine, sometimes as much as 30%, and if used in an indiscriminate way can induce the same adverse effects as ephedra, including arrhythmias, ischemic stroke, syncope, QT interval prolongation, myocardial infarction, rhabdomyolysis, and ischemic colitis.

Reports of these problems are exceedingly rare, and in some cases they occurred in people taking bitter orange

with other stimulants such as caffeine and the popular South American herb, guarana, Dr. Gregory said.

But given the seriousness of these potential side effects, physicians should discourage patients from using this herb for weight loss. "The risks outweigh the potential benefits, in my mind," he said.

Be aware that some products containing bitter orange are promoted as "ephedra free," leading consumers to

believe that they're getting a safer alternative. Although these products may technically be free of ephedra, they're not necessarily free of ephedralike risks.

► **Glucosamine and chondroitin plus warfarin.** Several years ago, there was a widely publicized case report of bleeding and bruising in a patient on warfarin who also was taking this popular combination as an arthritis remedy. Since then, there have been 40 reports to the FDA and the



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**Glucosamine should be used with care by patients also taking warfarin.**

product labels. In reality, most companies have not yet complied, so adverse event and interaction surveillance is spotty, he noted at a meeting sponsored by the Scripps Center for Integrative Medicine.

Nonetheless, Dr. Gregory, editor of the Natural Medicines Comprehensive Database, and his team of researchers there have identified a number of significant concerns, and also exonerated herbs or nutrients that have been unduly vilified. They have screened tens of thousands of published and unpublished research reports, surveys, and regulatory alerts worldwide in an effort to help physicians figure out which potential interactions and adverse events warrant serious attention. Dr. Gregory highlighted a few of their findings:

► **Bitter orange and cardiovascular effects.** Also known as *Citrus aurantium* and *Fructus aurantii*, bitter orange has been used in traditional Chinese medicine for hundreds of years in herbal decoctions used to treat digestive problems. More recently, it has become a common ingredient in weight loss and energy supplements, owing to its stimulant and thermogenic properties. The popularity of bitter orange has soared over the past few years, following the FDA's ban on the herb ephedra.

For patients with  
type 2 diabetes whose  
blood glucose control  
is not on track  
with orals alone

“YOU MAY WANT TO  
HAVE THE INSULIN  
TALK SOONER”



“By the time of diagnosis, up to 50% of patients' beta-cell function may have been lost.”<sup>4</sup>

World Health Organization of interactions between warfarin and glucosamine alone or between warfarin and the glucosamine/chondroitin combination.

On closer examination of the reports, most involved individuals taking very high doses of the supplement, in some cases up to six times the recommended dose.

"It is probably not a real problem in people who take the recommended doses of glucosamine/chondroitin, but patients taking warfarin should be careful," he said, adding that this message holds true for almost any drug or supplement added on top of warfarin.

Glucosamine has a "heparinoid" structure, which could explain a plausible mechanism for a mild anticoagulant effect, but data to support this notion are pretty weak, Dr. Gregory noted. Another possible explanation is that the supplement somehow modifies gastrointestinal tract flora, thus altering warfarin pharmacokinetics, but again, this is theoretical.

► **Calcium and cardiovascular risk.** Findings from a large study suggested that older women taking more than 1 g/day of calcium citrate had a twofold increase in myocardial infarctions and

significant increases in coronary artery calcification over a 5-year period (BMJ 2008;336:262-6).

These are worrisome findings, given how many postmenopausal women are taking calcium to prevent or attenuate osteoporosis, but this study was riddled with confounding variables and unanswered questions that make it difficult to draw a firm conclusion that calcium is problematic, Dr. Gregory said.

The study gives no data on the patients' magnesium levels, and since calcium and magnesium are antagonistic, the problems observed in the study may

reflect the fact that patients were given unopposed calcium without mitigation from magnesium. In those with already low baseline magnesium, that could be dangerous.

The observed increase in heart problems also may be related to low levels of vitamin D and vitamin K, which play a role in calcium metabolism and bone formation, he suggested.

"This study is an alert, not absolute proof, and the finding has not shown up in other calcium studies. So it is not appropriate to conclude that calcium is causing the problem. Do not dissuade patients from taking calcium, but don't overdo it: 1,200 mg/day is fine." He added that it's a very good idea to make sure patients are also getting enough magnesium.

► **Selenium and type 2 diabetes.** Selenium has been recommended as a possible preventive for several different conditions, including Alzheimer's disease, prostate cancer (though its merits in this context were challenged by the Se-

## The Food and Drug

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lenium and Vitamin E Cancer Prevention Trial [SELECT]), and type 2 diabetes. The latter recommendation is based on epidemiologic data showing a strong inverse correlation between incidence of diabetes and selenium intake.

But a secondary analysis of data from the Nutritional Prevention of Cancer Trial indicated that individuals taking 200 mcg of supplemental selenium daily had a significant increase of type 2 diabetes over an 8-year period (Ann. Intern. Med. 2007;147:217-23).

This unexpected finding was corroborated by SELECT, which also showed an increased rate of diabetes in those taking selenium alone, though the difference was not statistically significant.

Complicating matters, there was no diabetes increase in SELECT among patients taking selenium plus vitamin E, compared with those taking placebo. In fact, the incidence actually went down slightly, though, again, the difference was not significant.

"When selenium is taken by itself, it may be oxidative rather than antioxidative. So taking high doses of selenium or any other independent antioxidant may not be so healthy," Dr. Gregory hypothesized. He added that selenium may also stimulate glucagon release.

Though the picture is hardly clear, he advised against recommending selenium alone, especially for individuals prone to insulin resistance and diabetes. "The diabetes finding is a signal. We can't draw definitive conclusions from it, but we do need to be aware of it," he concluded.

Dr. Gregory reported having no financial conflicts of interest related to his presentation. ■

## It's never too early to have the "insulin talk"

Some conversations may be hard to initiate. Take the "insulin talk," for example. According to the American Diabetes Association, insulin is the most effective agent for lowering blood glucose.<sup>1</sup> It works as part of an overall diabetes treatment plan, which may include diet, exercise, and other diabetes medication. Having the "insulin talk" early may help patients accept insulin as a potential treatment option to help them achieve their A1C goals.<sup>2</sup>

The results of having a positive "insulin talk" can be impactful: in a survey, about 80% of patients with type 2 diabetes on OADs said they'd consider taking insulin if their doctor recommended it.<sup>3</sup> So by starting the dialogue now, you can help your patients have a better understanding of insulin as an effective treatment option for lowering blood glucose.

## Insulin—a chance for successful glycemic control, not a punishment for failure

Patients may focus on blaming themselves for their uncontrolled blood glucose, but you can help them focus on turning this negative mindset into positive action for managing their disease.<sup>2</sup> The United Kingdom Prospective Diabetes Study showed that by the time patients with type 2 diabetes are diagnosed, they may already have lost up to 50% of their beta-cell function, and this function may continue to decline.<sup>4</sup>

Because the disease is progressive, many patients with type 2 diabetes may eventually need insulin to achieve or maintain glycemic control.<sup>2,5</sup> But by the time patients with type 2 diabetes are prescribed insulin, they may have had diabetes for 10 to 15 years and may already have complications due to a prolonged period of uncontrolled blood glucose.<sup>6</sup> Starting insulin earlier in the disease continuum for appropriate patients can help improve glycemic control. Controlling blood glucose can reduce the risk of diabetes-related complications.<sup>5,6</sup>

Treatment plans and glycemic targets should be individualized for each patient.

Insulin is indicated to help improve glycemic control in patients with diabetes mellitus.

## Important Safety Information About Insulin

Possible side effects may include blood glucose levels that are too low, injection site reactions, and allergic reactions, including itching and rash. Other medications and supplements could change the way insulin works. Glucose monitoring is recommended for patients with diabetes.

## THE "INSULIN TALK"

### Have the talk early and as needed, to help destigmatize insulin<sup>2</sup>

- Reassure patients that using insulin doesn't mean failure and that insulin may help replace what the body is no longer adequately making
- Turn the negative mindset of failure into a positive opportunity to take personal control of A1C

### Put insulin therapy in context

- Explain the benefits of maintaining blood glucose goals and the risks associated with insulin therapy
- Talk about how insulin may be worth the effort—insulin is an effective treatment option that works as part of an overall treatment plan to lower blood glucose

### Identify patients' personal obstacles and help defuse the "scary" factor<sup>2</sup>

- Today's insulin injections generally cause little discomfort and are administered using small, thin needles<sup>2,6</sup>
- Insulin pens make insulin more convenient to administer and are discreet<sup>2</sup>
- Insulin dose may need to be adjusted up or down over the course of treatment depending on how a patient's body responds<sup>5</sup>

# INSULIN

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