

# 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 de-

signs 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. Coates said at meeting sponsored by the Scripps Center for Integrative Medicine.

Solid evidence-based recommendations for dietary supplements are rare. Dr.

SYMBICORT® (budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

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of COPD and asthma patients received tricyclic antidepressants, and, therefore, no clinically meaningful conclusions on adverse events can be made.

#### Beta-Adrenergic Receptor Blocking Agents

Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of SYMBICORT, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

#### Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of SYMBICORT with non-potassium-sparing diuretics.

#### USE IN SPECIFIC POPULATIONS

##### Pregnancy

##### Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies of SYMBICORT in pregnant women. SYMBICORT was teratogenic and embryocidal in rats. Budesonide alone was teratogenic and embryocidal in rats and rabbits, but not in humans at therapeutic doses. Formoterol fumarate alone was teratogenic in rats and rabbits. Formoterol fumarate was also embryocidal, increased pup loss at birth and during lactation, and decreased pup weight in rats. SYMBICORT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

##### SYMBICORT

In a reproduction study in rats, budesonide combined with formoterol fumarate by the inhalation route at doses approximately 1/7 and 1/3, respectively, the maximum recommended human daily inhalation dose on a mg/m<sup>2</sup> basis produced umbilical hernia. No teratogenic or embryocidal effects were detected with budesonide combined with formoterol fumarate by the inhalation route at doses approximately 1/32 and 1/16, respectively, the maximum recommended human daily inhalation dose on a mg/m<sup>2</sup> basis.

##### Budesonide

Studies of pregnant women have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (ie, Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs 3.3, respectively).

These same data were utilized in a second study bringing the total to 2534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses in rabbits less than the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis and in rats at doses approximately 6 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis. In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 3 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis.

Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

##### Formoterol

Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats when given at oral doses 1400 times and greater the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis. Umbilical hernia was observed in rat fetuses at oral doses 1400 times and greater the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis. Brachygnathia was observed in rat fetuses at an oral dose 7000 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis. Pregnancy was prolonged at an oral dose 7000 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis. In another study in rats, no teratogenic effects were seen at inhalation doses up to 500 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis.

Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose 54,000 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis. No teratogenic effects were observed at oral doses up to 3200 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis.

##### Nonteratogenic Effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

##### Labor and Delivery

There are no well-controlled human studies that have investigated the effects of SYMBICORT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of SYMBICORT for management of asthma during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

##### Nursing Mothers

Since there are no data from controlled trials on the use of SYMBICORT by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue SYMBICORT, taking into account the importance of SYMBICORT to the mother.

Budesonide, like other corticosteroids, is secreted in human milk. Data with budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother [see CLINICAL PHARMACOLOGY in full Prescribing Information (12.3)]. For SYMBICORT, the dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be similar.

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk.

##### Pediatric Use

Safety and effectiveness of SYMBICORT in asthma patients 12 years of age and older have been established in studies up to 12 months. In the two 12-week, double-blind, placebo-controlled US pivotal studies 25 patients 12 to 17 years of age were treated with SYMBICORT twice daily [see CLINICAL STUDIES in full Prescribing Information (14.1)]. Efficacy results in this age group were similar to those observed in patients 18 years and older. There were no obvious differences in the type or frequency of adverse events reported in this age group compared with patients 18 years of age and older.

The safety and effectiveness of SYMBICORT in asthma patients 6 to <12 years of age has not been established.

Overall 1447 asthma patients 6 to <12 years of age participated in placebo- and active-controlled SYMBICORT studies. Of these 1447 patients, 539 received SYMBICORT twice daily. The overall safety profile of these patients was similar to that observed in patients ≥12 years of age who also received SYMBICORT twice daily in studies of similar design.

Controlled clinical studies have shown that orally inhaled corticosteroids including budesonide, a component of SYMBICORT, may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effect of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final height are unknown. The potential for “catch-up” growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

In a study of asthmatic children 5-12 years of age, those treated with budesonide DPI 200 mcg twice daily (n=311) had a 1.1 centimeter reduction in growth compared with those receiving placebo (n=418) at the end of one year; the difference between these two treatment groups did not increase further over three years of additional treatment. By the end of 4 years, children treated with budesonide DPI and children treated with placebo had similar growth velocities. Conclusions drawn from

this study may be confounded by the unequal use of corticosteroids in the treatment groups and inclusion of data from patients attaining puberty during the course of the study.

The growth of pediatric patients receiving orally inhaled corticosteroids, including SYMBICORT, should be monitored. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, each patient should be titrated to the lowest strength that effectively controls his/her asthma [see DOSAGE AND ADMINISTRATION].

##### Geriatric Use

Of the total number of patients in asthma clinical studies treated with SYMBICORT twice daily, 149 were 65 years of age or older, of whom 25 were 75 years of age or older.

In the COPD studies of 6 to 12 months duration, 349 patients treated with SYMBICORT 160/4.5 twice daily were 65 years old and above and of those, 73 patients were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

As with other products containing beta<sub>2</sub>-agonists, special caution should be observed when using SYMBICORT in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta<sub>2</sub>-agonists.

Based on available data for SYMBICORT or its active components, no adjustment of dosage of SYMBICORT in geriatric patients is warranted.

##### Hepatic Impairment

Formal pharmacokinetic studies using SYMBICORT have not been conducted in patients with hepatic impairment. However, since both budesonide and formoterol fumarate are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of budesonide and formoterol fumarate in plasma. Therefore, patients with hepatic disease should be closely monitored.

##### Renal Impairment

Formal pharmacokinetic studies using SYMBICORT have not been conducted in patients with renal impairment.

##### OVERDOSAGE

##### SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage for the individual components described below apply to SYMBICORT. In pharmacokinetic studies, single doses of 960/54 mcg (12 actuations of SYMBICORT 80/4.5) and 1280/36 mcg (8 actuations of 160/4.5), were administered to patients with COPD. A total of 1920/54 mcg (12 actuations of SYMBICORT 160/4.5) was administered as a single dose to both healthy subjects and patients with asthma. In a long-term active-controlled safety study in asthma patients, SYMBICORT 160/4.5 was administered for up to 12 months at doses up to twice the highest recommended daily dose. There were no clinically significant adverse reactions observed in any of these studies.

Clinical signs in dogs that received a single inhalation dose of SYMBICORT (a combination of budesonide and formoterol) in a dry powder included tremor, mucosal redness, nasal catarrh, redness of intact skin, abdominal respiration, vomiting, and salivation; in the rat, the only clinical sign observed was increased respiratory rate in the first hour after dosing. No deaths occurred in rats given a combination of budesonide and formoterol at acute inhalation doses of 97 and 3 mg/kg, respectively (approximately 1200 and 1350 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis). No deaths occurred in dogs given a combination of budesonide and formoterol at the acute inhalation doses of 732 and 22 mcg/kg, respectively (approximately 30 times the maximum recommended human daily inhalation dose of budesonide and formoterol) on a mcg/m<sup>2</sup> basis).

##### Budesonide

The potential for acute toxic effects following overdose of budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur [see WARNINGS AND PRECAUTIONS]. Budesonide at five times the highest recommended dose (3200 mcg daily) administered to humans for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

In mice, the minimal inhalation lethal dose was 100 mg/kg (approximately 600 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis). In rats, there were no deaths following the administration of an inhalation dose of 68 mg/kg (approximately 900 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis). The minimal oral lethal dose in mice was 200 mg/kg (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis).

##### Formoterol

An overdose of formoterol would likely lead to an exaggeration of effects that are typical for beta<sub>2</sub>-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol. No clinically significant adverse reactions were seen when formoterol was delivered to adult patients with acute bronchoconstriction at a dose of 90 mcg/day over 3 hours or to stable asthmatics 3 times a day at a total dose of 54 mcg/day for 3 days.

Treatment of formoterol overdosage consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage.

No deaths were seen in mice given formoterol at an inhalation dose of 276 mg/kg (more than 62,200 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis). In rats, the minimum lethal inhalation dose was 40 mg/kg (approximately 18,000 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis). No deaths were seen in mice that received an oral dose of 2000 mg/kg (more than 450,000 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis). Maximum nonlethal oral doses were 252 mg/kg in young rats and 1500 mg/kg in adult rats (approximately 114,000 times and 675,000 times the maximum recommended human inhalation dose on a mcg/m<sup>2</sup> basis).

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The recent vitamin E/C combination trial had its roots in population studies.

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.

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 op-

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timal 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.”

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 sys-

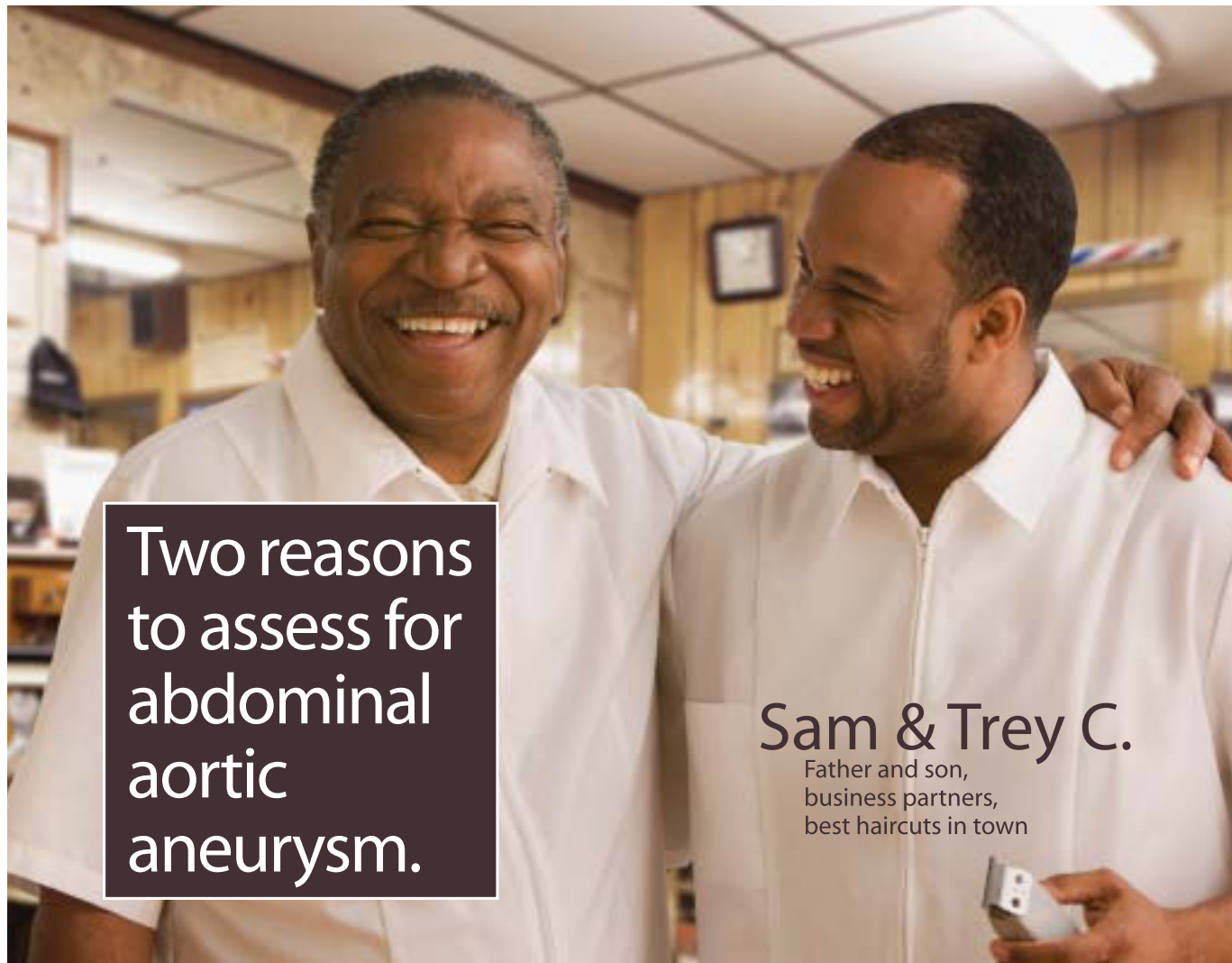
tematic reviews, Dr. Coates said. Of the role of the ODS, Dr. Coates said, “We set the questions, and then we walk away. The Evidence-Based Practice Centers do the actual reviews.”

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](http://www.ahrq.gov/clinic/epcindex.htm). The goal is “to re-

view 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.” ■



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