



**Q & A on Bisphosphonate Safety
(from Practical Management of Common Medical Problems CME)
Nov. 27, 2010**

Q1. How long is a patient recommended to be on a bisphosphonate?

The optimal duration of bisphosphonate treatment is not known. There is follow-up information from randomized controlled trials which show antifracture benefit for alendronate for 10 years and 7 years for risedronate.¹

The decision to use bisphosphonates for longer periods of time would depend on the individual patient – risk of fracture, comorbidities, introduction of new medications, life expectancies, etc.² In the Fracture Intervention Trial Long-Term Extension (FLEX) study, there was no statistical difference in the incidence of non-vertebral fractures between women who took alendronate for 10 years and those who took the drug for 5 years and then stopped for 5 years. The 5 year group however did report lower bone mineral density and an increased incidence of vertebral fractures.³

Patients should be re-evaluated annually^{4,5}. The decision to continue or stop bisphosphonate therapy will still depend on the patient's fracture risk. If high, the likelihood of benefit usually outweighs the risk of long-term adverse effects (atypical fracture, osteonecrosis of the jaw, etc.) but if fracture risk is low, then the benefit of bisphosphonate therapy may be too low to justify exposure to these risks.^{1,6}

1. Osteoporosis Comparison Chart – www.RxFiles.ca.
2. Sellmeyer D. Atypical Fractures as a Potential Complication of Long-term Bisphosphonate Therapy. JAMA 2010;304(13):1480–1484.
3. Black D, Schwartz A, Ensrud K et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA. 2006; 296:2927-38.
4. Favus M. Bisphosphonates for osteoporosis. N Engl J Med 2010;363:2027-35.
5. Schmidt G, Horner K, McDanel D et al. Risks and benefits of long-term bisphosphonate therapy. Am J Health-Syst Pharm. 2010; 67:994-1001.
6. Papaioannou A, Morin S, Cheung A et al. 2010 practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ 2010. DOI:10.1503/cmaj.100771.

Q2. One of my patient's repeat bone mineral density (BMD) scan showed an increase in hip density but a decline in spine density one year after initiation of a bisphosphonate. Is this regarded as a success or failure of therapy? How does one manage this patient?

The Canadian Osteoporosis Guidelines recommend a BMD scan 1 to 3 years after starting therapy.¹ However, it can take more than 1 year for medication to produce significant changes in BMD measurements.² A secondary analysis of data from the Fracture Intervention Trial (FIT) suggests a BMD in the first 3 years of therapy may not be necessary and may actually provide misleading data.³ Other factors to consider include measurement error (this should be calculated for each machine - on average, about 4 % for the spine and 6 % for the hip²) and variation between technicians (0.7 %³ to 10 %⁴). The hip has a larger surface area so this site might provide more reproducible results.² Change in medication should be considered only if there is significant loss of BMD.^{1,2}

1. Papaioannou A Morin S Cheung A et al. 2010 practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ 2010. DOI:10.1503/cmaj.100771.
2. Harrison's Principles of Internal Medicine, Chapter 348 Osteoporosis, 17th ed., 2008.
3. Bell K, Hayen A, Macaskill P et al. Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data. BMJ 2009; 338:b2266.
4. Ladder M, Lems W, Ader H et al. Reproducibility of bone mineral density measurement in daily practice. Ann Rheum Dis 2004;63:285–289.
5. DXA scanning in clinical practice. QJM: An International Journal of Medicine 2008;101:605-17.

Q3. Can duration of therapy be prolonged if no significant BMD changes with oral bisphosphonate therapy?

Maintaining BMD is considered successful therapy but the decision to continue therapy would have to factor in whether or not the patient's fracture risk is high enough to warrant ongoing bisphosphonate therapy.¹

1. Papaioannou A Morin S Cheung A et al. 2010 practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ 2010. DOI:10.1503/cmaj.100771.

Q4. Is IV bisphosphonate therapy more effective if there are no significant BMD changes with oral therapy?

There are no head to head comparisons between oral and IV bisphosphonates. The NNTs (numbers needed to treat) to prevent fracture are similar. If compliance or incorrect administration of oral bisphosphonates is an issue, then the IV bisphosphonate potentially could be more effective. However, there are some adverse effects associated with IV bisphosphonates (infusion reactions and renal) and drug cost would be higher.

1. Osteoporosis Comparison Chart – www.RxFiles.ca

Q. How long do people stay on IV therapy?

If the patient is at high risk of fracture, therapy may be continued indefinitely. Published evidence from studies is limited to three years of treatment.¹ An abstract of new data from a three year extension of the Horizon-Pivotal Fracture Trial reports that BMD was maintained or increased in patients who continued to receive zoledronic acid yearly for a total of six years with no significant increase in serious adverse effects.² BMD in patients who stopped therapy after three years was lower compared to patients who continued therapy but remained higher than pre-trial measurements.² There was no significant difference in the incidence of clinical fractures.²

1. Osteoporosis Comparison Chart – www.RxFiles.ca.
2. Black D, Reid I, Cauley J et al. The effect of 3 versus 6 years of zoledronic acid treatment in osteoporosis, a randomized extension to the HAORIZON-PFT. Annual meeting of the American Society of Bone and Mineral Research; Oct. 16, 2010; Toronto, Canada (abstract and oral presentation 1070).

Q. Some elderly patients decline a BMD due to transport issues, etc. Is a BMD always required for confirmation of osteoporosis prior to initiating a bisphosphonate in such cases?

BMD is just one of the criteria used to determine fracture risk. Advanced age is also a risk factor. If an elderly patient has any additional risk factors, e.g. frail, prior fragility fracture, smoker, etc., she (or he) would likely be a candidate for treatment irregardless of BMD data. The FRAX calculator can be used to estimate fracture risk with or without a BMD measurement. See <http://www.sheffield.ac.uk/FRAX/tool.js>.

Q. Do we have to do serum calcium vitamin D levels for all patients before starting bisphosphonates?

It is recommended that all patients have calcium and vitamin D levels done before IV zoledronic acid administration. Hypocalcemia, if present, must be corrected before zoledronic acid is administered.¹

For oral bisphosphonates, calcium and vitamin D levels should be done only if there is reason to suspect the patient is deficient. If hypocalcemia is present, it must be corrected before starting the bisphosphonate.²

Of note, the recently released Institute of Medicine Report on dietary reference intakes for calcium and vitamin D has opened debate on what the optimal level of vitamin D is. To view the report, go to <http://www.iom.edu/~media/Files/Report%20Files/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/Vitamin%20D%20and%20Calcium%202010%20Report%20Brief.pdf>

1. e-CPJ. Aclasta monograph.
2. Abrahamsen B. Adverse Effects of Bisphosphonates. Calcif Tissue Int 2010; 86:421–435.

Q. Any postulation on the mechanism of atypical fractures associated with the use of bisphosphonate?

It is thought that atypical fractures are the result of over-suppression of bone remodelling. This inhibits the ability of bone to heal microcracks and gradually increases skeletal fragility.¹

1. Abrahamsen B. Adverse Effects of Bisphosphonates. *Calcif Tissue Int* 2010; 86:421–435.

Q. What do you mean by two antiresorptive drugs?

Antiresorptives are drugs which inhibit the breakdown of bone. Bisphosphonates, estrogen, raloxifene and calcitonin are all antiresorptives. Atypical fractures are thought to be the result of over-suppression of bone remodelling. Concurrent use of two antiresorptive drugs long-term may increase the risk for adverse effects, has not been shown to improve benefit and therefore is not recommended.^{1,2} Short-term use of calcitonin for fracture pain with another resorptive drug would not likely be a concern.

2. Abrahamsen B. Adverse Effects of Bisphosphonates. *Calcif Tissue Int* 2010; 86:421–435.
3. Papaioannou A Morin S Cheung A et al. 2010 practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *CMAJ* 2010. DOI:10.1503/cmaj.100771.

Prepared by Karen Jensen, Saskatchewan Drug Information Service.
Reviewed by Loren Regier, RxFiles.