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SIDNEY M. WOLFE, M.D., EDITOR

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Postmenopausal Estrogen Replacement Therapy: Is Its Value Exaggerated and Its Role Vanishing?

The December 19, 2000, issue of *Annals of Internal Medicine* carried the results of an ongoing observational study begun in 1976 that is known as the Nurses' Health Study. Even after nearly a quarter of a century its main findings have not changed: Women past menopause who use estrogen, such as conjugated equine estrogen (PREMARIN) or estrogen plus a progestin, medroxyprogesterone (PROVERA), reduce their risk of heart disease by about 40 percent compared to women who have never used hormones. But wait a minute; keep reading.

The Nurses' Health Study is large, containing survey data from 70,533 postmenopausal women; its design is sound, and it provides follow-up information over 20 years. The women were first surveyed in 1976 to determine if they had ever used postmenopausal hormones, and information was gathered on their medical histories including cardiovascular factors. Then, beginning in 1978, information was collected on the type of hormones taken and, starting in 1980, on the estrogen dose taken. Follow-up surveys continued to update information and asked if the women had experienced heart attack or stroke. All events were confirmed, including deaths, using medical records and death certificates.

Regarding stroke, as distinguished from heart disease, the Nurses' Health Study has found that the risk of stroke due to a blockage in blood supply (what is known as "ischemic stroke") increased among hormone users compared to those who never used hormones. This risk was statistically significantly greater among women taking 0.625 milligrams or more of either type of estrogen.

Observational studies focus on individuals' behavior and health outcomes—in the case of the Nurses' Health Study, heart attack or stroke. They are very useful for generating hypotheses about possible benefits from a treatment, but the scientific "gold standard" for proof is the randomized controlled clinical trial. It is not unusual to see long-held beliefs based on observational studies turn out to be wrong once randomized controlled trials are conducted. And, as it turns out, the results of three such trials conflict with the results of the Nurses' study.

An editorial in the same issue of *Annals of Internal Medicine* by scientists from the University of California, San Francisco's Department of Epidemiology, posed an important question in view of this conflict between the studies: Could the conclusions of the Nurses' study about coronary heart disease benefits from hormone replacement

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ESTROGENS, *from page 9*
treatment be wrong? The editorial's authors went on to briefly review the randomized controlled trials:

1. The Heart and Estrogen / Progestin Replacement Study (HERS), published in the *Journal of the American Medical Association's* August 19, 1998 issue. This study found no overall benefit from four years of treatment with estrogen-plus-progestin compared to inactive drugs called placebos. A troubling aspect of the HERS trial was that the women assigned to take the active drug actually had an increased risk of coronary events in the first year of the trial compared to women receiving the placebo.

2. The Estrogen Replacement in Atherosclerosis trial, reported in the August 24, 2000 issue of the *New England Journal of Medicine.* In this study neither estrogen alone nor estrogen-and-progestin affected the progression of atherosclerosis (fat deposits in blood vessels) in the coronary arteries of women with established heart disease compared to placebo.

Both these efforts are what is known as secondary prevention studies, meaning that the subjects in the trials had already had episodes of heart disease, and were given the drug under investigation—or the placebo for the control group—to determine its effectiveness in preventing recurrence. But what about women without a prior history of the disease? Could they benefit from estrogen and / or progestin? That question was asked in a third randomized controlled trial:

3. The Women's Health Initiative is a primary prevention trial covering 27,000 women without heart disease. Currently in its third year, it is planned to run for nine, and already is yielding attention-grabbing results. On April 3, 2000, scientists in charge of the study issued a press release and notified participating women that in the first two years of the trial they had observed an increased risk of cardiovascular events in women receiving hormone treatment as compared to those receiving placebo. In other words, estrogen replacement appears to have the same initial adverse effect in healthy women as among women in the HERS trial with known heart disease.

The editorial concluded:

> *Despite strong observational evidence from the Nurses' Health Study and others, we believe that the disappointing results of three recent trials indicate that clinicians should not use hormone therapy for prevention of coronary disease until this practice is supported by evidence from randomized trials.*

We agree.

The professional product labeling (so-called "package insert") for estrogen-plus-progestin drugs such as PREMPRO and PREMPHASE now warn that "women with a history of coronary heart disease may have an increased risk of serious cardiac events during the first year of treatment with estrogen / progestin therapy."

In the title of this article we asked if a role for postmenopausal estrogen replacement treatment is vanishing. Our answer is yes.

The role of postmenopausal estrogen replacement therapy must now be restricted to its modest benefit in preventing and managing osteoporosis and to its unquestioned usefulness in the short term management of menopausal symptoms. At the same time, these two benefits must be balanced against these risks: (1) an increased risk of cardiac events in both women with and without existing heart disease when estrogen replacement is started; (2) the reported risk of endometrial cancer (2 to 12 times greater than in non-users) in women using estrogen alone—a risk that appears dependent on the duration of treatment and size of dose; (3) an increase in risk of breast cancer associated with long term estrogen use based on a re-analysis of results from 51 earlier studies that had seemed to show no increase of this disease in women using estrogen short term; (4) five observational studies that found an increased risk of blood clots in estrogen users, usually in the first year of use; and (5) a doubling of the risk of needing gall bladder surgery with estrogen use and a significant risk of needing a hysterectomy.

Women considering estrogen replacement to manage the symptoms of menopause, such as hot flashes, face a most difficult decision. Estrogen is very effective in controlling these symptoms, but the risk of cardiac events and blood clots is increased with short term estrogen replacement.

A decade ago, in our book *Women's Health Alert,* we said that female replacement hormones may someday be remembered as the most recklessly prescribed and dangerous drugs of the century. Since the 1940s, when estrogens were first manufactured cheaply and made available in pill form, the story of their widespread use in treating women's "problems" has been one of false promises, disregard for scientific evidence, and the wishful thinking of women and their doctors that all female health problems might evaporate by just "topping-up" with a little missing estrogen.

Replacement hormones were the "feminine forever" drugs of the 1960s and '70s, "guaranteed" to keep wrinkles away, hair glossy, and depression to a minimum. In the '80s they were advertised as a cure for osteoporosis and, therefore, the answer to brittle bones. Now these recycled wonder drugs have lost

their role as a solution to female heart disease. The "evidence" justifying postmenopausal estrogen replacement therapy is vanishing, but its disappearance does not seem to have affected sales.

And sales are tremendous. Almost 82 million prescriptions for estrogen or estrogen-plus-progestin products were dispensed in 1999 at an estimated wholesale cost of at least $1.8 billion—and who knows how much more after the retailers' generous markup.

While randomized controlled trials such as HERS are providing evidence for limiting a safe and useful role for postmenopausal estrogen replacement treatment complementary-alternative-medicine practitioners, compounding pharmacists and their close confederates, the purveyors of dietary and herbal supplements are taking the money of unsuspecting women by selling unproven "natural human" estrogen replacement products that are claimed to be free from the adverse effects of synthetic estrogen. Premarin, the most popular estrogen replacement, is derived from *pre*gnant *mar*es urine and is, therefore, also "natural."

Some compounding pharmacists are promoting their home-made natural or bioidentical hormone replacement drugs on the Internet. These products are made in facilities that are not required to meet Good Marketing Practice guidelines and are usually made from estrone, estradiol or estriol or a combination of the three. Estradiol (ESTRACE) and estrone (KESTRONE 5) are available from manufacturers regulated by the Food and Drug Administration (FDA). Estriol is not commercially available in the U.S.

The FDA-approved product labeling for estradiol and estrone is required to carry the following statement: *There is currently no evidence that 'natural' estrogen are more or less hazardous than 'synthetic' estrogen at equi-estrogenic doses.*

In fact, a study published in the May 29, 1999 issue of *The Lancet*, a highly respected British medical journal, found an increased risk of endometrial cancer with oral (but not vaginal) treatment with estriol.

Women should beware of complementary-alternative-medicine practitioners and compounding pharmacists offering hormone replacement treatment that they claim is risk-free.

The effectiveness of plant-derived estrogen or phytoestrogen in the treatment of menopausal symptoms is unknown at this time. Researchers reviewed what is known about phytoestrogen's effectiveness against menopausal symptoms in the December 16, 2000 issue of the *British Medical Journal*. They found three placebo-controlled trials, two of which evaluated soy supplements, which contain phytoestrogen, while the third evaluated isoflavone. The first trial involved 50 postmenopausal women and compared soy flour to wheat flour for 12 weeks and found that hot flashes were reduced significantly more in the group of women using soy (40 percent vs. 25 percent reduction). The second trial evaluated six weeks of 34 milligrams of soy protein daily. It found reduced severity but not frequency of hot flashes. The third trial conducted in 51 women compared 40 milligrams daily of isoflavone to placebo. It found a benefit from the placebo but not from the isoflavone.

What You Can Do

A decision to undertake estrogen replacement therapy requires a careful individual consultation with your doctor. Remember, many physicians have a distorted view of this kind of therapy—an overly optimistic confidence in the benefits and a lack of knowledge of the risks. These drugs are dangerously overused.

Editor: Sidney M. Wolfe, M.D.
Managing Editor: Phyllis McCarthy
Staff Researcher: Larry D. Sasich, Pharm.D.
Information Specialist: Jennifer L. Howard
Contributing Editor: William Hines
Graphic Production: Kristy I. Jackson

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Severe Liver Injury with the Asthma Drug Zafirlukast (ACCOLATE)

Physicians and pharmacists at the Albert Einstein College of Medicine and the University of California at San Francisco have seen three patients who suffered severe liver injury after using the asthma drug zafirlukast (ACCOLATE). The cases were described in the December 19, 2000 issue of *Annals of Internal Medicine*.

We reviewed zafirlukast and a related asthma drug, zileuton (ZYFLO) in the May 1997 issue of *Worst Pills, Best Pills News* and listed both as drugs you should wait at least five years after their approval to use—this coming September in the case of zafirlukast. The two drugs belong to a drug family known as leukotrine modifiers. Leukotrines occur naturally in the body and are thought to play a role in the inflammatory process that causes bronchoconstriction (narrowing of the airways) during an asthma attack.

Zafirlukast is not a bronchodilator and should not be used to treat acute asthma episodes. Almost 2.5 million prescriptions for zafirlukast were dispensed in 1999 in the U.S. despite the National Institutes of Health's July 1997 Guidelines for the Diagnosis and Management of Asthma, which stated that further clinical experience and study would be needed to establish the drug's role in treating asthma.

The three patients who experienced liver injury were women aged 42-49 years, all of whom were taking 20 milligrams of zafirlukast twice daily. The first patient developed elevations in liver enzymes—an early sign of liver toxicity—nine months after beginning the drug. When zafirlukast was stopped and zileuton was started her enzyme levels returned to normal after four months. Zafirlukast was then resumed and two months later she developed symptoms of liver toxicity including jaundice (yellowing of the skin and whites of the eyes). After stopping zafirlukast again, her liver enzymes returned to normal over a period of six months.

The second patient was on zafirlukast for five months before suffering elevated liver enzymes, at which point she was admitted to the hospital. She was discharged but readmitted two weeks later with jaundice, abdominal swelling and a tremor with flapping of the wrists—all signs of severe liver toxicity. She subsequently received a liver transplant and now has normal liver function.

The final patient was hospitalized with jaundice and elevated liver enzymes after six months on zafirlukast. She was treated with high doses of intravenous steroids and her liver tests improved rapidly.

The Food and Drug Administration required the following safety labeling change for zafirlukast on June 12, 2000, regarding potential liver toxicity with the drug:

> *Rarely, elevations of one or more liver enzymes have occurred in patients receiving ACCOLATE in controlled clinical trials. In clinical trials, most of these have been observed at doses four times higher than the recommended dose. The following hepatic [liver] events (which have occurred predominantly in females) have been reported from postmarketing adverse event surveillance of patients who have received the recommended dose of ACCOLATE (40 mg/day): cases of symptomatic hepatitis [inflammation of the liver] (with or without hyperbilirubinemia) [excessive levels of bile pigment in the blood] without other attributable cause; and rarely, hyperbilirubinemia [elevated levels of bilirubin in the blood] without other elevated liver function tests. In most, but not all, postmarketing reports, the patient's symptoms abated and the liver enzymes returned to normal or near normal after stopping ACCOLATE. In rare cases, patients have progressed to hepatic failure.*

The revised labeling instructs doctors to inform patients of the symptoms of liver toxicity and immediately contact the prescriber should symptoms of liver injury develop. These symptoms are pain below the right rib cage (where the liver is located), nausea, fatigue, lethargy, jaundice, flu-like symptoms, and loss of appetite.

What You Can Do

If you are taking zafirlukast and experience any of the symptoms of liver toxicity listed above, contact your physician immediately.

A Statistical Summary: Treatment Of Schizophrenia With Newer Antipsychotic Drugs

British physicians developing guidelines for treating schizophrenia with a group of new drugs called "atypical antipsychotics" have found no clear evidence that they are more effective or better tolerated than older, conventional antipsychotics. The guidelines were developed by systematically reviewing randomized controlled clinical trials and using a statistical technique known as "meta-analysis" to assemble the results of many published studies on the treatment of schizophrenia. The recommendation from this extensive effort—published in the December 2, 2000, issue of the *British Medical Journal* (BMJ)—was that the older, conventional antipsychotics should be tried first.

The volume of scientific information is enormous, and health professionals, patients, scientific researchers and policy makers are often overwhelmed with the unmanageable amount of literature which sometimes yields contradictory results. For example, each month the U.S. National Library of Medicine adds 40,000 citations to its MEDLINE database, which contains research studies from more than 4,300 medical journals published worldwide.

This problem was recognized 30 years ago by Dr. Archie Cochrane, a British epidemiologist who drew attention to the great collective ignorance about the effects on health care, including drug treatments, that stemmed from the fact that published research had not been summarized in a useful format for physicians having to make treatment decisions.

Using the techniques of meta-analysis, the authors of the BMJ study included randomized trials of the atypical antipsychotics amisulpride (a drug not available in the U.S., clozapine (CLOZARIL), olanzapine (ZYPREXA), quetiapine (SEROQUEL), risperidone (RISPERDAL), and sertindole (a drug withdrawn from the European market for safety reasons), compared to conventional antipsychotics, usually haloperidol (HALDOL) or chlorpromazine (THORAZINE).

In all, 52 clinical trials were identified, embracing results from 12,649 patients. Most of the studies were of short duration (median follow-up 6.5 weeks), but five trials lasted a year or more. Most compared the effectiveness of atypical antipsychotics to haloperidol. In a few studies, chlorpromazine was used as the benchmark. Perphenazine (TRILAFON) and two drugs not available in the U.S.—flupenthixol and zuclopenthixol—were used for comparison to an atypical drug in one trial each.

The dose of haloperidol significantly affected the outcome in a number of trials. The average dose of haloperidol ranged from 6 to 22.5 milligrams daily, and there was a significant advantage for atypical antipsychotics as the dose of haloperidol increased. But the evidence of superiority in efficacy or tolerability for the atypical antipsychotics as a class disappeared when the haloperidol dose (or the equivalent doses of other conventional antipsychotic drugs) was 12 milligrams or less.

Atypical antipsychotics are said to be more effective than the older ones against "negative" symptoms of schizophrenia, including emotional flatness or lack of expression, inability to start or follow through with activities, speech that is brief and lacks content, and lack of pleasure or interest in life. But overall, no evidence suggested that any of the atypical antipsychotics had a specific effect on either the negative or "positive" symptoms, which include delusions and hallucinations, that occur because the patient has lost touch with reality in important ways.

The review found that atypical antipsychotics cause fewer drug-induced nerve problems (so-called extrapyramidal adverse reactions); however, no difference was found in overall tolerability between the two groups of drugs.

All systematic reviews of published literature present problems. One is that the results are only as good as the trials themselves. Another is the fact that trials with positive results are more likely to be published than those with negative results—"publication bias," which is a problem particularly with small trials. What this means is that in a systematic literature review it is likely that the result will be based mainly on good news because bad news sees print less often.

An editorial accompanying the review notes that in North America the atypical drugs account for nearly three out of four new prescriptions for antipsychotics. The editorial poses a sobering question in view of the review's results: Is the prescribing of antipsychotics "largely a victory of clinical hope and marketing hype over hard evidence, or is there a truth that is missed in the meta-analysis"?

Truth was not missed in the BMJ review, which is simply a summary of available evidence. What is missing are the "gold standard" controlled trials comparing various

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Kidney-toxic And Cancer-causing Chinese Herbal Supplements Are Recalled

East Earth Herb, Inc. of Eugene, Oregon issued a recall on November 21, 2000, of its Jade Pharmacy brand Meridian Circulation tablets and liquid extract and Jade Pharmacy brand Quell Fire tablets because they present a serious health hazard to consumers. The products contain aristolochic acid, a potent cancer-causing and kidney-toxic agent found in certain plants and botanicals.

About 600 species of the plant family Aristolochiacea contain this chemical.

Meridian Circulation and Quell Fire were distributed throughout the U.S. through a variety of complementary-alternative-medicine proponents. A list of the recalled products and their lot numbers appears on this page.

We reported in the July 2000 issue of *Worst Pills, Best Pills News* that the Food and Drug Administration's (FDA) Office of Nutritional Products, Labeling, and Dietary Supplements wrote to trade and lobbying groups representing the herbal and dietary supplement producers asking these organizations to inform their members about the serious problems that had been seen with herbs containing aristolochic acid.

Kidney failure was reported in Belgium in 1993, where more than 70 cases were associated with the use of a weight loss product containing aristolochia, a source of aristolochic acid. An emergency ban on the import, sale and supply of products containing aristolochia went into effect in Britain on July 28, 1999, following a review by regulators of two cases of kidney failure in patients using Chinese herbal medicines containing aristolochia for the treatment of eczema.

The New England Journal of Medicine on June 8, 2000 published a study done by Belgian researchers on June 8, 2000 who looked at the risk of kidney and other types of urinary tract cancers in patients who had lost a kidney due to herbs containing aristolochia. Among 39 patients who agreed to participate in the study, there were 18 cases of various types of cancer. Nineteen of the remaining patients had pre-cancerous changes in the cells of the urinary tract and two patients were normal.

We contacted the East Earth Herb company and asked them how long their products had contained aristolochic acid. They did not know.

The FDA has no practical legal authority to protect the public from dangerous dietary and herbal supplements that are promoted for unsubstantiated uses since the passage of the Dietary Supplement Health and Education Act of 1994. In the unregulated marketplace for dietary and herbal supplements it's "let the buyer beware."

The lot numbers covered in this recall are:

Product	Lot Number	Expiration Date
Meridian Circulation tablets	#2404	9/01
Meridian Circulation tablets	#2952	5/03
Meridian Circulation tablets	#3506	2/04
Meridian Circulation liquid	#9609097	11/01
Meridian Circulation liquid	#9707062	9/02
Meridian Circulation liquid	#9804021	6/03
Meridian Circulation liquid	#9907026	9/04
Quell Fire tablets	#2079	4/01
Quell Fire tablets	#2623	4/02
Quell Fire tablets	#2832	11/02
Quell Fire tablets	#3012	8/03
Quell Fire tablets	#3140	11/03
Quell Fire tablets	#3553	4/04
Quell Fire tablets	#3830	7/05

What You Can Do

Using unregulated dietary and herbal supplements is like playing Russian (Chinese?) Roulette with one's health and safety. These products should not be used.

Consumers who have purchased Jade Pharmacy brand Meridian Circulation tablets or liquid extract or Jade Pharmacy brand Quell Fire tablets should stop its use immediately and return it to the place of purchase for a full refund. Consumers with questions should contact East Earth Herb at 1-800-827-4372.

Beyond this latest instance of unsafe herbals and food supplements, there is an urgent need to repeal or drastically amend the 1994 Dietary Supplement Health and Education Act.

Ginkgo Biloba Is Found Ineffective for Dementia and Age-Associated Memory Impairment in the Elderly

Researchers from the Netherlands reported in the October 2000 issue of the *Journal of the American Geriatrics Society* that a standardized extract of the widely hyped herb ginkgo biloba has been found ineffective for older adults with dementia and age-associated memory impairment. The results of this study contrast sharply with those of previous ginkgo biloba trials.

The trial lasted 24 weeks and involved 214 residents of homes for the elderly. Their average age was greater than 80 years. Of these 214 patients, 63 were demented and 151 were not but had substantial cognitive decline. The trial was randomized, placebo-controlled, and double blind. This type of study design is the scientific "gold standard" for testing a hypothesis about the effectiveness of drugs or other medical interventions.

Potential trial subjects were screened to ensure that those who participated had dementia, either mild to moderate Alzheimer's dementia or vascular dementia, or age-associated memory impairment. A battery of eight rating scales were used to compare 160 milligrams or 240 milligrams of ginkgo biloba extract per day to an inactive placebo used as the control.

A unique feature of this trial was the special effort made to improve similarities between the ginkgo biloba and placebo tablets with respect to appearance, color, smell, taste, granularity, and solubility. In order to imitate the distinct taste of ginkgo biloba extract, 2 milligrams of quinine was added to the placebo tablets. Quinine is a very old drug, first used to treat malaria, that has an exceptionally bitter taste. (More later on why we think this is so important.)

The researchers had three questions they wanted to answer: (1) How effective is ginkgo extract? (2) Does increasing the dose of ginkgo also increase its effectiveness? (This is called a dose-response effect and is very important in showing if, in fact, an agent has biological activity.) And (3) Does the effect of ginkgo biloba persist?

After 24 weeks of treatment, the ginkgo biloba was found to be statistically superior to placebo in only two of the eight rating scales used in the study. The first concerned the subject's self-perceived level of activities of daily living and the second was based on a test in which 30 numbers were to be connected in the right sequence as quickly as possible. (This latter scale measures cognitive speed, planning and organization.) Both of these effects were not impressive and disappeared after adjustment for other factors that may have led to a positive finding for the ginkgo extract. After adjustment, only a 12-week difference between ginkgo and placebo in the activities of daily living score persisted. The placebo was found to be statistically superior for self-perceived memory status after 12 weeks. When corrected for other factors that might have led to this result the positive effect of the placebo also disappeared.

The results of this trial led the

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antipsychotic drugs, both atypical and conventional, that could provide information on safety and effectiveness that would make prescribing more rational. In the absence of evidence, it seems more likely that the shift to the atypical drugs is largely "a victory of clinical hope and marketing hype."

Comparative safety and effectiveness studies between old drugs and new ones are not required in the United States for approval of a new drug. This makes it possible for new drugs to be approved without a showing that they are more effective than those already on the market; in fact, they can be less effective or perhaps more dangerous.

The review's final recommendation—that conventional antipsychotics should usually be used first in treating an episode of schizophrenia—is sound advice both scientifically and economically. But this recommendation does not, and should not, preclude the use of an atypical antipsychotic first if there is a sound reason for doing so.

What You Can Do

You should carefully discuss the adverse effects of various antipsychotic drugs with your doctor if you must make the decision for yourself or a family member to begin treatment. Because there is little evidence available to differentiate the effectiveness of these drugs, the choice may best be made on the basis of their potential toxicity.

GINKGO BILOBA, *from page 15*
researchers to conclude "... that treatment with ginkgo is not efficacious, irrespective of dose, in older patients with mild to moderate dementia or age-associated memory impairment."

Why did the results of this trial contrast so sharply to several recent randomized, placebo-controlled, double blind trials showing a benefit for ginkgo biloba? There are some differences between this study and those showing a positive effect for the herb, including the diagnosis of the patients, severity of disease, age, and the rating scales used to test ginkgo's efficacy.

There are other possible explanations for the results of this study. As was mentioned above, careful steps were taken to ensure the similarities between the placebo and the ginkgo pills that included giving the placebo a bitter taste. This was done to ensure that both patients and researchers were "blind" as to who was receiving the placebo or the ginkgo. This is important because if patients in a clinical trial detect a taste this may lead them to believe they are taking the active drug and this could bias their responses on some rating scales.

To verify that patients and researchers were, in fact, blinded to which drug was being used, all were asked to guess if the placebo or ginkgo was given. This check did not show any association between actual and perceived type of treatment.

This is by far the most rigorous clinical trial we have seen of ginkgo biloba. But, as the researchers correctly point out, any time statistics are used to interpret the results of a clinical trial it is possible that the results were due to chance.

Manipulation of data is also a possible reason for the different results seen in the ginkgo trials. The boundaries between published research and promotion have become blurred and the manipulation of data and putting a spin on clinical trial results can explain, in part, the different results seen in ginkgo biloba trials. Journal editors must accept the veracity of the studies submitted to them for publication. They have neither the authority nor resources to ensure that data have not been "cooked." This is one reason why the Food and Drug Administration's (FDA) review process is so critical. The FDA has the authority and does audit clinical trials to ensure that the data used in making a decision about the safety and efficacy of a product are valid. This trial was sponsored by a German ginkgo producer and we have no reason to believe that the German company influenced the results of this study.

Consumers should not be misled into believing that ginkgo biloba has undergone regulatory scrutiny for safety and efficacy, similar to an FDA review, in Germany because this herb is listed in the German Commission E Monographs. The Commission E was created in 1976 to protect the herbal drug industry when German law was changed to require proof of safety and efficacy before a product could be marketed. The law required that products, including herbals, already on the market be reviewed according to modern scientific standards to determine their safety and efficacy. This has never been done.

As dietary and herbal supplements, such as ginkgo biloba, are subjected to more rigorous scientific scrutiny, it is becoming clearer that their success in the marketplace in many cases is a result of misleading advertising rather than any type of proven benefit to consumers.

What You Can Do

Save your money. Any benefit of ginkgo biloba extract for any purpose remains dubious at best.