

# ALTERNATIVE THERAPIES IN WOMEN'S HEALTH

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## Glucosamine Sulfate for Osteoarthritis

*By Dónal P. O'Mathúna, PhD*

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OSTEOARTHRITIS IS THE MOST COMMON FORM OF ARTHRITIS AND A leading cause of disability in the United States.<sup>1</sup> The prevalence of osteoarthritis is expected to double in the next 20 years.<sup>2</sup> As many as 40% of those older than 65 years may have symptomatic osteoarthritis of the hip or knee, the large joints most commonly affected by osteoarthritis.<sup>1</sup> It is estimated that almost every one 75 years of age or older is affected by osteoarthritis in at least one joint. However, only about half of the people who show evidence of the disease on X-ray report having any symptoms.<sup>3</sup>

Osteoarthritis was once viewed as a consequence of aging, but is now known to develop due to complex interactions involving genetics, age, gender, obesity, joint injury, and muscle weakness.<sup>2</sup> Osteoarthritis tends to affect women at an earlier age than men, making it an important area of investigation for women's health.

### Background

Medically speaking, osteoarthritis refers to a disease in which the cartilage inside joints gradually degenerates. This exposes the bone inside the joint and causes narrowing of the joint-space leading to stiffness and pain. In the end, the joint may become so immobile and painful that joint replacement surgery is the best alternative. (See Figures 1 and 2, page 91.)

Osteoarthritis is only one of a number of arthritic diseases, resulting in the term arthritis being used commonly to refer to any pain and stiffness in the muscles and joints. For this reason, some who have osteoarthritis refer to it as arthritis. Technically speaking, arthritis involves inflammation in the joints and osteoarthritis is a non-inflammatory degenerative disease. All of the studies reviewed here were carried out with older adults diagnosed with osteoarthritis.

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Dr. Balk (peer reviewer) reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Currently, osteoarthritis does not have a cure.<sup>4</sup> Management of symptoms includes pharmacological and non-pharmacological strategies.<sup>1</sup> Weight control, pain relief, exercise to maintain and improve the range of motion and stability of the joints, and limiting functional disability are important strategies in treating osteoarthritis. Frequently, drug therapy, including analgesics like acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), is needed. The newer cyclooxygenase-2 (COX-2) inhibitors are recommended widely as being safer than older NSAIDs. Although all of these are important for managing symptoms, they do not treat the underlying pathology.

Concerns about the toxicity and side effects of pharmaceutical drugs have fueled interest in complementary approaches to managing osteoarthritis symptoms. Some dietary supplements are alleged to treat the underlying condition. Foremost among these are glucosamine sulfate and chondroitin sulfate, which are some of the most popular dietary supplements sold in the United States.<sup>5</sup> Although the two supplements are usually taken together, most of the studies have tested them separately.<sup>2</sup> This review will focus on the use of glucosamine sulfate.

Glucosamine occurs naturally in the body as one component of the cartilage and synovial fluid found within joints.<sup>5</sup> Glucosamine forms part of the structure of some compounds whose levels are reduced with

## Summary Points

- Glucosamine sulfate has been shown to be effective in relieving the symptoms of osteoarthritis, though studies have conflicting results.
- Most studies with positive results used a formulation available by prescription in Europe, while studies with negative results typically used products available in the United States as dietary supplements.
- Research with glucosamine hydrochloride or combining glucosamine with chondroitin is lacking.

osteoarthritis. A number of salts of glucosamine are available, with some debate over their relative effectiveness. While the exact mechanism of action of glucosamine remains unknown, it is presumed that glucosamine supplementation facilitates the production and regeneration of cartilage.

## Clinical Studies

Clinical studies have been conducted on glucosamine sulfate for osteoarthritis for more than 20 years. Many of the early studies were conducted in Europe using a product available there by prescription as 1,500 mg sachets to be dissolved in water (manufactured by Rotta Pharmaceuticals of Italy). These studies were sponsored by its European manufacturer and generally had favorable results. Later independent studies tended to have negative results, raising concerns about bias. However, the differences are more complicated, involving different glucosamine formulations and study designs. The independent studies have used products available in the United States as dietary supplements, which are formulated as capsules and may not be absorbed well.<sup>3</sup>

An important publication in the history of glucosamine was a systematic review and meta-analysis published in 2000.<sup>6</sup> This review identified six double-blind, randomized, controlled trials (RCTs) in which glucosamine sulfate was administered for at least four weeks. The trials were conducted between 1980 and 1997 and all evaluated knee osteoarthritis symptoms. The analysis revealed moderate-to-large benefits from taking glucosamine sulfate. However, all of the trials were of relatively short duration and had methodological limitations that are known to exaggerate beneficial effects.

Another meta-analysis was published in 2003 which reviewed trials published between 1980 and 2002.<sup>7</sup> Seven RCTs of glucosamine sulfate for osteoarthritis

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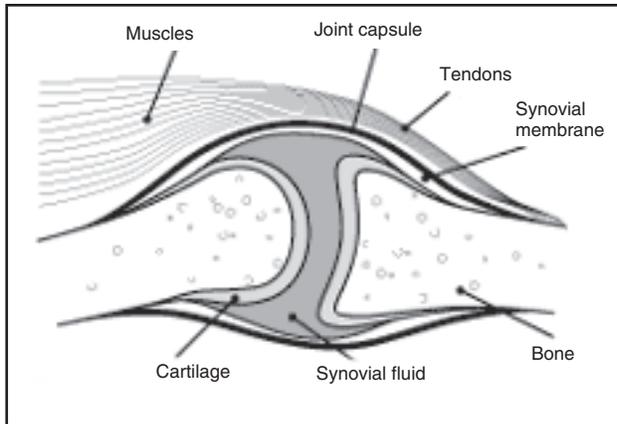
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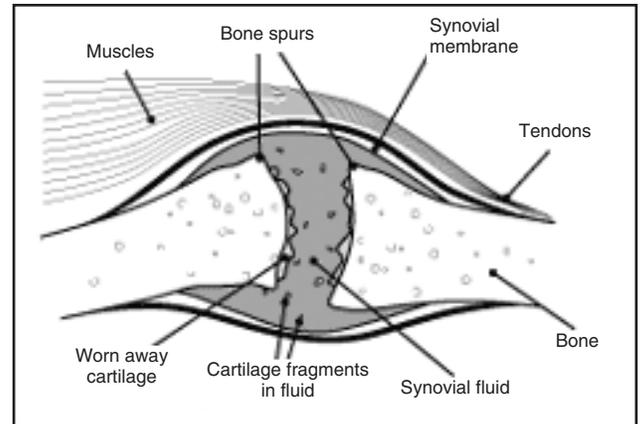
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**A healthy joint and a joint with osteoarthritis**



*Figure 1:* In a healthy joint, the ends of bones are encased in smooth cartilage. Together, they are protected by a joint capsule lined with a synovial membrane that produces synovial fluid. The capsule and fluid protect the cartilage, muscles, and connective tissues.



*Figure 2:* With osteoarthritis, the cartilage becomes worn away. Spurs grow out from the edge of the bone, and synovial fluid increases. Altogether, the joint feels stiff and sore.

**Source:** National Institutes of Health. Handout on Health: Osteoarthritis. Available at: [www.niams.nih.gov/hi/topics/arthritis/oahandout.htm](http://www.niams.nih.gov/hi/topics/arthritis/oahandout.htm). Accessed Nov. 6, 2008.

were included in the analysis. The treatment periods ranged from four weeks to three years, and only high-quality studies were included. Glucosamine was found to significantly improve symptoms as measured by the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index, Lequesne Index (LI), visual analog scale (VAS) for pain, and mobility tests. The effect sizes were less than those found in the 2000 meta-analysis, which was interpreted as being due to the inclusion of only higher-quality studies. The 2003 review also included two studies in which joint space reduction was measured by X-ray. Both found significant improvements, which suggested slowing of the joint cartilage degenerative process.

A subsequent review included all RCTs of glucosamine for osteoarthritis published up until 2005.<sup>8</sup> Twenty studies were included in the analysis which showed much variability in their results. Overall, glucosamine showed a 28% improvement in pain and a 21% improvement in function as measured by LI. Sub-group analyses shed some light on the sources of variability. The eight studies of highest quality (which had adequate allocation concealment) showed no benefit in pain and WOMAC function scores. Ten of the studies were conducted with the Rotta product and their pooled

results found glucosamine superior for pain and function. The 10 studies using non-Rotta products did not show statistical differences between glucosamine and placebo.

Since those reviews were published, the much-anticipated Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) published its results.<sup>9</sup> This study randomized more than 1,500 patients with symptomatic knee osteoarthritis to daily doses of either 1,500 mg glucosamine hydrochloride, 1,200 mg chondroitin sulfate, both glucosamine and chondroitin, 200 mg celecoxib, or placebo. Two-thirds of the participants were women. The primary outcome measure was a 20% reduction in knee pain measured by the WOMAC scale after six months of treatment. No significant reduction in pain occurred for the groups taking glucosamine or chondroitin, alone or together, compared to placebo, while pain was significantly reduced in the celecoxib group.

Those participants in the GAIT study with moderate-to-severe pain, had significantly better pain reduction after six months with combination therapy compared to placebo ( $P = 0.002$ ). Those patients with moderate-to-severe joint damage as revealed by X-ray were asked to continue in a follow-up study focused on joint

space width.<sup>2</sup> Patients continued to take the same treatment to which they had been assigned for a total of two years, with X-rays obtained at baseline, 12 months, and two years. No statistically significant differences in joint space width were observed between any of the groups.

### Adverse Effects

The GAIT study reported no significant differences in adverse effects between the groups, with a similar number of participants withdrawing from each group because of adverse events.<sup>9</sup> No differences in serious adverse events between groups were reported in the meta-analyses.<sup>7</sup> Its safety profile is thus considered excellent.

Concerns have been raised that glucosamine might interfere with glycemic control in diabetic patients since animal models have demonstrated such effects. However, a double-blind RCT of type 2 diabetes patients receiving either placebo or 1,500 mg glucosamine sulfate plus 1,200 mg chondroitin sulfate found no changes occurred in glycemic control after 90 days.<sup>10</sup>

Glucosamine sulfate is obtained from chitin extracted from marine exoskeletons, which has raised concerns about allergic reactions. Those with seafood allergies should probably avoid glucosamine, depending on the severity of their allergy, or be carefully monitored if they try it.<sup>4</sup>

### Conclusion

The results of the GAIT study are consistent with previous research on glucosamine hydrochloride: It does not have the effectiveness found for glucosamine sulfate. Only the Rotta brand has consistently demonstrated effectiveness in reducing symptoms and slowing joint deterioration. The glucosamine may be more readily absorbed from this product as it is dissolved in water before consumption. Questions have been raised about the bioavailability of glucosamine in general.<sup>3</sup> In addition, quality varies considerably among those products available in the United States as dietary supplements.<sup>11</sup>

For those with osteoarthritis, a trial of glucosamine sulfate may be warranted, especially for those who do not respond well to conventional treatments. However, even in those trials where glucosamine sulfate has been found effective, participants continued to use other analgesics when pain or discomfort were particularly problematic. Symptoms should be evaluated carefully over 2-3 months, at which time those who are likely to benefit will have responded.<sup>12</sup> As with many chronic conditions, control of weight, exercise, and other symp-

tom-relieving strategies will remain important in the overall management of osteoarthritis. ♦

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# Teens Having a Cow: Red Meat and Breast Cancer

ABSTRACT & COMMENTARY

By *Russell H. Greenfield, MD*

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**Source:** Linos E, et al. Red meat consumption during adolescence among premenopausal women and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2008;17:2146-2151.

CONCERNS HAVE LONG BEEN RAISED ABOUT AN ASSOCIATION between animal protein intake, specifically red meat, and risk of breast cancer. Red meat consumption during early adulthood has been associated with an increased risk of premenopausal breast cancer, while data for postmenopausal breast cancer risk are less consistent. This study focused on the dietary habits of adolescents, both because there is a paucity of data on this group and later risk of breast cancer, and because some experts believe adolescence may be a period of increased susceptibility to environmental factors leading to later development of breast cancer due to the regular occurrence of undifferentiated cell division until first pregnancy.

The authors of this prospective cohort trial (part of the Nurses' Health Study II, NHS II) had access to information supplied by more than 39,000 women aged 25-43 years in 1989, who in 1998 (mean age, 44 years) completed a validated food frequency questionnaire (FFQ) on their diet during high school. The FFQ assessing dietary habits during high school was completed in 1998, and specifically included reference to foods commonly available from 1960 to 1980. Subjects were followed for seven years or until either a diagnosis of breast cancer was made or death occurred. Specific nutrient and caloric intakes were calculated, as were breast cancer rates.

At trial's end the researchers identified a total of 455 cases of invasive premenopausal breast cancer from the cohort. Subjects who ate the most red meat during high school had a significantly increased risk of breast cancer (relative risk = 1.34) in energy-adjusted and multivariate-adjusted models compared with those who ate the least red meat during adolescence. This association persisted after adjustment for intake of heme iron and ani-

mal fat. Risk of breast cancer increased 20% for every 100 g of red meat ingested daily, with the association being slightly stronger for ER- and PR-positive tumors. In contrast, no association between breast cancer risk and red meat consumption was identified for red meat intake during adulthood. As regards types of red meat and breast cancer risk, the association was greatest for frequent consumption of hot dogs. A borderline significant association was also identified for consumption of processed meat.

The researchers conclude that high levels of red meat intake during the teenage years may increase the risk of premenopausal breast cancer by 30-40%.

## ■ COMMENTARY

Recent years have seen a greater degree of attention being paid to early life exposures and later risk of cancer, with data accumulating that raise the specter of windows of significant susceptibility. The conclusions of the current study are extremely concerning, but at least one shortcoming impacts the reliability of their findings, that being the potential for recall bias. The authors used a validated and reproducible retrospective questionnaire, and even contacted participants' mothers where available, but subjects still had to try to recreate their diets from 16 to 35 years past. In addition, only half the available cohort completed the questionnaire. Significant flaws aside, the findings merit our attention because the methodological strengths of the trial outweigh its weaknesses. The prospective nature of the investigation, its large sample size and high compliance rate, and multivariate modeling make for an impressive work.

Diet is one of the few potentially modifiable risk factors for cancer, and data like these help us shape the recommendations for our young patients and their parents. As the authors note, possible ways that regular red meat intake might promote carcinogenesis include increased iron load (animal data suggest that dietary iron may increase estrogen carcinogenicity), increased exposure to hormones used in the raising of cattle, and increased risk with select methods of preparation (e.g., formation of heterocyclic amines at high temperatures, which are estrogenic in vitro). We do not yet know the exact times of increased susceptibility if present, nor exactly to which agents people may be sensitive, but in light of the risk associated with regular hot dog intake, one area of investigation should be the processing of meats and associated physiologic effects after ingestion. Until more data are available, it seems prudent to recommend that young girls be exposed to red meat products less often than they typically are now. ❖

# The Effect of Race, Culture, and Values on the Patient-Physician Relationship

ABSTRACT & COMMENTARY

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**Source:** Street RL Jr, et al. Understanding concordance in patient-physician relationships: Personal and ethnic dimensions of shared identity. *Ann Fam Med* 2008;6:198-205.

ONE OF THE FOREMOST GOALS FOR THE HEALTHY PEOPLE 2010 program<sup>1</sup> is the elimination of health disparities among different segments of the population. Reported data are clear that barriers in the patient-physician relationship contribute to racial disparities in the experience of health care.<sup>2,3</sup> Since differences exist in patients' perceptions of their physicians, which can impact health care utilization, status, and outcomes, it would be prudent to identify and measure such differences in a manner such that those inequalities may be better understood.

Concordance is defined as a similarity, or shared identity, between the physician and patient based on a demographic attribute, such as race, sex, or age. Race concordance between the patient and physician is well established. Such race concordance leads to higher patient ratings of care and satisfaction.<sup>4,5</sup> Much less evidence points toward gender or age concordance or the interactions thereof. Furthermore, it is yet unclear whether such concordance may lead to better outcomes rather than just improvements in patient satisfaction.

In their study, Street et al hypothesized that the link between concordance and outcomes is mediated through perceptions of relational similarity. Thus, when patients perceive a physician similar to themselves, they may feel more comfortable in trusting such a physician with recommendations, which may lead to more action on their part and better outcomes. The authors set out three main objectives for the study: 1) to create a self-report measure of perceived similarity, 2) to evaluate the influence of concordance by race and sex on perceived similarity alone and in the context of other factors, and 3) to examine the relationship of patients' perceptions of sim-

ilarity to physicians to the quality of care outcomes.

The study included a total of 269 patients and 29 physicians recruited from 10 primary care clinics in the Houston area from private and Veterans Affairs/county hospital settings. Neither Asian patients nor Hispanic physicians participated. All spoke English and were older than 18 years of age. Patients answered a subjective set of questions, which were matched to physicians to determine traits of personal and ethnic similarity. Interaction with physicians was audio tape recorded and later coded. The data were analyzed into three groups: race concordant, race discordant (White), and race discordant (minority: Blacks and Hispanics).

Patients in racially concordant (patient and physician of same race) encounters reported more personal similarity to their doctors than did minority patients in racially discordant (patients are Hispanic or Black but physicians are of different race) interactions. Similarly, patients in racially concordant encounters saw themselves as more ethnically similar to their physicians than did minority or White patients in racially discordant visits. Also, older and more educated patients, as well as those whose physicians used more patient-centered communication, perceived themselves to be more personally similar to their physicians.

Patients who believed they were more similar to their physician with respect to personal beliefs, values, and ways of communicating reported more trust in the physician, more satisfaction with care, and a stronger intention to adhere to recommendations. On the other hand, patients' perceptions of being similar to the physician in terms of race, ethnicity, and community were not related to patient outcomes. The degree to which physicians were patient-centered in their communication not only was related to patients' perceptions of personal similarity to their doctors, but it also predicted outcomes. Regardless of race, when physicians were more informative, supportive, and facilitative, the patients were more active participants, were more satisfied with care, expressed greater trust, and had a stronger intention to adhere to recommendations.

## ■ COMMENTARY

This study is another example of the fact that while we may not have become an entirely racially liberated society, cultural competence plays a great role in the educational training of a physician. A physicians' communication style and perceptions do affect patient outcomes. A patient-physician relationship must build itself on the basic concept of partnership: mutual respect, support, trust, and proper dissemination of information. Data suggest that patients are able to perceive when

they are respected by their physicians and are willing to give the benefit of doubt to their physicians.<sup>6</sup>

As a primary care physician, I take pride in the fact that I begin any such relationship by finding common ground rather than attempting to ram my personal philosophy through each patient. I treat each patient individually, looking for a different similarity for each person I come in contact with and duly note such in my progress notes for review on subsequent visits. This builds a life-long relationship with an individual who understands that I value his/her input into our conversation and provides abundant opportunity for us to come to a mutual informed decision on any issue. Often, this is all it takes to make our patients happy and content, resulting in improved outcomes and adherence to recommendations.

It is interesting that data have also shown that physicians who reported a patient-centered orientation to the doctor-patient relationship were also more patient-centered in their communication.<sup>7</sup> In other words, it is basically a matter of setting your mind to it. While some may feel that current and past data could be justified to demand training more physicians from a certain ethnic group to “pair up” with patients of a similar ethnic group, what is imperative is that we emphasize the cultural competency and communication skills components of developing physicians. ❖

## CME Questions

**36. The clearest evidence of effectiveness in relieving symptoms of knee osteoarthritis is available for:**

- glucosamine sulfate.
- glucosamine hydrochloride.
- glucosamine sulfate plus chondroitin sulfate.
- chondroitin sulfate.

**37. Osteoarthritis is a degenerative disease involving primarily:**

- ligaments.
- weight-bearing bones.
- cartilage in joints.
- fingers.

**38. The formulation of glucosamine with the best evidence supporting its effectiveness with osteoarthritis is:**

- capsules available as dietary supplements.
- sachets available to dissolve in water.
- an ointment for topical use.
- that available in the diet from shellfish.

Answers: 36. a, 37. c, 38. b.

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## CME Objectives

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

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

## CME Instructions

Physicians participate in this continuing medical 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. Upon receipt of your evaluation, a certificate will be mailed.

### NCCAM Adds Four New Research Centers

The National Institutes of Health's National Center for Complementary and Alternative Medicine (NCCAM) has added four new Centers of Excellence for Research on Complementary and Alternative Medicine (CERCs) to its research centers program.

The new centers and their projects are as follows:

• **Wisconsin Center for the Neuroscience and Psychophysiology of Meditation**; Principal Investigator: Richard J. Davidson, PhD; University of Wisconsin, Madison.

Davidson's team will examine the impact of two forms of meditation—loving-kindness/compassion meditation and mindfulness meditation—on the brain and body, focusing on the regulation of emotion and on emotional reactivity. Potential applications in health include biological and behavioral processes linked with emotions and/or stress, such as recurrent depression.

• **Metabolic and Immunologic Effects of Meditation**; Principal Investigator: Frederick M. Hecht, MD; University of California, San Francisco.

Hecht and his colleagues will study a program combining mindfulness meditation, mindful eating, and a diet and exercise program for use in obesity and metabolic syndrome. They will test whether this program helps alter participants' hormonal responses to stress and helps enhance and maintain weight loss.

• **CAM as Countermeasures Against Infectious and Inflammatory Disease**; Principal Investigator: Mark A. Jutila, PhD; Montana State University, Bozeman.

This center will study biologically based CAM therapies and their effects on immune system function in infectious and inflammatory diseases. One project focuses on effects of botanical extracts—from apple polyphenols, which are concentrated in apple skins, and from yamoa, which comes from the bark of an African gum tree—on white blood cells, using models of infection and inflammation of the intestinal mucosa. A second project examines two compounds in licorice root—glycyrrhizin and 18-glycyrrhetic acid—for their poten-

tial antiviral effects in models of influenza and stomach virus. A third project will focus on bacterial products to see how they treat autoimmune diseases, like arthritis, which may also help build understanding of probiotics' action.

• **Center for Herbal Research on Colorectal Cancer**; Principal Investigator: Chun-Su Yuan, MD, PhD; University of Chicago, Illinois.

Yuan and his colleagues will examine the antitumor effects of different preparations of the herbs American ginseng (*Panax quinquefolius*) and notoginseng (*Panax notoginseng*). They will seek to learn more, through laboratory and animal studies, about how these herbs act upon cellular and molecular pathways of the mechanisms of cancer inhibition.

The grants provide five years of support and bring the total number of CERCs to 11. To learn more about NCCAM's research centers, go to [www.nccam.nih.gov/training/centers/](http://www.nccam.nih.gov/training/centers/). ❖

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### In Future Issues:

**Omega-3 Fatty Acids and Preterm Delivery**

**Health Benefits of Stress Reduction**

**Vitamin D and Bone Health**

# ALTERNATIVE THERAPIES IN WOMEN'S HEALTH

*Science-based Information for Clinicians*

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January 2008–December 2008

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