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# Long-term bisphosphonate therapy and atypical femoral fracture: Can you have too much of a good thing?

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**Running head:** Long-term bisphosphonate therapy and atypical femoral fracture

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**Story from the front lines**

A woman in her 70's presented to the emergency department in considerable pain following a minor bump of her hip on the corner of her dining table. Radiography revealed she had sustained a non-comminuted, transverse fracture along the femoral diaphysis with associated periosteal 'beaking.' The minor nature of the incident and features of the imaging confirmed an atypical femoral fracture. She had commenced bisphosphonate therapy over 20 years ago due to a strong family history of osteoporosis. Is there a right time to deprescribe bisphosphonate therapy?

In the UK, approximately 536,000 new fragility fractures occur each year which costs the National Health Service (NHS) over £4.4 billion [1]. The ageing UK population means a doubling in the number of fragility fractures is predicted to occur over the next 50 years unless changes are made urgently to current practice [1, 2]. The recently updated NICE accredited guideline for the assessment and management of osteoporosis in the UK makes a number of recommendations for the prevention of fragility fractures in postmenopausal women and in men aged 50 years or over. Bisphosphonate (BP) therapy is recommended in those with a bone mineral density (BMD) T-score of -2.5 or less by dual-energy X-ray absorptiometry (DXA) scan, the preferred site being the femoral neck. Importantly, BMD predicts fracture risk with high specificity (risk increases approximately 2-fold for each SD decrease in BMD [3]) but low sensitivity. Improved sensitivity can be achieved through consideration of several additional independent clinical risk factors including low BMI [4], history of a prior fracture [5], parental history of hip fracture [6], smoking [7], alcohol [8] and rheumatoid arthritis [9, 10]. Glucocorticoid [11, 12], proton pump inhibitors [13] and psychoactive drug use [14] have also been implicated.

The Task Force of the American Society for Bone and Mineral Research recommends extended BP therapy beyond 5 years for women considered to be at high fracture risk. Three clinical trials involving postmenopausal women have provided evidence to support long-term BP use for fracture prevention; the extended Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Pivotal Fracture Trial (HORIZON-PFT) [15], the Fracture Intervention Trial Long-term Extension (FLEX) trial [16] and the Actonel Vertebral Efficacy with Risedronate Therapy–Multinational Trial (VERT-MN) extension. Both HORIZON

and FLEX showed that prolonged treatment, 6 and 10 years respectively, resulted in fewer clinical vertebral fractures with no increased risk of adverse events. For women not at high fracture risk after 3-5 years of BP treatment, a drug holiday of 2–3 years can be considered, with periodic reassessment. No adequate clinical trials have yet delineated how long the drugs' benefits are maintained in bone after cessation.

It is important to consider the option to discontinue BP therapy as long-term treatment is not entirely without risk. Post marketing reports have identified rare but serious adverse consequences associated with BPs, including osteonecrosis of the jaw, oesophageal cancer and atypical femoral fracture (AFF), the risks of which increase with increased therapy duration [17].

Prolonged treatment (longer than 5 years) raises the theoretical risk of over-suppression of bone turnover which may lead to increased skeletal fragility and susceptibility to non-spinal fractures occurring with minimal or no trauma [18, 19]. Cases of severely suppressed bone turnover and associated atypical fracture have been reported [18, 20]. The US Food and Drug Administration (FDA) performed a pooled analysis of all data on vertebral and nonvertebral osteoporotic fractures across the three major bisphosphonate extension studies (2496 patients) and found that fracture rates are relatively constant over time [21]. Patients that received continuous BP treatment for more than 6 years had fracture rates ranging from 9.3 to 10.6%, whereas the rate for patients who switched to placebo was 8.0 to 8.8%. Statistical limitations including power, selection bias, sample size, and timing issues vary among the studies; however, the question of whether continued BP therapy beyond 5 years imparts additional fracture-risk reduction benefit remains uncertain, particularly in light of safety concerns. 10 years ago, Black and colleagues examined the association between prolonged BP use and atypical hip/femur fractures in their secondary analysis of FLEX and the Fracture Intervention Trial (FIT), both of alendronate and HORIZON-PFT of zolendronic acid [22]. At that time, they concluded that even among women who were treated for as long as 10 years, there was no significant association between the use of BPs and the risk of AFF [22]. However, the number of patients treated for longer than 3-4 years was minimal and the dose of alendronate for many was lower than the standard. In addition, the statistical power of the study was very low, compounding the difficulty of detecting rare complications. Subsequently, they published their 10-year follow-up study

involving 196, 129 women over the age of 50, published in the New England Journal of Medicine in 2020 [23]. Prior to this update, the data to guide decisions on long-term therapy was limited to mostly Caucasian postmenopausal women and only for vertebral fracture reduction. Black and colleagues identified an increased hazard ratio relevant to AFF compared to under 3 months of use from 8.86% (95% confidence interval 2.79-28.20) for 3-5 years rising to 43.51% (95% CI 13.7-138.15) for 8 years or more of continuous use. Stopping BPs led to a rapid reduction in risk of AFF. Asian women were found to be at much greater risk of AFF than whites. Importantly, the number of fractures prevented by BP use outweighed bisphosphonate associated AFF at all age ranges. Indeed, 100 osteoporotic fractures were saved for every 1 AFF caused and this benefit persisted. However, by 10 years, in Asians, the number of BP-use AFF was only slightly lower than osteoporotic fracture. They identified a number of other, previously unknown risks for AFF alongside Asian ancestry including short stature, being overweight and steroid use for more than 1 year. This updated study helps to support individualised decision making when it comes to determining the risk-balance of long-term use. The National Osteoporosis Guidance Group (NOGG) recommends fracture risk re-assessment in all after 5 years of BP therapy (figure 1). If the risk of fracture remains high, or BMD <-2.5, then continue. Incident vertebral fracture, independent of BMD, may be an indication for commencement of an alternative agent such as denosumab or teriparatide and should be considered by a specialist. Other alternative strategies may include reduced BP dose (i.e., alternate week dosing), alternative anti-resorptive agents such as raloxifene or menopausal hormonal therapy, or indeed a 2-3 year drug holiday can be considered followed by reassessment, including clinical risk factors and BMD. It is important to remember that the guidance on drug holidays only applies to BPs. For the monoclonal antibody denosumab, following cessation the bone benefit of the drug is lost and an associated risk of rebound osteoporotic fracture is very high [24]. Alternative anti-resorptive therapy is strongly recommended if the decision to stop denosumab is made.

Given the complexities of prescribing and discontinuing BPs, and the difficulties in accurately assessing the long-term benefits and harms, the optimal duration of BP use should be individualised and reviewed regularly on the basis of risk assessment. This should include an individualised assessment of fracture risk using a tool such as the fracture risk

assessment tool (FRAX®) to estimate the probability of major fracture over the course of the next 10 years. Ultimately, communicating some of the uncertainty around prolonged use in low-risk patients on long-term BPs is an essential component of the shared decision making process.

**Figure legends:**

Image 1 Atypical Femoral Fracture radiograph

Figure 1: National Osteoporosis Group Guidelines for assessment of fracture risk and thresholds for pharmacological intervention (www.shef.ac.uk/NOGG)

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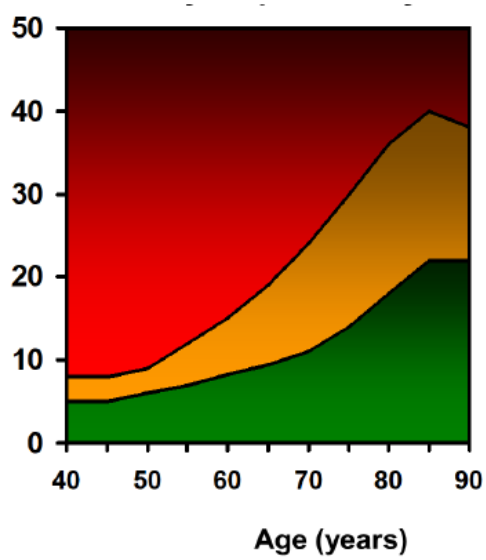
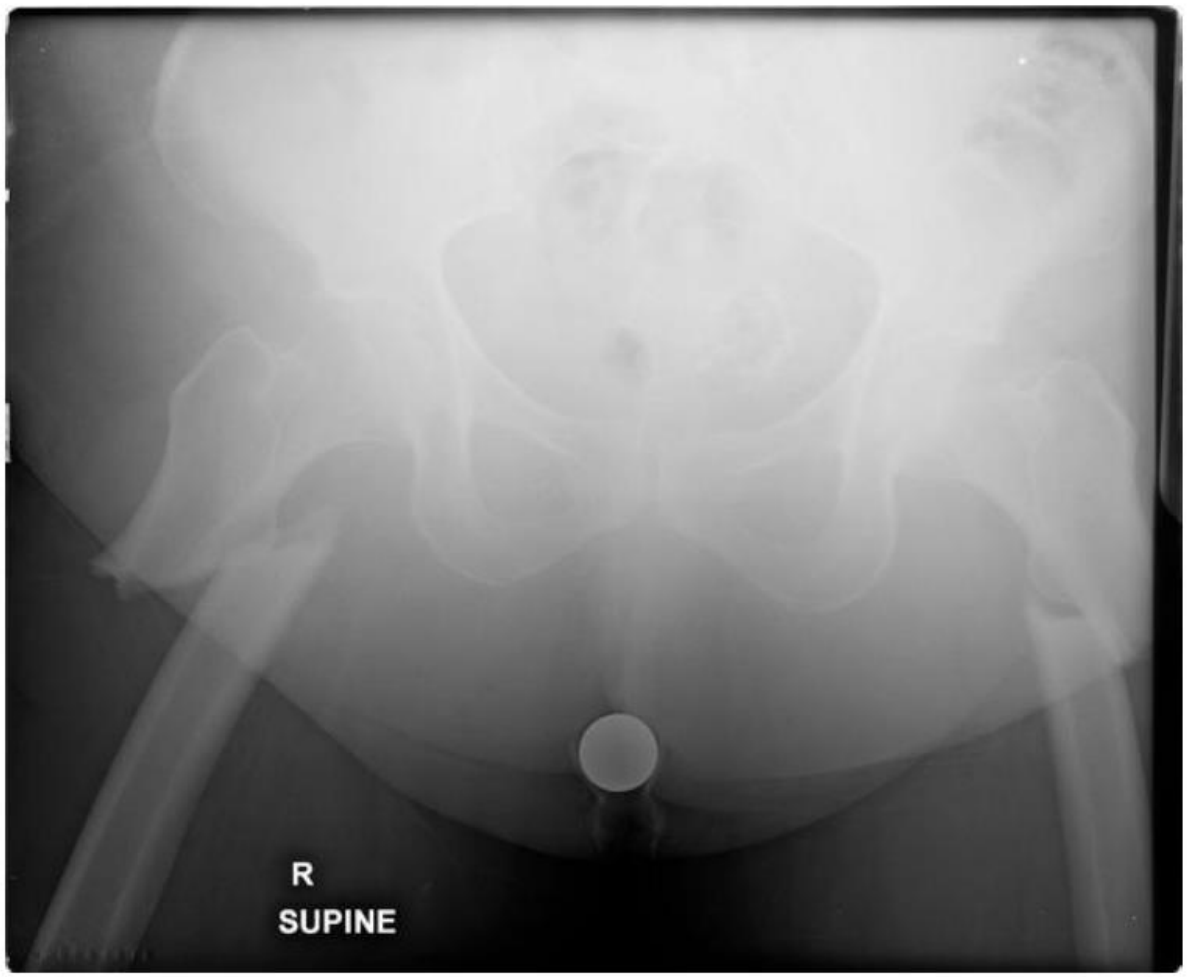
Figure 1. National Osteoporosis Group Guidelines for assessment of fracture risk and thresholds for pharmacological intervention (www.shef.ac.uk/NOGG)




Clinicians should assess the 10-year probability of major osteoporotic fracture after 5 years of bisphosphonate therapy using a fracture risk assessment tool such as FRAX®. If the fracture risk falls within the red area then treatment is recommended, in the amber area bone mineral density should be measured and in the green area, lifestyle and advice and reassurance should be offered. These tools do not replace clinical judgement and ultimately the decision to prescribe or discontinue therapy lies with the prescriber but they can guide clinicians based on a more accurate representation of risk.

Image1. Atypical Femoral Fracture radiograph

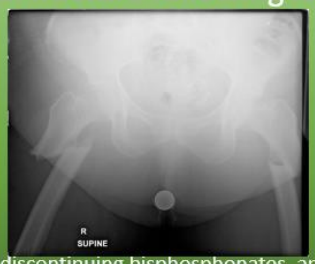
Case courtesy of RMH Core Conditions, Radiopaedia.org, rID: 28937



Graphical Abstract

## Is there ever a right time to deprescribe bisphosphonate therapy?

### Avoiding atypical femoral fracture following long-term bisphosphonate use




Given the complexities of prescribing and discontinuing bisphosphonates, and the difficulties in accurately assessing the long-term benefits and harms, the optimal duration of their use should be individualised and reviewed regularly on the basis of risk assessment.

*Case courtesy of RMH Core Conditions, Radiopaedia.org, rID: 28937*

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