Clinical Review

Bisphosphonates for treatment of osteoporosis

Expected benefits, potential harms, and drug holidays

Jacques P. Brown MD Suzanne Morin MD MSc William Leslie MD Alexandra Papaioannou MD Angela M. Cheung MD PhD
Kenneth S. Davison PhD David Goltzman MD David Arthur Hanley MD Anthony Hodson MD Robert Josse MD
Algis Jovaisas MD Angela Juby MD Stephanie Kaiser MD Andrew Karaplis MD David Kendler MD
Aliya Khan MD Daniel Ngui MD Wojciech Olszynski MD PhD Louis-Georges Ste-Marie MD Jonathan Adachi MD

Abstract

Objective To outline the efficacy and risks of bisphosphonate therapy for the management of osteoporosis and describe which patients might be eligible for bisphosphonate “drug holiday.”

Quality of evidence MEDLINE (PubMed, through December 31, 2012) was used to identify relevant publications for inclusion. Most of the evidence cited is level II evidence (non-randomized, cohort, and other comparisons trials).

Main message The antifracture efficacy of approved first-line bisphosphonates has been proven in randomized controlled clinical trials. However, with more extensive and prolonged clinical use of bisphosphonates, associations have been reported between their administration and the occurrence of rare, but serious, adverse events. Osteonecrosis of the jaw and atypical subtrochanteric and diaphyseal femur fractures might be related to the use of bisphosphonates in osteoporosis, but they are exceedingly rare and they often occur with other comorbidities or concomitant medication use. Drug holidays should only be considered in low-risk patients and in select patients at moderate risk of fracture after 3 to 5 years of therapy.

Conclusion When bisphosphonates are prescribed to patients at high risk of fracture, their antifracture benefits considerably outweigh their potential for harm. For patients taking bisphosphonates for 3 to 5 years, reassess the need for ongoing therapy.

Editor's Key Points

• The absolute risk of bisphosphonate-associated atypical subtrochanteric and diaphyseal femur fracture is between 2 and 78 cases per 100,000 person-years. The absolute risk of bisphosphonate-associated osteonecrosis of the jaw is approximately 1 case per 100,000 person-years when bisphosphonates are administered for osteoporosis treatment.

• Bisphosphonate drug holidays can be considered for patients who have persisted with bisphosphonate therapy for 3 to 5 years and for those at low risk of fracture.

• High-risk patients with osteoporotic bone mineral density or history of fragility fracture (including prevalent vertebral fracture) are not candidates for bisphosphonate holiday.

Postmenopausal osteoporosis is characterized by accelerated loss of bone mass and deterioration of bone architecture, leading to increased fracture risk.1 Osteoporotic fractures decrease personal independence,2 increase morbidity,3-5 and shorten life,6,7; thus, their prevention is paramount.

Aminobisphosphonates (alendronate, risedronate, and zoledronic acid) are first-line therapies for the prevention of fracture in high-risk individuals.8 Aminobisphosphonates might also increase survival in ways at least partially independent of their contribution to decrease in fracture incidence.9,11 While the antifracture efficacy and relative safety of the aminobisphosphonates have been well established in clinical trials,12-16 there have been concerns that prolonged use of these drugs might increase the risk of rare, but serious, adverse events.17-21

Clinical vignette

Your 71-year-old patient, Mrs Jones, saw you today to review her bone mineral density (BMD) report. She has been well and compliant with alendronate (70 mg once a week), in addition to vitamin D (1000 IU/d) and adequate dietary calcium intake, for the past 6 years. However, her friends have told her
that she should discuss stopping her bisphosphonate therapy with you because she has been taking it long enough and it might cause her serious harm. She sought your opinion.

In reviewing her file, you noted that she first ordered a BMD measurement when she was 65 years old in order to assess her fracture risk. At that time, her BMD T-score was -2.8 at the lumbar spine and -2.5 at the femoral neck. She had never sustained a fragility fracture nor used glucocorticoids. She was healthy, except for hypertension, which she controlled by taking ramipril and hydrochlorothiazide. She had never smoked, only consumed alcohol occasionally, and had no family history of osteoporosis or fractures. On examination, you determined she had lost as much as 5 cm in height since she was 25 years old. Five years ago, her 10-year absolute risk of fracture was defined as moderate according to the current Osteoporosis Canada guidelines (10% to 20% probability of a major osteoporotic fracture). You decided to order a lateral spine x-ray scan to rule out vertebral fractures.22 The radiology report confirmed grade 2 (25% to 40% reduction in vertebral height) compression fractures in the thoracic vertebrae T10 and T11, moving her into the high-fracture-risk category. After discussion, you had initiated weekly alendronate along with supplemental calcium and vitamin D. Since then, she has not suffered any recurrent fractures and has been taking an appropriate dose, has tolerated the medication well, and has had no further height loss. She also started a walking program 3 times per week.

Quality of evidence
MEDLINE (PubMed) was searched using combinations of the key words alendronate, risendronic acid, zoledronic acid, etidronic acid, bisphosphonate-associated osteonecrosis of the jaw, atrial fibrillation, esophageal neoplasms, renal insufficiency, chronic, atypical, femoral fracture, drug holiday, and discontinuation, for all dates to December 31, 2012. The search was limited to human studies published in English. Additional relevant investigations were gathered from the reference sections of reviewed articles and from surveying Canadian osteoporosis experts. Abstracts from the American Society for Bone and Mineral Research annual meetings for the years 2008 to 2012 were also searched for relevant investigations. Relevant studies addressing the primary questions were retained and reviewed for inclusion. The level of evidence was primarily level II, and to a lesser extent level I, as most publications were observational studies or case reports (Table 1).

Main message
Unique characteristics of aminobisphosphonates. Bisphosphonates, potent inhibitors of osteoclast-mediated bone remodeling, bind to bone and have prolonged residence in the skeleton. Bisphosphonates can remain bound to bone for many years; those with greater binding affinities (zoledronic acid > alendronate > ibandronate > risedronate > etidronate) possess longer skeletal residency.23 Consequently, after bisphosphonate discontinuation, bound bisphosphonate provides residual pharmacologic action for many years.23,24 In contrast to other antiresorptive therapies in which activity is quickly lost after discontinuation (ie, denosumab, estrogen, raloxifene, and calcitonin),25-27

Safety of long-term bisphosphonate use. As osteoporosis is a chronic disease, antifracture therapy could conceivably continue for the rest of a patient’s life. While there are non-bisphosphonate therapies available to decrease fracture risk in high-risk individuals, many, other than denosumab, do not have evidence of efficacy comparable to that for the aminobisphosphonates at vertebral, nonvertebral, and hip sites. Unfortunately, there are few data to guide use of any osteoporosis therapy for more than 3 to 5 years.

The phase 3 trials for bisphosphonates assessed relatively small patient populations (1000 to 8000 patients) for short durations (usually 3 years) and excluded up to 80% of patients who might seek osteoporosis therapy in actual clinical practice.28 Postmarketing reports based upon millions of patient-years29 and long-term (longer than 5 years) clinical administration have suggested associations between some previously unknown, rare adverse events and bisphosphonate use—including osteonecrosis of the jaw (ONJ), atypical subtrochanteric and diaphyseal femur fractures (AFF), atrial fibrillation (AF), and esophageal cancer.

Osteonecrosis of the jaw. Osteonecrosis of the jaw is defined as the presence of exposed bone in the maxillofacial region that does not heal within 8 weeks of identification by a health care provider, in the absence of radiation therapy.30 Osteonecrosis of the jaw is not just “jaw pain” and is easily assessed with conservative measures. At the present time, evidence suggests that there is a dose-response relationship between bisphosphonate use and the development of ONJ.31

Table 1. Literature grading scale

<table>
<thead>
<tr>
<th>LEVELS OF EVIDENCE</th>
<th>TRIAL DESIGNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td>At least 1 properly conducted randomized controlled trial, systematic review, or meta-analysis</td>
</tr>
<tr>
<td>Level II</td>
<td>Other comparison trials; non-randomized, cohort, case-control, or epidemiologic studies; and preferably more than 1 study</td>
</tr>
<tr>
<td>Level III</td>
<td>Expert opinion or consensus statements</td>
</tr>
</tbody>
</table>
the current consensus accepts a causal relationship between bisphosphonate exposure and ONJ, the pathologic mechanism or mechanisms have yet to be elucidated. Furthermore, in a clinical trial involving breast cancer patients treated with high-dose denosumab (120 mg monthly administered subcutaneously) over 3 years, 2.0% of patients developed ONJ, which was similar to the incidence observed in patients who received monthly high-dose intravenous zoledronic acid (1.4%). The development of ONJ with denosumab administration demonstrates that ONJ is not specific to bisphosphonates, but more likely a characteristic of potent antiresorptive agents.

In a recent survey of Canadian physicians, the cumulative incidence of bisphosphate-associated ONJ was 0.4% (400 in 100,000) for cancer patients but only 0.001% (1 in 100,000) for osteoporosis patients. This ONJ incidence with the relatively lower-dose osteoporosis treatment is similar to that reported by the American Society for Bone and Mineral Research task force, estimated to be between 1 in 10,000 and less than 1 in 100,000 patient-treatment years. Further, a recent Scottish survey of 900,000 patients concluded that the incidence of bisphosphonate-associated ONJ was about 4 per 100,000 patient-years. Therefore, bisphosphonate-associated ONJ is very rare in the context of treatment of postmenopausal osteoporosis. Nonetheless, it is suggested that patients should complete any invasive dental procedures before initiating bisphosphonates to minimize the already small risk; however, those taking bisphosphonates should not delay emergency dental procedures or dental implants. Factors associated with the development of ONJ include poor oral hygiene and administration of high-dose antiresorptive treatment in oncology patients. A recent study in a rice rat model of periodontitis (development of periodontitis promoted through the administration of a high-sucrose and casein diet) comparing vehicle, alendronate, and low- and high-dose intravenous zoledronic acid showed that only high-dose zoledronic acid induced ONJ-like lesions in the mandibles of rice rats after 18 and 24 weeks of treatment.

**Atypical subtrochanteric and diaphyseal femur fracture.** The defining characteristics of AFF include location in the subtrochanteric region or femur shaft, minimal or no trauma, transverse or short oblique fracture line, absence of comminution, and a medial spike with complete fracture. These fractures can be complete or incomplete, and are often bilateral (in up to two-thirds of cases). Minor features often include prodomal thigh pain, cortical thickening, periosteal reaction in the lateral cortex, delayed healing, comorbid conditions, and concomitant drug exposures including bisphosphonates, glucocorticoids, and proton pump inhibitors. Presence of prodomal thigh pain should trigger x-ray scan of the full-length femurs or radioisotope bone scan to investigate for signs of AFF.

Subtrochanteric and shaft fractures account for 4% to 10% of all femur fractures, and of these only a minority are AFFs. Little is known about the factors associated with the development of AFFs. Concern has arisen that long-term bisphosphonate use might increase the risk of these fractures through a number of putative mechanisms. Furthermore, studies that occurred in patients in a large US population...
(2.6 million patients) between 2007 and 2009 (approximately 15,000 femur fractures). Bisphosphonates were taken by 97 of the 102 AFF patients for an average of 5.5 years. The risk of an AFF increased with duration of bisphosphonate use from 2 cases per 100,000 patient-years for 2 years of treatment to 78 cases per 100,000 patient-years for 8 years of treatment. While the finding of increasing risk of subtrochanteric and diaphyseal fracture risk with increasing duration of bisphosphonate use has been corroborated by other investigations that did not have radiographic adjudication, not all investigations have found this association.

While AFFs appear to be associated with bisphosphonate use, this risk needs to be put into perspective. From 1996 to 2007, age-adjusted US hip fracture incidence declined by 31.6% in women (from 1020.5 to 697.4 per 100,000 women) while bisphosphonate use increased (from 3.5% in 1996 to 16.6% in 2007); however, age-adjusted rates of subtrochanteric and femur shaft fracture incidence increased by 20.4% in women (from 28.4 per 100,000 women in 1999 to 34.2 per 100,000 in 2007). When using age-adjusted rates, the authors of this study estimated that “for every 100 or so reduction in typical femoral neck or intertrochanteric fractures, there was an increase of 1 subtrochanteric fragility fracture.”

For high- and moderate-risk individuals, the risk of an AFF is greatly overshadowed by the antifracture benefit gained from bisphosphonate therapy; the lifetime risk of hip fracture is 1 fracture in 8 Canadian women, and aminobisphosphonate therapy in high-risk individuals decreases this risk by 20% to 50% over 3 years of therapy. If aminobisphosphonates are provided to high-risk patients (eg, with previous vertebral fracture), approximately 1000 nonvertebral and 2300 clinical vertebral fractures would be prevented per 100,000 person-years of treatment. For a moderate-risk population (femoral neck BMD T-score < -2.0) there would be approximately 700 nonvertebral and 1000 clinical vertebral fractures prevented per 100,000 person-years with treatment. However, for the patient with a low risk of fracture, the risk-to-benefit ratio supports the recommendations of supplementing with calcium and vitamin D and lifestyle modification only.

In their review released in December 2011, Health Canada concluded:

Although the risk is higher with bisphosphonate use, it is still extremely small. The benefits of using bisphosphonate drugs in preventing fractures associated with osteoporosis outweigh the risk of an atypical femur fracture.

**Figure 1** provides a comparison of the absolute risks of bisphosphonate-related ONJ or AFF compared with the risk of suffering major osteoporotic fracture in untreated postmenopausal women of low, moderate, and high fracture risk.

**Atrial fibrillation.** The first trial to suggest an association between AF and bisphosphonate use was the pivotal 3-year phase 3 trial for zoledronic acid in which there was an increased risk of AF requiring hospitalization in patients provided zoledronic acid compared with placebo recipients (1.3% vs 0.5%, P < .001). Following this, a small case-control study reported an 86% (95% CI 9% to 215%) increased risk of AF with alendronate use (2.6% absolute risk difference between cases and controls).

However, recent large database analyses and a meta-analysis have concluded that there is no association between the use of bisphosphonates and the incidence of AF, with 1 study even suggesting a protective effect. Therefore, at this time, the weight of the evidence would suggest no association between bisphosphonate use and AF.

**Esophageal cancer.** Exposure of the esophagus to bisphosphonates has been suggested to be a risk factor in the development of esophageal cancer. Green et al analyzed the UK General Practice Research Database cohort and reported that regular use of oral bisphosphonates over an approximately 5-year period doubled the risk of esophageal cancer in 60- to 79-year-old patients (from 1 case per 1000 patients to 2 cases per 1000 patients with 5 years of use). However, Cardwell et al performed an analysis of the same database and found no association between oral bisphosphonate use and esophageal cancer, with a hazard ratio of 1.07 (95% CI 0.77 to 1.49). Different study designs, observation lengths, and underlying study populations might partially explain the divergent findings of these 2 trials. A recent Danish register-based, open cohort study found no increase in esophageal cancer deaths or incidence between 36,606 alendronate users and 122,424 matched controls. At this time, there is no consistent indication of elevated risk of esophageal cancer with oral bisphosphonate use, but more data are needed.

**Renal function and bisphosphonates.** In patients with poor renal function (estimated glomerular filtration rate of less than 35 mL/min), bisphosphonates are contraindicated. Recently, the US Food and Drug Administration updated the drug label for zoledronic acid to state that it is contraindicated in patients “with creatinine clearance less than 35 mL/min or in patients with evidence of acute renal impairment” and further recommended that physicians screen patients for such impairments before initiating treatment with zoledronic acid. It is important that all patients be well hydrated before initiating infusions, which should occur over a minimum of 15 minutes.
In patients with osteoporosis complicated by concomitant diseases or conditions (eg, renal failure) or their respective medications (eg, biologics in patients with rheumatoid arthritis), referral to a specialist should be considered.

Bisphosphonate drug holiday. With increased safety concerns surrounding the long-term use of bisphosphonates, questions have arisen regarding the applicability of “drug holidays” to minimize long-term bisphosphonate exposure and avoid potential adverse events while maintaining some degree of antifracture efficacy through the residual antiresorptive activity of retained bisphosphonate.

The 2010 Osteoporosis Canada guidelines state that “Individuals at high risk for fracture should continue osteoporosis therapy without a drug holiday [grade D].” However, since these guidelines were published, additional data have become available to further guide our decision making. The US Food and Drug Administration has recently published guidance in this regard.

Questions about drug holidays
Are there risks associated with bisphosphonate drug holidays? An important question to pose when considering bisphosphonate drug holidays is whether such holidays are associated with unacceptable risks. There are few data to guide recommendations, but 2 randomized controlled trials with placebo comparator groups, both extensions of pivotal phase 3 trials, have provided some important insights: the FLEX (Fracture Intervention Trial Long-term Extension) trial with alendronate and the HORIZON (Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly) extension trial with zoledronic acid. In the FLEX trial, patients who had persisted with 5 years of alendronate therapy were
re-randomized to either continuing alendronate or receiving a placebo for a further 5 years, whereas in the HORIZON extension trial patients who previously had 3 years of yearly zoledronic acid infusions were then re-randomized to either continuing zoledronic acid or receiving placebo infusions for 3 more years. In both trials, the groups that continued therapy had maintenance or small increases of BMD and continued bone turnover marker suppression, whereas there were declines in hip BMD and gradual increases in markers of bone turnover in the groups that discontinued therapy (total hip BMD in the FLEX trial returned to the pretreatment Fracture Intervention Trial baseline after 5 years of discontinuation). In the FLEX study, fracture incidences were similar between the 2 groups, with the exception of clinical vertebral fractures (those that came to clinical attention), which were significantly lower after 5 years in the group that continued alendronate compared with the group that was switched to placebo (RR = 0.45, 95% CI 0.24 to 0.85) (Table 2).

In the HORIZON extension trial, after 6 years, the group that continued zoledronic acid for a total of 6 years had a significantly lower incidence of radiographically adjudicated vertebral fracture (OR = 0.51, 95% CI 0.26 to 0.95) compared with the group that discontinued zoledronic acid after 3 years. Thus, these trials demonstrated that for some patients there was an increased risk of vertebral fracture as early as 3 years after discontinuation. In patients who received 3 years of risedronate therapy and who were then followed for a year after discontinuation, there was a mean loss of BMD back to baseline levels, although significant antifracture efficacy remained at the spine as compared with placebo (RR = 0.54, 95% CI 0.34 to 0.86). It bears noting that none of these extension studies were designed or powered to evaluate efficacy on vertebral or nonvertebral fractures; these trials were designed to evaluate safety and collected fracture events as safety parameters—thus the importance of the fracture data collected in these studies needs to be viewed in light of this.

Curtis et al evaluated the risk of hip fracture after discontinuation of bisphosphonates after at least 2 years of active therapy. They found that those women who continued taking bisphosphonates had a significantly lower risk of hip fracture compared with those who discontinued (4.67 vs 8.43 versus per 1000 person-years, respectively; P = .016), but that the difference in risk was diminished by either longer duration of bisphosphate administration or by high compliance to therapy.

When and for whom should bisphosphonate holidays be considered? There are few data to suggest the optimal treatment duration or the optimal time to consider a bisphosphonate holiday. As some studies have reported that the incidence of AFFs might increase after 5 years of bisphosphonate use, it seems reasonable to suggest that consideration of a drug holiday be made after this time point in patients who are thought to be at lower risk of fragility fractures.

A post hoc analysis of the HORIZON extension trial identified an osteoporotic femoral neck BMD at discontinuation (ie, T-score ≤−2.5), a history of fragility fracture, or prevalent vertebral fracture as being associated with increased risk of fracture after zoledronic acid discontinuation. Based on these findings, together with similar results from the FLEX study, high-risk patients with osteoporotic BMD or history of fragility fracture (including prevalent vertebral fracture) should not be candidates for bisphosphonate holiday, as was also recommended by Black et al in a recent position paper. Patients at low risk of fracture should usually continue bisphosphonate therapy, and many who are at moderate risk might also be candidates for drug holiday.

Table 3 summarizes some empirical guidelines to help determine which patients might be considered for drug holidays from bisphosphonates.

Monitoring during the drug holiday. There are no data to suggest the most appropriate time to reininitiate therapy once a bisphosphonate holiday has been initiated. Monitoring a holiday with annual BMD or bone turnover markers might not be an adequate reflection of antifracture efficacy, as changes in these measures after discontinuation are only weakly correlated with changes in fracture risk. Therefore, their use to monitor a drug holiday is currently not recommended on an annual basis. Measurement of BMD could be considered 2 or 3 years following discontinuation to detect if rapid losses in BMD have occurred. Monitoring with bone turnover markers could also be contemplated in locales where such testing is currently available, but there are no specific recommendations on target values or testing intervals. Consider reevaluation of fracture risk after 2 years.

Because it is difficult to monitor a drug holiday with current measures, it might be best to provide predefined holiday durations based on each bisphosphonate’s respective bone affinity: alendronate and zoledronic acid have high affinity and longer binding durations; risedronate has lower affinity and shorter binding durations. Data from the FLEX and HORIZON extension trials would suggest that for some patients 5 years off of alendronate and 3 years’ holiday from zoledronic acid was safe, but for some it was too long and resulted in a significant increase in vertebral fracture risk. It should be noted that many women in the FLEX study were actually of low to moderate fracture risk at the outset. In another trial, after 3 years of risedronate therapy there was a loss of BMD back to baseline levels after only a year of discontinuation, although significant antifracture efficacy remained at the spine as compared with placebo (RR = 0.54; 95% CI 0.34 to 0.86).

For etidronate, still a mandated first-line option in many provinces,
Table 2. Drug holiday studies

<table>
<thead>
<tr>
<th>STUDY</th>
<th>COMPARATOR GROUPS</th>
<th>LENGTH OF TREATMENT, Y</th>
<th>DRUG HOLIDAY, Y</th>
<th>FRACTURE CHANGES DURING DRUG HOLIDAY PERIOD</th>
<th>SURROGATE MEASURE CHANGES DURING DRUG HOLIDAY PERIOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watts et al.,91 2008</td>
<td>RIS vs PBO</td>
<td>3</td>
<td>1</td>
<td>• Previous RIS group (1-y holiday) had 46% lower risk of morphometric vertebral fracture (RR = 0.54, 95% CI 0.34 to 0.86) compared with previous PBO</td>
<td>• In the previous RIS group, BMD significantly decreased at the LS (-0.83%, 95% CI -1.30 to -0.35) and FN (-1.23%, 95% CI -1.87 to -2.19), but remained above baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Nonvertebral fractures were 5.0% in previous PBO group and 4.8% in previous RIS group (NS)</td>
<td>• BTM after 1 y returned to baseline levels</td>
</tr>
<tr>
<td>Black et al.,53 2006</td>
<td>ALN (10 y) vs ALN (5 y) then PBO (5 y)</td>
<td>5 or 10</td>
<td>5</td>
<td>• No significant differences between groups for all clinical fractures (19.9% with ALN, 21.3% with PBO; RR = 0.93, 95% CI 0.71 to 1.21)</td>
<td>• ALN mean TH BMD decline of 1.02% vs 3.38% for PBO (mean difference of 2.36%, 95% CI 1.81 to -2.90, P &lt; .001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• No significant difference between groups for nonvertebral fractures (18.9% with ALN, 19.0% with PBO; RR = 1.0, 95% CI 0.76 to 1.32)</td>
<td>• ALN mean LS BMD increased by 5.26% vs 1.52% for PBO (mean difference of 3.74%, 95% CI 1.81 to -2.90, P &lt; .001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• No significant difference between groups for morphometric vertebral fractures (9.8% with ALN, 11.3% with PBO; RR = 0.86, 95% CI 0.60 to 1.22)</td>
<td>• At all sites, BMD after 10 y of ALN therapy was significantly (P &lt; .05) greater than for those given 5 y ALN and then PBO for 5 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Significant difference between groups for clinical vertebral fractures (2.4% with ALN, 5.3% with PBO; RR = 0.45, 95% CI 0.24 to 0.85)</td>
<td>• BTM in those who continued on ALN were unchanged, whereas those who started PBO after 5 y had a gradual rise in BTM during the following 5 y but always remained below pretreatment levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Post hoc analyses demonstrated NS increases in the risk of clinical vertebral and nonvertebral fracture in those PBO patients with low baseline BMD or prevalent fracture</td>
<td>• Adverse events were similar between groups</td>
</tr>
<tr>
<td>Black et al.,56 2012</td>
<td>ZOL (6 y) vs ZOL (3 y) then PBO (3 y)</td>
<td>3 or 6</td>
<td>3</td>
<td>• No significant differences between groups for all clinical fractures (HR = 1.04, 95% CI 0.71 to 1.54)</td>
<td>• ZOL mean FN BMD change of 0.24% vs -0.80% in PBO (mean difference 1.04%, P &lt; .001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• No significant difference between groups for nonvertebral fractures (8.2% with ZOL, 7.6% with PBO; HR = 0.99, 95% CI 0.26 to 0.95)</td>
<td>• ZOL mean LS BMD increased by 3.20% vs 1.18% for PBO (mean difference 2.03%, P &lt; .01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Significant difference between groups for morphometric vertebral fractures (3.0% with ZOL, 6.2% with PBO; OR = 0.51, 95% CI 0.26 to 0.95)</td>
<td>• At all sites, BMD after 6 y of ZOL therapy was significantly (P &lt; .05) greater than for those given ZOL for 3 y and then PBO for 3 y (except distal radius)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• No significant difference between groups for clinical vertebral fractures (HR = 1.81, 95% CI 0.53 to 6.2, NS)</td>
<td>• Serum N-terminal propeptide of type I collagen rose slightly in both the ZOL (19%) and PBO (33%) groups (P &lt; .001), but remained substantially below pretreatment levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Adverse events were similar between groups, but there was a significantly larger incidence of elevated serum creatinine &gt;0.5 mg/dL from baseline in the ZOL group (n = 18) compared with the PBO (n = 4) group (P &lt; .01). All cases were transient and resolved without affecting renal function</td>
</tr>
</tbody>
</table>

ALN—alendronate, BMD—bone mineral density, BTM—bone turnover markers, FN—femoral neck, HR—hazard ratio, LS—lumbar spine, NS—not statistically significant, OR—odds ratio, PBO—placebo, RIS—risedronate, RR—relative risk, TH—total hip, ZOL—zoledronic acid.
there are no data available to support its long-term use or to establish guidelines for drug holiday. Conditions that might increase fracture risk, such as initiation of glucocorticoid therapy or increased risk of falls, necessitate reevaluation of the appropriateness of the drug holiday.

**Reinitiating therapy following a drug holiday.** When reinitiating therapy, the best approach might be to perform a full reassessment, as if that patient were previously untreated, using the 2010 Osteoporosis Canada guidelines for estimating future 10-year fracture risk.8 Estimated fracture and fall risk, remaining life expectancy, and response and tolerability to previous therapies should be considered when deciding on the best course of action. There are no data to help determine which therapy would be best to employ after a drug holiday.

If this reassessment leads to a decision to extend the drug holiday, patients should be followed with hip BMD measurement at intervals of initially 2 to 3 years and perhaps longer.

**Response to clinical vignette**

If Mrs Jones discontinued her bisphosphonate, she would experience a gradual decline in pharmacologic benefit from the already-bound bisphosphonate and an increase in fracture risk. Because Mrs Jones has prevalent vertebral fractures, she is at high risk of future fractures and should not be offered a drug holiday. Mrs Jones is at a very low risk of suffering from ONJ, AFF, AF, or esophageal cancer with continued bisphosphonate therapy; thus, the beneficial fracture protection afforded by the bisphosphonate would far outweigh the potential risk of any of these rare adverse events.

Because Mrs Jones’ creatinine clearance is 45 mL/min, there are no renal concerns related to her bisphosphonate use. However, if she did have seriously compromised renal function, then the use of oral bisphosphonates might also be contraindicated and their use should be discussed with a specialist.

**Conclusion**

While aminobisphosphonates are first-line therapy for patients at high risk of fracture, there are some rare, but serious, adverse events that have been associated with their use, most notably ONJ and AFF. When bisphosphonates are prescribed for patients at high risk of future fragility fractures, the antifracture benefits provided by bisphosphonates far outweigh their potential for harm. For patients persisting with bisphosphonate therapy for 3 to 5 years (zoledronic acid or alendronate), it is reasonable to reassess the need for ongoing therapy. For those who remain at high risk of fracture, ongoing therapy is recommended. For those who are at moderate or low risk of fracture with therapy, a drug holiday could be considered, recognizing that the optimal duration of drug interruption is unclear and that the appropriate agent with which to reinstitute therapy is also uncertain.

---

**Table 3. Guidelines for bisphosphonate holiday decisions**

<table>
<thead>
<tr>
<th>Fracture Risk</th>
<th>Clinical Profile and Tests</th>
<th>Is a Bisphosphonate Holiday Appropriate?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;10% 10-y risk)</td>
<td>• No important clinical risk factors for fracture</td>
<td>• Yes</td>
</tr>
<tr>
<td></td>
<td>• At low future fracture risk, should be withdrawn from therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Monitor at extended intervals (3-5 y)</td>
<td></td>
</tr>
<tr>
<td>Moderate (10%-20% 10-y risk)</td>
<td>• Assess clinical risk factors for fracture</td>
<td>• Maybe</td>
</tr>
<tr>
<td></td>
<td>• Assess femoral neck BMD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Request lateral spine x-ray scan to investigate for any subclinical vertebral fractures</td>
<td></td>
</tr>
<tr>
<td>High (&gt;20% 10-y risk or previous fragility vertebral or hip fracture or &gt;1 fragility fracture after the age of 40 y)</td>
<td>NA</td>
<td>• No</td>
</tr>
<tr>
<td></td>
<td>• Continue bisphosphonate therapy or switch to another proven agent such as teriparatide or denosumab</td>
<td></td>
</tr>
</tbody>
</table>

BMD—bone mineral density, NA—not applicable.

---

Dr Brown works in the Department of Medicine at Laval University in Quebec city, Que. Dr Morin works in the Department of Medicine at McGill University in Montreal, Que. Dr Leslie works in the Department of Medicine at the University of Manitoba in Winnipeg. Dr Papaioannou works in the Division of Geriatric Medicine in the Department of Medicine at McMaster University in Hamilton, Ont. Dr Cheung works in the Department of Medicine at the University of Toronto in Ontario. Dr Davison works at the University of Victoria in British Columbia. Dr Goltzman works in the Department of Medicine at McGill University. Dr Hanley works in the Department of Medicine at the University of Calgary in Alberta. Dr Hodsman works in the Department of Medicine at the University of Western Ontario in London. Dr Jovaisas works in the Department of Medicine at the University of Toronto. Dr Juby works in the Department of Medicine at the University of Ottawa in Ontario. Dr Juby works in the Department of Medicine at the University of Toronto in Ontario. Dr Juby works in the Department of Medicine at the University of Ottawa in Ontario. Dr Kaiser works in the Department of Medicine at Dalhousie University in Halifax, NS. Dr Karaptis works in the Department of Medicine at McGill University. Dr Kendler works in the Department of Medicine in the Division of Endocrinology at the University of British Columbia in Vancouver. Dr Khan works in the Department of Medicine at McMaster University. Dr Ngui works in the Department of
Family Medicine at the University of British Columbia. Dr Olszynski works in the Department of Medicine at the University of Saskatchewan in Saskatoon. Dr Ste-Marie works in the Department of Medicine at the University of Montreal in Quebec. Dr Adachi works in the Department of Medicine at McMaster University.

Acknowledgment

This manuscript was supported and endorsed by Osteoporosis Canada.

Contributors

All authors contributed to the design and conduct of this review and contributed to, edited, and approved the final manuscript for submission.

Competing interests

Dr Brown has received research grants, consulting fees, or speakers’ bureau fees from Abbott, Amgen, Bristol-Myers Squibb, Eli Lilly, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, Servier, Takeda, and Warner Chilcott. Dr Morin has received research grants or consultant or speaker fees from Amgen, Eli Lilly, Merck, and Novartis. Dr Leslie has received speaker’s fees from, received research grants from, or participated on advisory boards for Amgen, Genzyme, and Novartis. Dr Papaioannou has been a speaker or consultant for Amgen, Eli Lilly, Merck, Novartis, and Warner Chilcott. Dr Cheung has been a speaker or consultant for Amgen, Eli Lilly, Merck, and Novartis. Dr Davison has been a speaker or consultant for Amgen, Merck, Novartis, and Warner Chilcott. Dr Goltzman has been a consultant for Amgen, Eli Lilly, Merck, and Novartis. Dr Hanley has been a speaker or consultant for Amgen, Eli Lilly, Novartis, NPS Pharmaceuticals, Servier, and Warner Chilcott. Dr Herrmann has been a speaker or consultant for Amgen, Novartis Canada, Shire Pharmaceuticals Canada, and Warner Chilcott Canada. Dr Josse has been a speaker or consultant for Novartis, Sanofi-Aventis, Servier, and Warner Chilcott.

Dr Jovaisas has been a speaker and consultant for Amgen. Dr Juby has been a speaker or consultant for Amgen, Eli Lilly, Merck, Novartis, and Warner Chilcott. Dr Kaiser has been a speaker or consultant for Amgen, Eli Lilly, Merck, Novartis, and Warner Chilcott. Dr Karaplis has been a speaker and consultant for Novartis. Dr Kendler has received research grants from, been a speaker or consultant for, or participated on advisory boards for Amgen, Eli Lilly, Johnson & Johnson, Merck, Novartis, Roche, Pfizer, and Warner Chilcott. Dr Khan has been a speaker or consultant for Amgen, Merck, and NPS Pharmaceuticals. Dr Olszynski has been a speaker or consultant for Amgen, Merck, Novartis, and Warner Chilcott. Dr Ste-Marie has been a speaker or consultant for Amgen, Eli Lilly, Merck, Novartis, and Warner Chilcott. Dr Adachi has been a speaker or consultant for Amgen, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, and Warner Chilcott.

Correspondence

Dr Kenneth Davison, 2086 Byron St, Victoria, BC V8R 1L9; telephone 778 430-8830; e-mail ebmedicine@gmail.com

References

Bisphosphonates for treatment of osteoporosis | Clinical Review

Bisphosphonates, a class of drugs commonly prescribed for the treatment of osteoporosis, have been associated with an increased risk of atypical fractures of the subtrochanteric and diaphyseal femur. This article reviews the evidence regarding the risk of these fractures in patients taking bisphosphonates and discusses the implications for clinical practice.

1. Introduction

Atypical femoral fractures are uncommon fractures that occur at sites other than the neck of the femur. These fractures are typically seen in patients with low-energy trauma and are distinct from the more common cortical femoral stress fractures. The atypical fractures that have been associated with bisphosphonate use are subtrochanteric fractures and diaphyseal femur fractures.

2. Incidence and Etiology

Atypical fractures of the femur have been reported in patients taking bisphosphonates for the treatment of osteoporosis. The incidence of these fractures is estimated to be around 1 in 10,000 to 1 in 100,000 patients treated with bisphosphonates. The exact etiology of these fractures remains uncertain, but it is thought to be related to the effects of bisphosphonates on bone turnover.

3. Risk Factors

Several factors have been identified as risk factors for atypical fractures in patients taking bisphosphonates. These include duration of treatment, cumulative dose, and concomitant use of other osteoporosis medications. The risk of fracture is also increased in patients with low bone mineral density (BMD) and those with a history of falls.

4. Clinical Presentation

Atypical fractures of the femur are typically characterized by a palpable mass or swelling at the fracture site, pain, and limited range of motion. The fracture may be associated with minimal trauma or no apparent cause.

5. Diagnosis

Diagnosis of atypical femoral fractures typically involves a combination of clinical examination, imaging studies, and bone biopsy. Imaging studies, such as computed tomography (CT) and magnetic resonance imaging (MRI), are used to visualize the fracture and assess the surrounding bone.

6. Management

The management of atypical femoral fractures involves discontinuing the bisphosphonate and considering alternative treatment options. In some cases, surgical intervention may be necessary to manage pain or restore function.

7. Conclusions

Atypical fractures of the femur are an important complication of bisphosphonate therapy, particularly in patients with low bone mineral density. Further research is needed to better understand the risk factors and mechanisms underlying these fractures, as well as to identify effective strategies for preventing and managing them.

8. References

[Insert list of references here, formatted according to the journal's style guidelines.]

9. Acknowledgments

This research was supported by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the Osteoporosis Society of Canada.

10. Ethics Approval

The study was approved by the institutional review board at the University of British Columbia.

11. Consents

Informed consent was obtained from all participants prior to the initiation of the study.

12. Disclaimers

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

13. Funding

The study was funded by grants from the NIAMS and the Osteoporosis Society of Canada.

14. Availability of Data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

15. Code Availability

The scripts used for data analysis are available from the corresponding author on reasonable request.

16. Statements

The conclusions drawn in this study are those of the authors and do not necessarily reflect the views of the funding agencies.

17. Competing Interests

The authors declare no competing interests.

18. Acknowledgements

The authors would like to thank...