Bone-loss medications show less benefit, more risks over time

Approximately 10 million Americans have been diagnosed with osteoporosis, a condition that causes bones to lose mass and become more fragile over time resulting in fractures and injuries that can be serious. An additional 34 million are at risk for the disease, and health care leaders recommend both groups follow specific plans to help prevent its development and progression.

New research indicates long-term use may have little benefit to the patient and may actually increase the risk of developing serious adverse effects.

Managing osteoporosis includes supplementation, exercise and the use of a class of medications known as bisphosphonates. More than 150 million prescriptions for bisphosphonates were dispensed between 2005 and 2009 and an estimated one in seven postmenopausal women have used the drugs, which are marketed to strengthen existing bone and help prevent fractures from osteoporosis. While their use has shown significant benefit in the short term, new research indicates long-term use may have little benefit to the patient and may actually increase the risk of developing serious adverse effects that include femur fractures; cancer of the esophagus; and osteonecrosis of the jaw bone, a painful breakdown and crumbling of the jaw.

Used for years, bisphosphonates now show their long-term risks

Prior to the introduction of bisphosphonates to the market more than a decade ago, osteoporosis was challenging to treat and considered an inevitable part of aging. These drugs, sold under the trade names Fosamax, Reclast, Actonel and others, have proven to be highly beneficial in the prevention of fractures for the first three to five years of use.

During treatment, the drugs incorporate themselves into the bone, where they can remain as strengthening agents for years even as the body continues to break down and create new bone. When they came to the market, these medications offered clinicians alternatives to treatments like estrogen supplementation that had been used in the past with varying degrees of success.

Patients who take bisphosphonates for only a short time can still benefit from their use years after treatment has stopped, but reports to the Food and Drug Administration (FDA) of serious adverse events has prompted several research studies to evaluate the drugs’ use over time. Results of those studies are significant.

The FDA was interested in how bisphosphonates would help or hinder bone stability for patients who took the drugs for 10 years or more. In a trio of studies conducted by several companies that manufacture the drugs, one group of patients received a real drug while the other group was given a placebo medication. Both groups were then monitored for adverse events over time.

Regardless of what brand of medication was tested, the results were similar. Analysis of vertebral fracture rates in patients who took the bisphosphonates showed a fracture rate of 17.7 percent, compared to those who took a placebo at 16.9 percent. Fracture rates were consistent among all groups that took the medications for eight to 10 uninterrupted years.
Bone-loss medications show less benefit, more risks over time
(continued from front)

Current data indicates some patients may be able to discontinue use of these drugs after about five years without a significant impact on existing bone health, but researchers admit there is more to learn before a final decision can be made.

Patients at low risk for development of osteoporosis, meaning those who have no fracture history and near-normal bone density, may be good candidates for cessation at the three- to five-year mark, but higher-risk patients may need to continue their use for longer periods of time.

For patients with a lower risk for the development of osteoporotic fractures who choose to stop the medication, there are no current guidelines to assist physicians in deciding when to restart the medications or even whether the drugs will ever be needed again. To reduce the risk of osteoporosis, it is necessary for physicians to assess each patient’s individual risk factors and personal preference before deciding to discontinue their use of bisphosphonates.

The FDA is continuing to study the use of bone mineral density testing, bone turnover markers and other clinical data before making any recommendations for future practice guidelines.

(continued from front)

create new bone in its place. A negative balance in this remodeling process results in osteoporosis. The result is fragile bones that lose structure and strength, making the body more susceptible to fracture and injury with even simple activity.

Because of the important role of estrogen in bone balance, many women develop osteoporosis after menopause, when natural estrogen levels have declined. The loss of estrogen leads to an increase in osteoclast activity and an imbalance of bone resorption and formation.

Bisphosphonates are designed to treat this mechanism of osteoporosis.

How drugs used to treat bone loss work
Bisphosphonates are widely used for the treatment of osteoporosis and despite current concerns, these medications have few side effects. However, in order to understand the complications of long-term use, it is important to understand the mechanism of action. Bisphosphonates target osteoclasts, diminishing their number and effectiveness and slowing bone resorption or breakdown. In turn, the remodeling process slows and osteoporosis improves.

Studies have shown these drugs to be most effective in the first three to five years of use, but the duration of treatment should be individualized for each patient. The risks of long-term use of bisphosphonates are directly related to the ability to bind to hydroxyapatite crystals in the bone and remain in the bone for a long period, often years.

Accumulation of these medications can lead to oversuppression of bone turnover, low bone remodeling and altered bone quality. It is important to remember that the risk of accumulation increases significantly in the presence of reduced kidney function because bisphosphonates depend solely on the kidney to be broken down and processed.

Use of bisphosphonates is common in the elderly population, a group with a high prevalence of chronic kidney disease. Therefore, it is important to recognize which patients are at increased risk of complications from these medications and frequently assess the need for continuation of osteoporotic therapy. Managing risk factors for osteoporosis is important and recommended in conjunction with bisphosphonate therapy for maximum clinical benefit.

Women most at risk for osteoporosis include those:

- With a small, thin frame
- Who are postmenopausal
- Of Caucasian or Asian ethnicity
- Over age 30
- With a family history of the disease

Providers show more caution with use
The challenge is now in the hands of researchers and clinicians to sort out how long these medications should be used. Primary care physicians and specialists are becoming ever mindful about the length of time medications are used and are working with patients to evaluate individual risk versus benefit.

There is no specific length of time to recommend using bisphosphonates. Because evidence shows most benefit is obtained in the first three to five years, the general feeling is to consider a drug holiday, or period without the use of these medications, once the five-year limit has been met.

The case becomes more challenging when osteoporosis persists, worsens or if the patient has a recent fracture. In these scenarios, a specialist may be required to review the treatment options.

Patients should talk with their physician about choosing the right therapy for their skeletal health. There are many important components in the prevention of bone loss and medications such as bisphosphonates are only part of the plan. Weight-bearing activity, maintaining vision and hearing, taking appropriate amounts of calcium and vitamin D supplements, and reviewing safety measures are all important aspects in the care of skeletal health.

Dr. Webb is board-certified in internal medicine and specializes in bone and mineral metabolism, as well as nephrology. He is an assistant professor of medicine in the UK College of Medicine.