

## **Breast Cancer Adjuvant Therapy May Trigger Joint Pain**

**BOSTON, Sept. 2-**The coming wave of agents for adjuvant breast cancer therapy can be a pain in the neck -- or knee, or elbow, or other joint -- to the women who take them, researchers suggest.

Aromatase inhibitors -- and potentially any drug that lowers estrogen levels -- can cause joint pain in a "small but significant proportion of women," contend David Felson, M.D., of Boston University Medical School and Steven Cummings, M.D., of the University of California at San Francisco.

The researchers, writing in the September issue of *Arthritis & Rheumatism*, linked historical case series of so-called "menopausal arthritis" with symptoms reported in major drug trials. They also pointed to reports of joint pain as the major symptom of menopause among Asian women.

The aromatase inhibitors -- such as Femara (letrozole), Arimidex (anastrozole), and Aromasin (exemestane) -- work by blocking the conversion of androgen precursors into estrogen, which lowers plasma estradiol and estrogen levels in peripheral tissues.

The joint pain effect "has not been widely appreciated," they said, adding that the symptoms are transient and disappear when the drugs are stopped or estrogen therapy is started.

"Estrogen's effects on inflammation within the joint are not well known," Dr. Felson and Dr. Cummings wrote, adding that it has no specific effects on joints that would cause pain.

On the other hand, estrogen is known to affect inflammatory cytokines -- a role that might lead to increased sensitivity to pain when estrogen is depleted, either naturally at menopause or because of the effects of drugs.

The authors noted that when estrogen levels are naturally high -- during pregnancy, for example -- women tend to have higher pain thresholds.

In clinical trials, the authors noted, women treated with aromatase inhibitors "have consistently shown higher rates" of joint pain than have women not given the drugs.

For example, the ATAC trial, which tested Arimidex against tamoxifen, showed that 27.8% of women getting the aromatase inhibitor had joint pain, compared with 21.3% of those treated with tamoxifen.

Similarly, in the National Cancer Institute of Canada Clinical Trials Group MA17 trial -- in which 5,187 postmenopausal women were given either Femara or placebo -- 21.3% of those taking Femara reported joint pain, compared with 16.6% of those on placebo.

A similar effect has been seen with other estrogen-lowering drugs.

Lupron (leuprolide), a gonadotropin-releasing hormone agonist used to treat infertility and a variety of gynecological disorders, blocks estrogen production. In a 1993 study of 102 pre-menopausal women, subjects began to suffer joint pain between three and seven weeks of starting treatment.

Overall, one in four of the women developed persistent joint pain. Stopping the drug resolved the pain, Drs. Felson and Cummings said.

Also, the most common forms of arthritis are most prevalent in post-menopausal women, suggesting that estrogen may play a role in those conditions as well, the authors said, although "the contribution of estrogen deficiency to this high rate of arthritis is unknown."

### **Action Points**

Caution patients that all powerful drugs have some side effects; one such appears to be joint pain in a small but significant proportion of women taking aromatase inhibitors. Recognize that the symptoms are usually transient and resolve with estrogen therapy or when these agents are discontinued.

Note that, according to this study, a similar effect might be seen in any case where estrogen is depleted, either naturally or because of drug therapy.