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Osteoporosis and Soy Products

*By Lynn Keegan, RN, PhD, HNC, FAAN,
and Gerald T. Keegan, MD, FACS*

AS THE PERCENTAGE OF THE U.S. POPULATION AGE 65 AND OLDER continues to increase every year, osteoporosis and osteopenia (low bone density) progressively are becoming more important public health problems. It is estimated that at least 10 million people in the United States have osteoporosis, and another 34 million have osteopenia, which places these individuals at significant risk for osteoporosis and related bone fractures. Eighty percent of the 10 million Americans estimated to have osteoporosis are women. One in two women and one in four men older than age 50 will have an osteoporosis-related fracture in her/his remaining lifetime.¹

History of the Disease

Osteoporosis develops as a result of defective bone remodeling and an imbalance in the dynamic interaction of osteoclasts and osteoblasts. Osteoclasts, the cells that resorb bone, respond to many signals, the most important of which is osteoprotegerin ligand. Osteoblasts, the cells that build bone, respond to a variety of factors including estrogens, vitamin D, cytokines, and growth factors. Risk factors for osteoporosis include age, female sex, family history, white race, estrogen deficiency, medications including steroid use, low calcium intake, tobacco use, physical inactivity, and low body weight.

Hormone replacement therapy commonly has been used in postmenopausal patients. Estrogenic compounds increase osteoblastic activity and lead to enhanced pro-collagen production and increased alkaline phosphatase production and thus inhibit bone loss. The Women's Health Initiative (WHI) studies demonstrated a 33% decrease in hip fractures and a 24% decrease in total fractures in postmenopausal women treated with estrogens.² However, recent results from the WHI² and the long-term follow-up of the Heart and Estrogen/progestin Replacement Study³ show an increased risk of both cardiovascular disease and breast cancer among those women randomized to the hormonal therapy group.⁴ For this reason, many women are seeking alternatives to prescribed estrogen/progestin compounds and have started using dietary supplements containing phytoestrogens derived from soy protein and red clover.^{5,6}

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Plant-derived phytoestrogens have been a focus of research for osteoporosis treatment. Their estrogenic activity generally is much less than that of human estrogens. Whether phytoestrogens have any effect at all in human patients is debated and the data are still unclear. However, the protective effects of soy protein on bone health may be somewhat encouraging.⁷

Constituents and Metabolism

Soybean is an annual legume of the Fabaceae or Leguminosae family (*Glycine max.*). This bean, which originated in Asia, has been cultivated widely for more than 2,000 years.⁸ Soybeans contain a number of active substances in addition to protein, including several classes of phytoestrogens. The three main classes of phytoestrogens are the isoflavones, coumestans, and lignans.⁹ Some of these agents are thought to have antioxidant, anti-inflammatory, antibacterial, antiangiogenic, antiproliferative, and antiparasitic effects, but only four agents (genistein, daidzein, biochanin, and formononetin) have potent phytoestrogenic activity.⁹ There are limited data on the quantitative absorption, protein-binding, or the specific metabolism of dietary estrogens. Dietary phyto-

estrogens are metabolized by intestinal bacteria, absorbed then conjugated in the liver, circulated in the plasma, and excreted in the urine.¹⁰

Proposed Mechanisms of Action

Multiple mechanisms may play distinctive and separate roles in the protective effect of soy products on bone health. The substitution of soy protein for animal protein may have less of a calciuric effect, perhaps related to an insulin-modulated effect at the renal level.¹¹ The retardation of the excretion of calcium in the urine may preserve the body's calcium stores.¹²

Another postulated mechanism involves the direct effect of phytoestrogens on bone remodeling. Isoflavones are polyphenolic compounds that are structurally related to estrogens. These so-called phytoestrogens have been shown to bind to estrogen receptors,¹³ and have greater affinity for estrogens-receptor beta than alpha.¹⁴ Because isoflavones bind to estrogen receptors, they are considered to be possible estrogen receptor modulators. However, isoflavones also can exert biological effects independent of their phytoestrogenic activities.¹⁵ Isoflavones have been found to affect bone cells in culture.⁷ Both daidzein and genistein have been found to suppress osteoclastic activity. Genistein has been discovered to have a stimulatory effect on osteoblasts in vitro as well as anabolic effects on bone in animal models.¹⁶

A third postulated mechanism is based on the anti-inflammatory effects of soy. Both animal and human studies have indicated that an increased intake of n-6 fatty acids from vegetable oils elevates prostaglandin E(2) levels as well as pro-inflammatory cytokines. It also has been found that lack of estrogen increases the production of these cytokines by immune cells and thereby activates osteoclasts during the perimenopausal period.

In a study assessing the use of n-3 fatty acids and soy protein, the authors postulate that the anti-inflammatory effect might protect against bone loss by decreasing osteoclast activation and subsequent bone resorption. One of the mechanisms appears to be decreasing the receptor activator of NF-kappaB ligand on T cells, which has been found to increase osteoclast activation along with increasing pro-inflammatory cytokines in ovariectomized (OVX) mice.¹⁷

Animal Studies

Much of the evidence suggesting a beneficial effect of soy products in preventing bone loss in the environment of estrogen deficiency is derived from experimental animal studies. A recent study in aged OVX rats demonstrated that dietary soy had a beneficial effect on the

Alternative Therapies in Women's Health,
ISSN 1522-3396, is published monthly by Thomson
American Health Consultants, 3525 Piedmont Rd., NE,
Bldg. 6, Suite 400, Atlanta, GA 30305.
VICE PRESIDENT/PUBLISHER: Brenda L. Mooney.
EDITORIAL GROUP HEAD: Lee Landenberger.
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EDITOR: Leslie G. Coplin.
GST Registration Number: R128870672.
Application to mail at periodical postage rates is pending
at Atlanta, GA 30304.
POSTMASTER: Send address changes to *Alternative
Therapies in Women's Health*, P.O. Box 740059,
Atlanta, GA 30374.

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preservation of bone mineral density (BMD) associated with estrogen-deficiency bone loss. These data also show that at the tissue level, soy functions in a manner different from estrogen by increasing or sustaining elevated bone formation rates after ovariectomy.¹⁸

Although soybean isoflavones may reduce bone turnover, they do not reverse established osteopenia. A study in France that assessed the dose-dependent effects of daily soybean isoflavone consumption in reversing bone loss in adult OVX rats found neither BMD nor cancellous bone area was greater in soy phytoestrogen-fed rats than in OVX rats.¹⁹

A study of soy phytoestrogens compared with conjugated equine estrogen (Premarin) in postmenopausal monkeys concluded that there was no beneficial effect of soy phytoestrogens on bone mass.²⁰

Human Clinical Studies

The results of the human clinical studies are somewhat difficult to interpret, especially because of the lack of adequate control groups, the mostly homogeneous populations in which the studies have been performed with their lifetime consumption of soy products, and the various types of soy/isoflavone products that were evaluated.

Isoflavones. A recent review of 15 clinical trials examined the effects of isoflavones or isoflavone-rich soy protein on BMD. Although there were inconsistencies, the results in general suggested that isoflavones reduce bone loss in younger postmenopausal women. Similarly, limited epidemiologic data show that among Asian populations isoflavone intake is associated with higher BMD. The authors conclude that although soy foods and isoflavones cannot be viewed as substitutes for established anti-osteoporotic medications, health professionals can feel justified in encouraging postmenopausal women concerned about bone health to incorporate soy foods into their diet.²¹

A study from China examined whether the associations between isoflavone supplementation and rates of change in bone mineral content (BMC) could be modified by years since menopause, body weight (BW), and dietary calcium intake. A group of 203 postmenopausal women between ages 48 and 62 were randomly assigned to three treatment groups: placebo (0 mg/d isoflavones), mid-dose (40 mg/d isoflavones); and high-dose (80 mg/d isoflavones). All groups also took 500 mg/d calcium. Both univariate and multivariate analyses observed significant favorable effect of isoflavone supplementation on rates of change in BMC at the total hip and trochanter among later postmenopausal women (> 4 y), in women with lower BW (\leq median, 55.5 kg), or among women with lower level of calcium intake

(\leq median, 1,095 mg/d).²²

These same researchers conducted a double-blind, placebo-controlled, randomized trial examining the effects of soy isoflavones on bone loss in 203 postmenopausal Chinese women, ages 48-62 years. Subjects were randomly assigned to three treatment groups with daily doses of placebo (1 g starch), mid-dose (0.5 g starch, 0.5 g soy extracts, and approximately 40 mg isoflavones), and high-dose (1.0 g soy extracts and approximately 80 mg isoflavones). All were given 500 mg calcium and 125 IU vitamin D(3). Both univariate and multivariate analyses showed that women in the high-dose group had mild, but statistically significant, favorable change rate in BMC compared with the placebo and mid-dose groups. Further stratified analyses revealed that the positive effects of soy isoflavone supplementation were observed only among women with lower initial baseline BMC (median or less). The authors conclude that soy isoflavones have a mild, but significant, independent effect on the maintenance of hip BMC in postmenopausal women with low initial bone mass.²³ Another study from the same group reported the results of the baseline cross-sectional analysis of the association between dietary soy protein intake and BMD/BMC in a population-based study of more than 400 healthy Chinese women within the first 12 years of postmenopause. This study demonstrated that soy protein/isoflavone intake had a modest but significant association with hip BMD as well as total body BMC among women after the initial few years of postmenopause.²⁴

In a two-year study in Denmark, postmenopausal Caucasian women with established osteoporosis or at least three risk factors for osteoporosis were randomly assigned to one of four treatment groups: soy milk containing isoflavones (soy+), transdermal progesterone (TDP+), the combination of soy+ and TDP+, or placebo (isoflavone-poor soy milk, soy- and progesterone-free cream). The investigators found that the percentage change in lumbar spine BMD and BMC did not differ from zero in the soy+ and TDP+ groups, but significant bone loss occurred in the control and combined treatment groups. The authors concluded that drinking two glasses of soy milk containing 76 mg isoflavones prevented lumbar spine bone loss in postmenopausal women. Transdermal progesterone had bone-sparing effects, but when combined with soy milk, a negative interaction between the two treatments occurs, resulting in bone loss to a greater extent than either treatment alone.²⁵

Soy protein. A 15-month pilot study designed to investigate the effect of soy protein isolate with varying concentrations of isoflavones on early postmenopausal

bone loss and lipids concluded that there was no significant positive effect of soy protein isolate supplemented with isoflavones on BMD and the serum lipid profile in early postmenopausal women.²⁶

One of the above postulated mechanisms for preservation of calcium in bone was the selective retention of calcium in soy protein as opposed to animal protein diets. This theory is challenged to some extent by a study examining the effects of substituting 25 g soy protein for meat on calcium retention and bone biomarkers. Thirteen postmenopausal women ate similar diets, but in one diet 25 g high-isoflavone soy protein was substituted for an equivalent amount of meat protein for seven weeks. Despite a 15-20% lower renal acid excretion during the soy protein diet, urinary calcium loss was unaffected by diet. The authors concluded that substituting high-isoflavone soy protein for meat, in the presence of typical calcium intakes, did not improve or impair calcium retention or other indicators of bone health in postmenopausal women.²⁷

Ipriflavone. Daidzein is a metabolite of ipriflavone (IP), a synthetic derived from soy protein. In animals, daidzein contributes to bone sparing. Early studies with this agent combined with calcium in women ages 65 and older showed significant increase in BMD.²⁸ Some studies have demonstrated that IP reduces bone mass loss caused by glucocorticoids²⁹ and gonadotropin-releasing hormone agonists used in producing pharmacological menopause in women.³⁰ IP may prevent bone loss by an anti-inflammatory effect.³¹ IP has been found in some studies to be anti-resorptive and possibly mildly stimulatory on bone in the treatment of osteopenic and osteoporotic postmenopausal women.³² The bone-sparing effects of this substance have been noted primarily at the lumbar spine, but it has also been noted to affect radial bone and femoral neck density as well.

A randomized placebo-controlled study in Japan evaluated the effect of IP against bone loss in premenopausal OVX women and postmenopausal women. Thirty-seven Japanese women who underwent premenopausal bilateral ovariectomy within three months (early-stage group) and 52 Japanese women who were ovariectomized or who had undergone menopause more than three years before the start of the study (late-stage group) were enrolled. The first group received 600 mg/d IP; the second received placebo. In the early-stage group, the IP group showed a 6.7% decrease in BMD from baseline levels, whereas the placebo group showed a 10.7% decrease at 12 months of treatment; the two groups showed 7.1% and 12.6% decreases at 24 months, respectively. In the late-stage group, there was a 0.3% increase in BMD in the IP group and a 2.3% decrease in the

placebo group at six months of treatment. Similar changes were seen at 18 months (1.4% increase and 3.9% decrease). IP suppressed bone loss compared with placebo; however, it did not prevent acute bone loss in the early stage following ovariectomy. The effect of IP alone on bone loss in the early stage is not sufficient to reduce the risk of osteoporosis in later life.³³

Dosage

The American Heart Association recommends 20-50 g/d of soy protein. Isoflavone supplements should contain about 50 mg/d and should not exceed 100 mg/d. IP is administered as 200 mg tid, and if used should be combined with both calcium and vitamin D supplements.

Other non-prescription medication treatment options for bone health include calcium supplementation (1,500 mg/d) from dietary dairy products with added calcium citrate, vitamin D supplementation (800 IU in high-risk patients), exercise, and abstaining from tobacco smoking.

Adverse Effects of Soy Products

Synthetic IP is contraindicated in pregnant and lactating women and very cautious use should be counseled in patients with liver or kidney disease.³⁴ IP also potentiates the toxic effects of theophylline. Although there are reports of a reversible lymphocytopenia in human patients using IP,³⁵ the effect of this phenomenon on immunological status is unknown. Animal studies in OVX mice showed that the increased lymphopoiesis and subsequent leucocytosis produced by ovarian hormone deficiency was restored to normal levels by the use of this agent.³⁶

Conclusion

Although basic research indicates that dietary soy products may have definitive effects in protecting estrogen-deficient animals from the development of osteoporosis and osteopenia, there is little clear evidence that these products will work in treatment of already established osteopenia. The human clinical studies are inconclusive and lack adequate controls and specificity as to product, dosage, and duration of treatment. In addition, most of the positive human studies are in populations that have a life-long use of soy products. Interpretation of data must be taken in this light.

Recommendations

Although human studies do not indicate an unequivocal effect of consumption of soy products on the development of osteoporosis in postmenopausal women, there seems little harm and probably some distinct benefits in recommending diets high in soy products, espe-

cially when substituted for the animal fat and protein so common in the Western diet. In many cases osteoporosis can be considered as a pediatric disease with geriatric manifestations, and as such any preventive modalities need to begin in youth and continued through the teenage years into adulthood to be effective. ❖

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Oh, My Aching Back: What's A Mother to Do?

By Mary L. Hardy, MD

BACK PAIN IS A COMMON COMPLAINT DURING PREGNANCY. Up to three-fourths of all pregnant women report having low back or pelvic pain with the highest pain intensity noted at 36 weeks.^{1,2} Management of pain with conventional analgesics presents a potential risk to the fetus and, thus, both patients and physicians may be reluctant to use such medication. Not only can back pain be a problem during pregnancy, but for 21% of these patients, pain may persist for more than two years after delivery.¹ Patients at highest risk for developing persistent back pain were older patients, patients with a previous history of back pain, patients with more severe symptoms at an earlier stage of pregnancy and those with a higher weight gain at 24 months.¹ Unfortunately, neither physiotherapy nor a patient education program prevented the development of back pain during pregnancy.² Although there is no evidence that successful management of pain would decrease the persistence of pain after delivery, it seems desirable to find a safe strategy to manage pain as early and as effectively as possible. Acupuncture may be that strategy.

Two recent randomized controlled trials were performed using acupuncture in the third trimester to treat pelvic and/or low back pain. The first trial compared the use of acupuncture to physiotherapy in 60 pregnant patients enrolled between 20 and 32 weeks gestation (mean 24 weeks).³ The groups were equivalent at baseline for maternal age, gestational age, and percentage of primigravida patients. Interventions included an individualized physiotherapy program (10 50-minute treatments within 6-8 weeks, including pool therapy) or a semi-structured acupuncture treatment (10 30-minute treatments within one month). Acupuncture was initiated

with the use of ear acupuncture for all patients followed by individualized body points as needed to relieve symptoms. The most commonly used points were listed and the needles were stimulated manually while inserted to increase the effect. The training of the acupuncturist was not noted.

Outcomes measured included a visual analog scale (VAS) for pain as well as a Disability Rating Index (DRI) that measured the ability to perform 12 common daily tasks. Interestingly, all the acupuncture patients completed treatment, but there were 12 dropouts in the physiotherapy group. Reasons included delivery (3), premature labor (3), inconvenient treatment hours (3), and failure to return for therapy (3). No such events were recorded for the acupuncture group. The results demonstrate that pain in both the morning and evening was lower in the acupuncture group following treatment (AM: VAS 3.4 vs. 0.9, $P < 0.01$; PM: VAS 7.4 vs. 1.7, $P < 0.01$). For the physiotherapy group, treatment led to a significant decrease in evening pain, but not morning pain. Results for the acupuncture group were significantly better for both morning and evening scores compared to the physiotherapy group (AM: $P = 0.02$; PM: $P < 0.01$). DRI values also were significantly better in the acupuncture group after treatment compared to the physiotherapy group. It is worth noting that an intention-to-treat analysis was not performed in this study. Thus, the six subjects who were lost to follow-up and reasonably may be presumed to be non-responders were not included in the analysis. If they were included, it is likely that the preference for acupuncture would be even more marked. No adverse events were recorded in this study.

A similar study was performed using 72 women at 24-37 weeks of gestation (mean 30 weeks) who were complaining of pelvic and/or low back pain.⁴ Patients were assigned randomly to receive either acupuncture (one to two times per week until they delivered or the pain resolved) or to be part of a control group (presumably usual and customary care group, although this was not explicitly stated). The acupuncture strategy was different than the previous study. No ear points were included and a written semi-structured protocol was followed. Individual variation was allowed at the discretion of the acupuncturist. Needles also were stimulated manually, but the treatment time seemed to be shorter than in the previous study. The total number of visits per patient was not reported. Schematic diagrams accompanied this article to make location of the points explicit, but the training of the acupuncturist again was not noted.

Outcomes measured included a VAS pain scale and influence of pain on defined common daily activities. Data also were collected about delivery and APGAR

scores of the babies at birth. The results are less fully reported here than in the previous study, but additional outcomes of interest are included here. Complete resolution of pain was reported in two acupuncture patients and no control patients. Pain intensity significantly decreased in the experimental group (60% vs. 14%, $P < 0.01$). Similar results were seen for pain associated with daily activities. Forty-three percent of the acupuncture patients vs. 9% of the control patients reported a decrease in pain related to daily activities ($P < 0.001$). No mothers in the acupuncture group reported using analgesic drugs, while five subjects in the control group needed medication for pain. Control patients also used more adjunctive therapy, such as TENS units, sacroiliac belts, or physiotherapy, compared to acupuncture patients. No serious adverse events were recorded in the acupuncture group and the birth outcomes were similar.

Similar results have been seen with a quasi-randomized, prospective effectiveness study conducted by a group in Brazil involving 61 women.⁵ Thus, the effectiveness of acupuncture for pelvic and low back pain in pregnancy has been replicated in three different settings.

However, there are a few caveats to keep in mind before sending all pregnant patients with back or pelvic pain to acupuncturists. First, patients with serious back problems should be dealt with in a conventional manner. Second, patients with a bleeding diathesis have a relative contraindication to acupuncture. Finally, patients should

be referred to acupuncturists skilled in treating pregnant patients. Care should be taken especially in the first trimester to avoid certain points, which traditionally are felt to stimulate the uterus. As shown in the literature cited here, successful treatment involves individualization of therapy. The skill of the individual acupuncturists will influence the outcome. With these conditions being met, acupuncture is a very safe and effective therapy for the treatment of back and pelvic pain associated with pregnancy. Hopefully, management of pain will allow patients to address other risk factors for persistent pain, such as weight, thus avoiding pain after delivery. ❖

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2. Ostgaard HC, et al. Back pain in relation to pregnancy: A 6-year follow-up. *Spine* 1997;22:2945-2950.
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CE Objectives

After reading *Alternative Therapies in Women's Health*, the health care professional will be able to:

1. evaluate alternative medicine and complementary therapies for women's health concerns;
2. identify risks and interactions associated with alternative therapies;
3. discuss alternative medicine options with patients; and
4. offer guidance to patients based on latest science and clinical studies regarding alternative and complementary therapies.

CE/CME Instructions

Physicians and nurses participate in this continuing medical education/continuing education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form provided and return it in the reply envelope provided at the end of the semester to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

CE / CME Questions

15. **The estrogenic activity of plant-derived phytoestrogens generally is much less than that of human estrogens.**
 - a. True
 - b. False
16. **Much of the evidence suggesting a beneficial effect of soy products in preventing bone loss in the environment of estrogen deficiency is derived from:**
 - a. experimental animal studies.
 - b. randomized, placebo-controlled trials.
 - c. epidemiologic data.
17. **The effectiveness of acupuncture for pelvic and low back pain in pregnancy has been replicated in three different settings.**
 - a. True
 - b. False

Answers: 15. a, 16. a, 17. a.

Cost Concerns Turning More Americans to CAM Therapies

A growing number of consumers are turning to complementary and alternative medicine (CAM)—and it might not be whom you think. New survey data show that not only are cost concerns driving more lower-income, uninsured patients to try alternative therapies, but many of these patients aren't telling their health care providers about these treatments.

The people who are concerned about the cost of their health care may be particularly vulnerable as they seek cheaper—and potentially ineffective or unsafe—care outside the realm of conventional medicine, says Ha T. Tu, MPH, a health researcher for the Center for Studying Health System Change (HSC) in Washington, DC. HSC is a nonpartisan policy research organization funded principally by the Robert Wood Johnson Foundation.

HSC recently released data showing that nearly six million Americans have turned to CAM because conventional medical treatment is too expensive. The study is based on the 2002 National Health Interview Survey, a nationally representative government survey conducted by the Centers for Disease Control and Prevention's National Center for Health Statistics. Tu is a co-author of the study.

Tu and her co-author originally had a particular interest in how people with certain chronic conditions use CAM. The information, however, was not very good for that purpose. "So we just looked at what was interesting in the data," she says. "It led us to analyze this subgroup of people who resort to CAM because they say the cost of conventional medical treatment is too high for them."

This was a bit surprising to the researchers because the impression is usually that most CAM users tend to be somewhat better off and more educated than other people. "People who use certain CAM treatments, like massage and yoga for general well-being, generally have more disposable income. They choose those CAM treatments to enhance their lifestyle and their overall health and well-being," Tu says.

The millions of adults who use CAM because of cost concerns, however, were four times as likely to be uninsured as the 38 million Americans who use CAM to treat specific health conditions without citing cost as a reason, according to the study. In addition, they were almost

twice as likely to have low incomes, defined as below 200% of the federal poverty level.

"It is somewhat troubling because the evidence seems to show that they are resorting to CAM because they can't afford conventional care," Tu says. "Our organization tracks a lot of trends in the health system over time, such as looking at the implications of rising costs. It seems to us that as health care costs keep rising well above the rate of income growth, this group of six million people is likely to grow."

Tu also is concerned about another finding in the data—in more than half of the cases where CAM is being used because of cost concerns, the patients did not tell their health care providers about using the therapies. Or if they did, the providers were not always well-versed about the therapies' potential side effects.

She is quick to point out that not all of the six million CAM users are a cause for concern for health care providers. "We try not to say that in our analysis. The conditions some of these people are using to treat with CAM are conditions like colds, and [the CAM consumers] are using echinacea to treat it. While the jury might be out about whether that is an effective treatment, there is no evidence it does any harm."

Instead, the researchers highlight the use of two herbal remedies that are thought to cause serious side effects. St. John's wort was used by one in eight of all CAM users citing cost concerns. Known as a potential treatment for depression, the herbal remedy may have potentially dangerous side effects when used with other drugs.

Kava was used by one in 12 of this subgroup of the study. Kava is used to treat anxiety, stress, and insomnia, and has been linked to liver damage.

It might not occur to patients that an herbal remedy might react with a prescription drug, Tu says. "Consumers often think that because a product is 'natural,' it is likely to be safe." Patients with multiple health conditions also might not be able to recall all the medications—CAM remedies included—that they have taken.

For these reasons, Tu urges health care providers to be proactive and ask patients about possible CAM use. "Asking is something the health system can do without adding to cost," she says. It also may be the only opportunity to provide basic education to the patients about CAM therapies. ❖

In Future Issues:

CAM Supplements for Fertility
Calendula Ointment for Dermatitis in Cancer Patients