

# Bisphosphonate Use Linked to Atypical Fractures

BY ELIZABETH MEHCATIE

FROM THE JOURNAL OF BONE AND MINERAL RESEARCH

Long-term treatment with bisphosphonates may be related to an increased risk of atypical femur fractures in patients, who may experience weeks or even months of pain before fracture diagnosis, according to the final report issued by a task force convened by the American Society of Bone and Mineral Research.

The society created the international, multidisciplinary task force to address reports of “atypical fractures of the subtrochanteric region of the hip and the femoral shaft” in patients on long-term bisphosphonate therapy. A statement issued by the society announcing the release of the report referred to it as “the most comprehensive scientific report to date” on this issue. The task force based its report on findings from a review of published and unpublished data, interviews with scientists at companies that manufacture these drugs,

and Food and Drug Administration data.

The review included an analysis of 310 published case reports of patients (aged 36-92 years) with atypical subtrochanteric and femoral shaft fractures. Of these patients, 291 (94%) had been treated with bisphosphonates, mostly for osteoporosis. The median duration of treatment was 7 years, and most were treated for more than 5 years, according to the report, which points out that these fractures are rare, accounting for less than 1% of the overall rate of hip and femur fractures (J. Bone Miner. Res. 2010 Sept. 14 [doi:10.1002/jbmr.253]).

More than half of the patients with such femur fractures had experienced a prodrome of pain in the groin or thigh for weeks or months, and fractures were bilateral in more than 25% of the patients.

“We are concerned that there may be a relationship between these fractures and long-term bisphosphonate use and, although the risk is low, we want to make sure that people know about the warning signs,” the task force

cochair and lead author of the report, Dr. Elizabeth Shane, said in the ASBMR statement. “Health professionals should know the warning signs of atypical femur fractures, and regularly ask patients on these drugs about groin or thigh pain,” added Dr. Shane, professor of medicine at Columbia University in New York.

She also recommended that every year, clinicians evaluate whether bisphosphonate therapy is appropriate for patients on these drugs, and that the drugs “be reserved” for patients with Paget’s disease, patients with osteoporosis who are at high risk of fractures, and patients with certain cancers, she added.

In the statement, Dr. Shane said that for the “vast majority of patients with osteoporosis, these drugs are an important weapon against fractures and their benefits far outweigh the risks.”

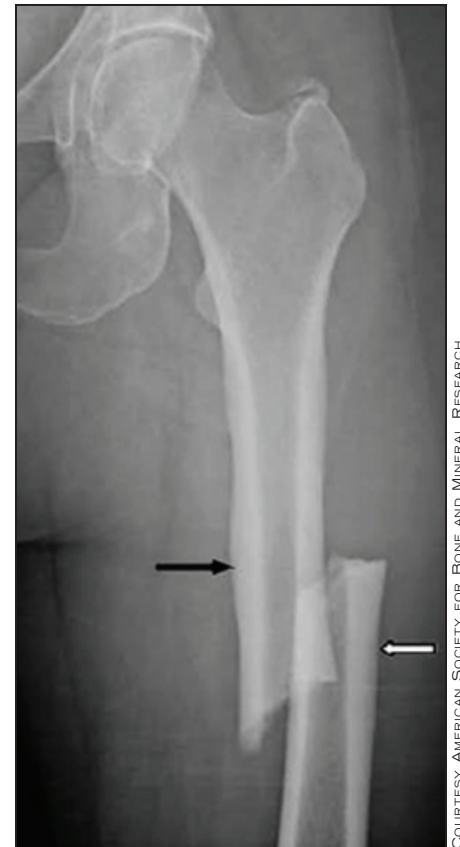
The ASBMR task force recommendations include establishing an international registry of patients with these fractures, increasing research to determine whether bis-

phosphonates are the cause, and improving the labeling of these products so that health care professionals and patients are more aware of the potential for these fractures and the associated symptoms.

A statement issued by the FDA said the agency “recommends that health care professionals be aware of the possible risk of unusual femur fractures in patients taking bisphosphonates. Patients should talk to their health care professional if they develop new thigh or groin pain so that they may be evaluated to rule out a femur fracture.”

Dr. Shane and other members of the task force disclosed relationships with manufacturers of bisphosphonates. ■

The task force report is available at [www.jbmr.org/details/journalArticle/843323/Atypical\\_subtrochanteric\\_and\\_diaphyseal\\_femoral\\_fractures\\_Report\\_of\\_a\\_task\\_force.html](http://www.jbmr.org/details/journalArticle/843323/Atypical_subtrochanteric_and_diaphyseal_femoral_fractures_Report_of_a_task_force.html). Serious adverse events associated with bisphosphonates should be reported to the FDA’s MedWatch program at 800-332-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).



This anterior-posterior radiograph of the left femur demonstrates a substantially transverse femoral fracture and associated diffuse periosteal new bone formation (black arrow) and focal cortical thickening (white arrow), consistent with atypical femoral shaft fracture.

## Oral Bisphosphonates Not Tied to Esophageal, Gastric Cancer

BY MARY ANN MOON

FROM JAMA

The use of oral bisphosphonates was not associated with esophageal or gastric cancer in a large cohort study in the United Kingdom, according to a large U.K. database analysis.

Oral bisphosphonates cause serious esophagitis in some users. Reflux esophagitis is a known risk factor for esophageal cancer, but it is not known whether bisphosphonate-associated esophagitis also predisposes patients to develop gastric cancer, said Chris R. Cardwell, Ph.D., of Queen’s University Belfast (Ireland) and his associates.

“The U.S. Food and Drug Administration recently reported 23 cases of esophageal cancer (between 1995 and 2008) in patients using the bisphosphonate alendronate and a further 31 cases in patients using bisphosphonates in Europe and Japan, possibly indicating risk of malignancy,” they noted.

Dr. Cardwell and his colleagues searched for a possible link between the drugs and esophageal or gastric cancer using the General Practice Research

Database (GPRD), “the world’s largest computerized database of anonymized longitudinal patient records,” which includes 500 general practices and covers about 6% of the population in the United Kingdom.

They reviewed the records of 41,826 patients aged 40 years and older who used bisphosphonates and the same number of control patients matched for age, sex, and medical practice. During a mean follow-up of 4.5 years, 287 of these patients developed esophageal or gastric cancer.

There were no significant differences between cases and controls in risk for esophageal cancer, gastric cancer, or both cancers combined. This result did not change when the data were adjusted to account for possible confounders of gastric cancer risk, such as smoking, alcohol use, and use of drugs including NSAIDs, proton pump inhibitors, and H<sub>2</sub> receptor antagonists.

Moreover, the risk of these cancers was no higher in patients who took larger daily doses of bisphosphonates or in those who had a longer duration of bisphosphonate use, the investiga-

tors said (JAMA 2010;304:657-63).

In addition, the risk of gastric cancer was not significantly different between men and women exposed to bisphosphonates, and it did not differ across several different bisphosphonate medications.

There also was no association between cancer risk and bisphosphonate use in the subgroup of patients who had a history of gastroesophageal reflux disease.

“In conclusion ... we found no evi-

dence for a substantially increased risk of esophageal (or gastric) cancer in persons using oral bisphosphonates.

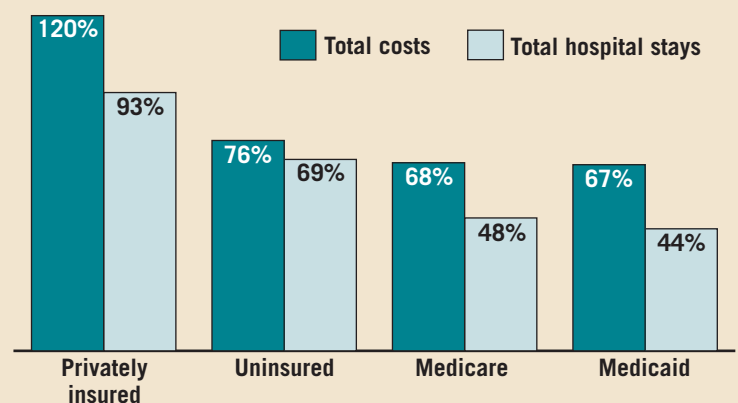
“These drugs should not be withheld, on the basis of possible esophageal cancer risk, from patients with a genuine clinical indication for their use,” they said.

Access to the GPRD database was funded by the Medical Research Council. No financial conflicts of interest were reported. ■

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### DATA WATCH

#### Inpatient Cost Increases for Osteoarthritis Were Highest For Privately Insured Stays, 2001-2007



Source: Agency for Healthcare Research and Quality, Nationwide Inpatient Sample