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When do bisphosphonates make the most sense?

A Cochrane Musculoskeletal Group review

Should you prescribe bisphosphonates for postmenopausal patients for primary as well as secondary prevention of osteoporotic fractures? Here's what the evidence tells us.

An estimated 10 million US residents, most of them women over the age of 50, suffer from osteoporosis, and another 33 million have low bone mass.¹ Together, they incur more than 2 million osteoporotic fractures annually.^{1,2} In addition to the high cost of a single osteoporotic fracture in terms of morbidity, mortality, and health care spending, individuals who sustain one such fracture are at high risk for another. That risk can be greatly reduced with appropriate treatment.

Bisphosphonates, which act on osteoclasts to inhibit bone resorption, are first-line therapy for prevention of osteoporotic fractures. Four bisphosphonates—alendronate, ibandronate, risedronate, and zoledronic acid—are approved by the US Food and Drug

Administration (FDA) for the treatment of postmenopausal osteoporosis.

While menopause itself increases a woman's risk for osteoporotic fracture, questions remain about when to initiate preventive therapy, which patients are candidates for bisphosphonates, and whether bisphosphonates are effective for primary as well as secondary prevention. This overview from the Cochrane Musculoskeletal Group (CMSG) addresses those questions.

To help you provide optimal treatment for postmenopausal patients, we present the findings of recently conducted systematic reviews of 2 bisphosphonates—alendronate and risedronate—from the *Cochrane Database of Systematic Reviews*,^{3,4} in context with the available evidence on the efficacy of iban-

How this series can help you

This is the second in a series of articles based on the findings of the Cochrane Musculoskeletal Group (CMSG), one of the largest review groups in the Cochrane Collaboration. The CMSG synthesizes the results of high-quality clinical trials to determine whether interventions for the prevention, treatment, and rehabilitation of musculoskeletal disorders are safe and effective. In this article and those that follow, CMSG's aim is to bring its findings to the attention of family physicians in a context that is relevant to clinical practice.



The benefits of bisphosphonate therapy in preventing fractures are greatest in women with a high underlying fracture risk.

dronate and zoledronic acid. Cochrane reviews of ibandronate and zoledronic acid are underway, but not yet completed.^{5,6}

Alendronate reduces vertebral fracture risk across the board

Wells et al identified 11 RCTs for the alendronate review (3 primary and 8 secondary prevention trials), representing a total of 12,068 women.³ (For definitions of what constituted a primary vs a secondary prevention trial, see the box on page 20.)

Doses of alendronate ranged from 1 to 20 mg daily, with most studies using doses of 5 or 10 mg. Treatment duration ranged from 1 to 4 years.

A look at the relative risk (RR) for primary and secondary prevention at different fracture sites (TABLE 1) highlights similarities and differences. The risk reduction for vertebral fractures was statistically significant—and about the same—for women being treated with alendronate for primary and secondary prevention (RR=0.55; 95% confidence inter-

val [CI], 0.38-0.80; RR=0.55; 95% CI, 0.43-0.69, respectively). For all other (nonvertebral) fractures in patients being treated with alendronate, only the outcomes for secondary prevention were statistically significant.

Risedronate is effective only for secondary prevention

Seven RCTs, including 2 primary and 5 secondary prevention trials, were included in the Cochrane review of risedronate, representing a total of 14,049 women.⁴ Doses ranged from 2.5 to 5 mg daily, but also included cyclical dosing—for example, taking 5 mg/d for the first 2 weeks of every month. Treatment duration ranged from 2 to 3 years.

At doses of 5 mg/d, there were no statistically significant decreases in fracture risk at any site in the primary prevention trials (TABLE 1), although the quality of evidence assessed was low. For secondary prevention, however, the risk reduction for vertebral fracture was significant (RR=0.61; 95% CI,

IMAGE © KO STUDIOS

> There is little evidence to support the use of bisphosphonates for primary prevention, with the exception of alendronate.

Primary vs secondary trials: A look at the definitions

The Cochrane reviewers studied the effects of alendronate and risedronate^{3,4} for both primary and secondary prevention of osteoporotic fractures in postmenopausal women, using the following definitions (with slight variations in definitions between trials):

Primary prevention. Randomized controlled trials were classified as primary prevention trials if the participants had baseline T-scores >-2.0 or a baseline prevalence of vertebral fracture $<20\%$.

Secondary prevention. Studies were classified as secondary prevention trials if the women had baseline T-scores ≤ -2.0 (ie, bone mineral density [BMD] ≥ 2 standard deviations below peak bone mass) or previous vertebral compression fractures. (In the ibandronate individual patient meta-analysis,¹⁴ secondary prevention was defined as lumbar spine T-score <-2.5 or baseline vertebral fracture prevalence $>20\%$ or mean age of participants >60 years.)

Age-based criterion. When data on T-scores and/or vertebral compression fractures were unavailable, age was the determinant: Trials were considered secondary prevention if the average age of the participants was >62 years, and primary prevention if the average age was ≤ 62 .

0.50-0.76), as were the reductions in risk for nonvertebral and hip fractures.

What are the absolute benefits?

A look at number needed to treat

In addition to looking at the RR, the authors of both the alendronate and risedronate reviews calculated the number needed to treat (NNT) to prevent one fracture (TABLE 2) in the trial participants;^{3,4} they focused on the secondary prevention outcomes, as these were statistically significant. The reviewers also estimated what the NNT would be if the risk reductions achieved with alendronate and risedronate in the reviews occurred when treating community-based samples of women at moderate compared with high fracture risk.

The biggest differences involved hip fracture: For alendronate, if a community-based sample of women at moderate risk of fracture were treated with the drug and the reduction in RR seen in the secondary prevention trials applied, the NNT would be 100. Thus, for every 100 women treated for 5 years with alendronate, 1 hip fracture would be prevented. However, if this same RR reduction were applied to women at high risk of fracture, the NNT would be only 22.³ For risedronate, the estimated NNT to prevent one hip fracture in women at moderate risk was 203, compared with only 45 for women at high risk.⁴ These estimates indicate that the ben-

efits of bisphosphonate therapy in preventing fractures are greatest in women with a high underlying fracture risk.

Adverse effects do not increase with longer-term treatment

In both the alendronate and risedronate reviews, adverse effects and the risk of discontinuing treatment due to adverse events were similar in the intervention and control groups.^{3,4} Postmarketing data suggest that there is potential for upper gastrointestinal (GI) problems, however;⁷ osteonecrosis of the jaw has also been reported infrequently.^{8,9} More recently, there have been reports of a possible link between bisphosphonates and atypical femoral fractures, which we'll say more about in a bit.

Some potential adverse events—eg, osteonecrosis of the jaw and atypical femoral fractures—may be related to treatment duration. The maximum duration of the trials included in these meta-analyses was 4 years for alendronate and 3 years for risedronate. However, additional published data do not appear to support a relation between adverse events and treatment duration.

■ For alendronate, researchers extended the Fracture Incidence Trial (FIT) for a 10-year follow-up,^{10,11} comparing women who took the drug for the first 5 years with

TABLE 1

Fracture risk reduction: How the bisphosphonates compare*

Study	Vertebral fracture RR (95% CI)	Nonvertebral fracture (hip, wrist, others) RR (95% CI)	Hip fracture RR (95% CI)	Wrist fracture RR (95% CI)
Primary prevention				
Alendronate ³	0.55 (0.38-0.80)	0.89 (0.76-1.04)	0.79 (0.44-1.44)	1.19 (0.87-1.62)
Risedronate ⁴	0.97 (0.42-2.25)	0.81 (0.25-2.58)	N/A	N/A
Secondary prevention				
Alendronate ³	0.55 (0.43-0.69)	0.77 (0.64-0.92)	0.47 (0.26-0.85)	0.50 (0.34-0.73)
Risedronate ⁴	0.61 (0.50-0.76)	0.80 (0.72-0.90)	0.74 (0.59-0.94)	0.67 (0.42-1.07) [†]
Ibandronate ^{15,16} Oral daily Oral intermittent	0.62 (0.42-0.75) 0.50 (0.26-0.66)	No effect [‡] No effect	N/A N/A	N/A N/A
Zoledronic acid ²²	0.30 (0.2-0.38)	0.75[§] (N/A)	0.59[¶] (0.42-0.83)	N/A

CI, confidence interval; N/A, not available; RR, relative risk.

*Bold type indicates statistical significance ($P < .05$).

[†] $P = .10$.

[‡]RR of nonvertebral fracture was 0.69 ($P = .013$) for daily oral ibandronate in the subgroup with femoral neck BMD T-score < -3.0 .

[§] $P < .001$.

[¶]Hazard ratio.

women who took it for 10 years. Adverse effects were similar in both groups.

■ **For risedronate, researchers followed a small subsample (n=164) of the participants in the Vertical Efficacy with Risedronate Therapy (VERT) Study Group for up to 7 years.**^{12,13} For the first 5 years, half of the participants took 5 mg/d risedronate, while the other half took a placebo. During the final 2 years, all participants received 5 mg/d risedronate. The incidence of adverse events among those who took the drug for 7 years was similar to that reported in the first 3 years of the original trial.¹³

■ **Ibandronate studies focus on dose Nonvertebral fracture.** The Cochrane systematic review examining ibandronate for postmenopausal osteoporosis is not yet completed.⁵ However, Cranney et al performed a pooled analysis of individual patient data

from 8 RCTs to examine the efficacy of different doses of the drug for the secondary prevention of nonvertebral fracture.¹⁴ (No studies of the drug for primary prevention have been done.) After 2 years of treatment at higher doses of ibandronate (annual cumulative exposure ≥ 10.8 mg, equivalent to 150 mg orally/month, 3 mg IV quarterly, or 2 mg IV every 2 months), the hazard ratio was 0.62 (95% CI, 0.396-0.974), compared with those taking lower doses (annual cumulative exposure of 5.5 mg). The individual results of the 2 largest trials did not demonstrate an effect on nonvertebral fracture, except in the subgroup of women with very low femoral neck bone mineral density (BMD) (T-scores < -3.0).¹⁵⁻¹⁷

■ **Vertebral fracture.** There is no meta-analysis available with vertebral fracture outcomes for ibandronate, so we present the results of individual secondary prevention trials.

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➤ The inability to remain upright for at least 30 minutes is an absolute contraindication for oral bisphosphonates.

TABLE 2

**NNT analysis:
Women at higher risk are most likely to benefit^{3,4}**

	NNT		
	Observed in secondary prevention trials in reviews	Estimated for community-based sample of women with	
		High fracture risk*	Moderate fracture risk*
Alendronate (10 mg/d)			
Vertebral fracture	19	20	42
Nonvertebral fracture	47	16	27
Hip fracture	146	22	100
Wrist fracture	69	N/A	N/A
Risedronate (5 mg/d)			
Vertebral fracture	19	23	49
Nonvertebral fracture	49	19	31
Hip fracture	138	45	203
Wrist fracture	N/A	N/A	N/A

N/A, not available; NNT, number needed to treat.

*NNT calculated by applying the relative risk reduction observed in the reviews to published estimates of 5-year fracture risk in a community-based sample of women >50 years of age at moderate and high risk.

> A possible link between bisphosphonates and atypical femoral fracture prompted the FDA to require a black box warning.

One was a double-blind RCT with 2496 participants, comparing women taking either 2.5 mg/d of ibandronate or 20 mg on alternate days with a group on placebo.^{15,16} The results? Those in both the daily and the intermittent treatment arms had significant risk reductions (RR=0.62; 95% CI, 0.42-0.75; RR=0.50; 95% CI, 0.26-0.66, respectively), after taking the drug for 3 years (TABLE 1), compared with those on placebo.^{15,16} The other RCT—a trial in which 2862 women received either quarterly intravenous (IV) injections of 1 or 0.5 mg ibandronate or placebo—did not demonstrate a significant reduction in vertebral fracture.¹⁷ This was attributed to an insufficient dose of the drug, a supposition supported by improvements in BMD in patients receiving higher doses of ibandronate.^{18,19}

Oral ibandronate has been well tolerated in clinical trials in terms of GI side effects.^{20,21} Injection site reactions have been reported in those receiving IV infusions,¹⁷

and both IV and monthly oral ibandronate may be associated with mild, self-limiting flu-like symptoms.

Zoledronic acid RCTs show reduced fracture, mortality risk

Black et al studied the efficacy of zoledronic acid in a randomized, double-blind, placebo-controlled trial of 7736 postmenopausal women between the ages of 65 and 89 years.²² The women, all of whom had osteoporosis, received an IV infusion of either zoledronic acid (5 mg) or placebo at baseline, and again at 12 and 24 months. Vertebral and nonvertebral fractures, as well as hip fracture, were significantly reduced in the treatment group compared with placebo (TABLE 1).

In another RCT with 2127 participants, Lyles et al examined the effectiveness of 5 mg zoledronic acid IV given within 90 days of surgical repair of a hip fracture. In the intervention group, there was a 35% risk reduction in new clinical fractures (8.6% vs 13.9%

How would you treat these patients?

CASE 1 ▶ Mrs. A is an active 67-year-old in good health. On a recent hike, she lost her footing and sustained a Colles' fracture when she fell, although her fall was only from standing height. Now, you are concerned that she might have osteoporosis.

A dual-energy x-ray absorptiometry (DXA) scan confirms this suspicion: Mrs. A's lumbar spine T-score is -2.6 . A dietary review reveals that she has a satisfactory calcium intake, and lab work shows that her serum vitamin D levels are normal. Mrs. A wants to discuss treatment options with you.

What immediate treatment do you consider?

Mrs. A has no contraindications to any FDA-approved treatment for osteoporosis; you suggest she begin taking bisphosphonates, explaining that they are first-line treatment to prevent subsequent osteoporotic fractures. You briefly discuss other options, but note that raloxifene only reduces the risk of vertebral fractures and parathyroid hormone is effective (but very expensive) and requires daily injections, and is therefore generally used for severe osteoporosis. Your patient asks about bisphosphonates' side effects, particularly the serious jaw problems she's heard about.

You explain that for the most part, oral bisphosphonates are well tolerated, but that there is a potential for upper gastrointestinal (GI) problems—which is why it's important to remain upright for at least 30 minutes after taking the medication. You tell her that the risk of developing osteonecrosis of the jaw is very low when the medication is taken at the doses needed for osteoporosis treatment, but that the risk may increase after tooth extraction or dental surgery. Mrs. A has no current dental symptoms and at her usual yearly dental check-up 9 months ago, there were no problems noted, so dental review before starting treatment is not needed. Should she develop any jaw pain, however, she should see you or her dentist immediately.

You also advise her of the possible link between bisphosphonates and atypical femoral fracture, but point out that such fractures are extremely rare—and that the medication prevents far more fractures than it has the potential to cause. You tell her to contact you immediately if she develops pain in the groin or thigh or experiences GI distress.

Which bisphosphonate do you prescribe?

You inform Mrs. A that alendronate has the longest follow-up data of the oral bisphosphonates and has demonstrated efficacy for the secondary prevention of wrist fractures, that risedronate and ibandronate have the advantage of being able to be taken monthly rather than weekly, and that zoledronic acid can be administered in a yearly infusion. She opts for alendronate. You prescribe a weekly dose of 70 mg and ask her to return in 3 months, and to call before then if any problems arise.

CASE 2 ▶ Mrs. Y, age 82, recently sustained a fractured femoral neck, which was treated surgically at the local hospital. She was discharged with a prescription for alendronate to treat her osteoporosis and prevent further fractures; her husband has brought her in today to get a new prescription.

During the visit, he reminds you that Mrs. Y has problems with memory. He also says he's finding it increasingly difficult to ensure that his wife remains upright for 30 minutes after taking alendronate, and that she has begun complaining of indigestion.

What do you decide to do?

An inability to stay upright for 30 minutes after drug administration is a contraindication to the use of oral bisphosphonates. The presence of upper GI symptoms is also a concern. You offer Mrs. Y the option of a once-yearly IV infusion of zoledronic acid instead, and she and her husband agree to this. Before scheduling a follow-up visit, you discuss the patient's nutritional intake, and discover that she consumes only a moderate amount of calcium—at most 2 servings of dairy products per day. You also note that her serum vitamin D level was not checked in the hospital. You order lab work, with a view to correcting any deficiency before proceeding with a zoledronic infusion (due to the risk of tetany) and to maintaining her on an appropriate level of calcium and vitamin D intake, using supplements only if necessary.

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➤ Depending on the particular agent and the delivery route, bisphosphonates may be administered daily, monthly, quarterly, or annually.

for those on placebo; $P=.001$); mortality was also lower in the zoledronic acid group (9.6% vs 13.3%; $P=.01$).²³

In both trials, the number of patients who had serious adverse events or dropped out because of an adverse event was similar in the treatment and placebo groups. In both studies, too, a sizeable number of patients treated with zoledronic acid reported flu-like symptoms up to 3 days after receiving an infusion, particularly after the first one. Cardiovascular events were similar across intervention groups in both studies, with one exception: In Black's study,²² there was an increased incidence of serious atrial fibrillation in the zoledronic acid group (1.3% vs 0.5% for the placebo group).

Other issues to keep in mind

Atypical femoral fractures. Published data suggest an association between bisphosphonate use and atypical femoral fractures, particularly with longer-term use,²⁴ although whether there is a causal link is unclear. Atypical femoral fractures occur with little or no trauma along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare.

In 2010, the FDA announced requirements for a black box warning about a possible link,²⁵ highlighting the uncertainty about both the optimal duration of bisphosphonate therapy and the cause of these fractures.

While concerns about such a link remain, it is important to note that atypical femoral fractures are very uncommon: Current estimates are that they account for less than 1% of hip/femoral fractures. What's more, far more fractures are prevented by the use of bisphosphonates than are associated with their use, with an estimated ratio of up to 29:1.²⁴

Dosing schedules. Adherence to treatment is of key importance in maximizing outcomes from osteoporosis treatments, and is frequently low.^{26,27} One way of improving adherence is to reduce the frequency of dosing required.²⁷ With that in mind, researchers have tested intermittent dosing regimens, using noninferiority or bridging trials.

Such studies have led to a number of approved dosing regimens—70 mg week-

ly for alendronate; 150 mg monthly and 35 mg weekly for risedronate; and 150 mg PO monthly and 3 mg IV quarterly for ibandronate among them. In making decisions about dosing, family physicians should consider patient preferences, but be aware that there are no direct efficacy data from RCTs to support these dosing regimens.

Calcium and vitamin D. The major fracture prevention trials of bisphosphonates have featured women who are calcium- and vitamin D-replete. In a recent study of 1515 women undergoing treatment with alendronate, risedronate, or raloxifene, however, that wasn't always the case.²⁸ After 13 months, 115 participants suffered from a new clinical fracture. The adjusted odds ratio for fractures in women with vitamin D deficiency compared with those with normal levels of vitamin D was 1.77 (95% CI, 1.20-2.59; $P=.004$), an indication of the importance of maintaining adequate vitamin D levels in patients taking bisphosphonates.

In clinical practice, it is important to ensure that patients being treated with bisphosphonates are not deficient in vitamin D. While direct evidence of poorer outcomes associated with low calcium levels is lacking, it is reasonable to also assess calcium intake and to ensure that patients have adequate intake of both. (For more on calcium and vitamin D requirements, see the Institute of Medicine's recent report at <http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/Report-Brief.aspx>) and "The IOM's report on calcium and vitamin D: Should it change the way you practice?" on page 27.

What's best for your patients?

All these bisphosphonates have demonstrated efficacy for the secondary prevention of vertebral fracture. All except ibandronate have demonstrated efficacy for nonvertebral fracture, as well, and the evidence suggests that ibandronate will also be effective if adequate doses are given. Thus, for women at significant risk for fracture, it seems clear that the benefits of treatment outweigh the risks. The case is not so clearcut for women at lower risk. Evidence to support the use of bisphosphonates

The IOM's report on calcium and vitamin D: Should it change the way you practice?

"Dietary Reference Intakes for Calcium and Vitamin D," the consensus report released by the Institute of Medicine (IOM) late last year (<http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx>) generated a great deal of attention because it concluded that postmenopausal women taking supplements may be getting too much calcium, and that few people need to take vitamin D. These findings, among others, left many physicians wondering how, or if, the IOM's report should change the way they practice.

The Journal of Family Practice posed that question to **Susan Williams, MD, MS, FACN, FACP**, an internist at the Cleveland Clinic and a diplomate with the American Board of Physician Nutrition Specialists. Her response: The report probably shouldn't change the way you practice.

Here, Dr. Williams explains why.

Recommended daily allowances are guidelines. The new dietary reference intakes (DRIs), like the recommended daily allowances (RDAs) they replace, are quantitative estimates of nutrient intakes intended for planning and assessing diets of healthy populations. They were never intended to be applied "across the board," or used as a benchmark for the dietary adequacy of individual patients.

Testing is still advisable when there is clinical suspicion of a calcium or vitamin D deficiency. Because parathyroid hormone (PTH) compensates for calcium deficiency by drawing calcium from the bones, an adequate serum calcium level alone does not necessarily reflect an adequate calcium intake. In fact, a low serum calcium level is likely to be the result of abnormally low levels of vitamin D. Thus, the best way to get an accurate picture of a patient's status is to simultaneously test serum calcium, vitamin D, and PTH levels.

Some patients require considerably larger doses of vitamin D than the recommended quantities.^{1,2} This is particularly true for obese individuals and patients who have undergone bariatric surgery, for example.³⁻⁵ The safety of daily dosing of vitamin D in far greater quantities has been established,^{6,7} and the risks of chronic undersupplementation⁸⁻¹⁰ outweigh the risks associated with hypervitaminosis D, particularly when D3 (cholecalciferol) supplements are recommended.

Calcium supplementation is safe for postmenopausal women. Many older women have poor dietary intake of calcium, and again, the consequences of a deficiency are far greater than those associated with an excess. The risk of kidney stones in women taking calcium supplements can be averted by advising patients to take calcium citrate, which tends to neutralize urine and has better fractional uptake into the bone than calcium carbonate.

The IOM report serves to remind us that getting adequate calcium and vitamin D is important for everyone. Age and gender-specific recommendations should be emphasized, remembering that in general, the IOM's DRIs are likely to meet the actual needs of most healthy patients, but may well fall short in the presence of chronic illness and disease.

Remember, too, that while we should always emphasize the importance of eating foods that are rich in calcium and vitamin D, patients' diets often fall short. In such cases—with the exception of patients with certain conditions (eg, renal failure or hyperparathyroidism)—supplements such as calcium citrate and vitamin D3 can be safely and confidently recommended.

Susan Williams, MD, MS, FACN, FACP, reported no potential conflict of interest relevant to this article.

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 In one study, the adjusted odds ratio for fractures in women taking bisphosphonates who had vitamin D deficiency was 1.77, compared with those with normal levels of vitamin D.

for primary prevention is limited, other than for alendronate—which has been shown to provide primary prevention of vertebral fracture.

Which bisphosphonate is best depends on patient preferences and individual profiles. (See “How would you treat these patients?” on page 23.) In the absence of head-to-head RCTs, it isn’t possible to comment on the relative efficacy of the various bisphosphonates or their adverse event profiles. Indeed, the authors of the 2 Cochrane reviews completed to date

note that trial participants have been healthier, with fewer comorbidities, than many of the postmenopausal women seen by primary care physicians. Head-to-head studies conducted in family practice settings would be an important addition to the body of evidence for the prevention of osteoporotic fracture. **JFP**

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