

Kaiser Permanente  
**Research**

# Drug holidays don't increase fracture risk

A look at possible harms, benefits of bisphosphonate "time-out"



# Impact»»

This Kaiser Permanente Southern California study found that women who take a “holiday” for at least 12 months after at least 3 years of bisphosphonate use are not at greater risk of osteoporosis-related fragility fracture than women who continue to use the drugs without interruption. The findings suggest that a drug holiday is a viable option for managing the potential benefits and harms associated with long-term bisphosphonate use.

This study helped inform KPSC’s updated clinical practice guidelines for osteoporosis and fracture prevention. “I see more and more physicians recommending a bisphosphonate drug holiday as a result of this study,” said orthopedist Gaurav Khanna, MD, vice area research chair, from our Baldwin Park Medical Center. “It certainly has affected how these drugs are prescribed.”

**B**isphosphonates are commonly prescribed to slow bone loss due to osteoporosis. In 2010, however, the Food and Drug Administration warned patients that the drugs might actually increase the risk of atypical thigh bone fractures. This warning added to a growing body of evidence that long-term bisphosphonate use may increase rare but serious health risks.

“Physician chiefs and other clinical leaders throughout Kaiser Permanente identified bisphosphonate safety as an important question to address,” said Elizabeth A. McGlynn, PhD, director of the Kaiser Permanente Center for Effectiveness & Safety Research.

## Balancing safety with impact

Clinicians wanted to know how to best balance the protective benefits of the drug versus the risks of prolonged use. What if they advised patients to stop taking the drug for a period of time? Would a “drug holiday” bring back the risk of osteoporotic fractures?

“This is an important clinical question because bisphosphonates are among the most commonly used treatments for osteoporosis management, but have been associated with some adverse events that are of concern,” said Annette L. Adams, PhD, MPH, research scientist for Kaiser Permanente Southern California and the study’s principal investigator.

“Our clinicians had been thinking about putting people on a drug holiday, but that only makes sense if it doesn’t increase their risk of the kinds of fractures that the drugs are supposed to prevent in the first place,” she said.



Dr. John Adams and Dr. Elizabeth McGlynn

*“The question was, if women stop taking these drugs, will they experience the fracture risk we’re trying to prevent?”*

— Elizabeth A. McGlynn, PhD

In 2013, Kaiser Permanente conducted a retrospective cohort study to compare the incidence of osteoporosis-related fragility fractures among women who took a bisphosphonate drug holiday for at least 12 months with that of the women who continued to use them without interruption.

This study was funded through internal operational funds provided by the Kaiser Permanente Center for Effectiveness & Safety Research.



Marguerite Koster and Dr. Annette Adams

*“This is an example of how Kaiser Permanente’s own internal research can really help inform patient care and clinical guideline recommendations.”*

— Marguerite Koster, MA, MFT

### Study benefits from diverse population

Researchers evaluated electronic medical record data from 4 Kaiser Permanente regions—Southern California, Colorado, Northwest, and Hawaii. The study included a racially and socioeconomically diverse group of 28,620 women ages 45 years and older who had used bisphosphonate medications for at least 3 years.

“This study demonstrates our ability to pull together a multi-region team of researchers and clinicians and to do a large scale study that would be really difficult to do in other settings,” said Dr. Adams.

## Findings provide valuable insight

The findings showed no apparent difference between the women who stopped taking the medications and those who did not. The bottom line? “Low-risk” patients—those who had no history of hip, vertebral, or fragility fracture—could discontinue bisphosphonate use for at least 12 months without an increase in fracture risk.

“Our findings show that taking a holiday from bisphosphonates may be a very reasonable choice for many women, particularly those at the lower end of the risk scale,” said Dr. Adams. “But it always boils down to a conversation between a patient and the clinician and taking into account individual risk factors and concerns.”

Dr. Adams and her team presented the study at the American Society for Bone and Mineral Research 2014 annual meeting, where she was recognized with the 2014 Most Outstanding Clinical Abstract Award.

“There was considerable interest in that presentation because people are grappling with the question about the long-term risk of treatment with these drugs,” said Marguerite Koster, MA, MFT, senior manager for Evidence-Based Medicine Services for the Southern California Permanente Medical Group. “This was really a groundbreaking study that filled an important gap in the literature.”

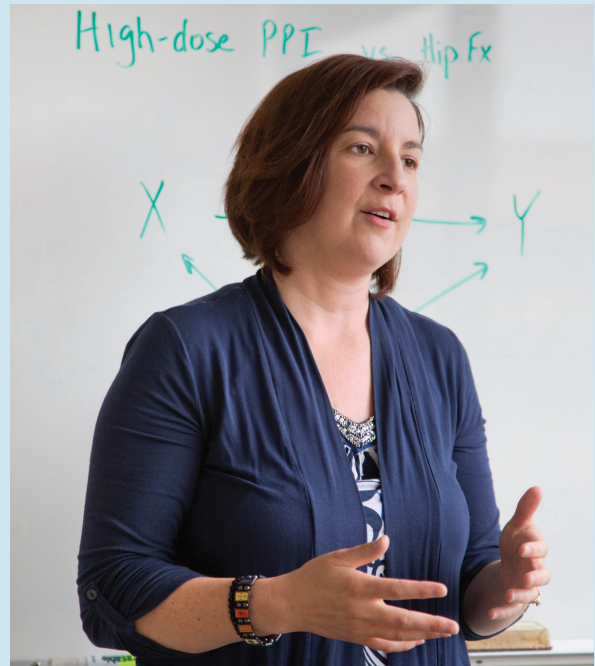
## Putting findings into practice

The study helped inform changes to the region’s clinical practice guidelines. “This study was key in helping us develop our recommendations around whether patients should go on a drug holiday or not,” said Koster. “This is an example of how Kaiser Permanente’s own internal research can really help inform patient care and clinical guideline recommendations not only within Kaiser Permanente, but can also help other organizations make decisions about what is the best course of treatment.”

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Dr. Mary Helen Black

## New study investigates PPI use and hip fractures

Proton pump inhibitors are among the most commonly prescribed drugs in the world for ulcers and gastroesophageal reflux disease. But do PPIs cause hip fractures, especially in the elderly, who often take high doses? And is the relationship between PPIs and hip fractures modified by variation in the *CYP2C19* gene involved in drug metabolism?

Although numerous observational studies associate PPI use with hip fractures, no one has yet established a causal relationship. That’s the goal of a U.S. Food and Drug Administration–funded study at Kaiser Permanente that may well determine the definitive guidelines for high-dose PPI use.

The feasibility study was completed in October 2013. The full study is now underway and will run until April 2017 at Kaiser Permanente Southern California, Northwest, and Hawaii. The Oregon Health & Science University will analyze samples from the participants for the pharmacogenetics study.

“Investigating a possible causal relationship requires sophisticated statistical methods,” said Mary Helen Black, PhD, MS, one of the study’s principal investigators. “In addition, the genetic component of this study is incredibly novel. The idea that it has the potential to help facilitate the implementation of precision medicine in this area is very exciting.”

Dr. Black and Dr. Annette L. Adams are the joint principal investigators for this study.