doi.org/10.58931/cdet.2024.2331

The Role of Bisphosphonate Drug Holidays in the Management of Osteoporosis

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Introduction

Osteoporosis is a chronic skeletal disorder of compromised bone strength leading to an increased risk of fragility fractures, particularly with advancing age.[1] More than 2 million Canadians are living with osteoporosis,[2] and osteoporotic fractures are associated with considerable morbidity, increased mortality, and high economic burden to the healthcare system.[3] The ultimate goal of osteoporosis pharmacotherapy is to reduce the risk of fragility fractures.

Bisphosphonates are the most widely used first-line medications for osteoporosis due to their robust anti-fracture efficacy and favourable safety profile,[4] as demonstrated in short-term randomized placebo-controlled trials of 3-years duration with fracture outcome assessed as the primary endpoint.[5] However, the optimal duration of bisphosphonate therapy has been questioned regarding their long-term efficacy and safety given their long half-life in bone.[6] Prolonged use is associated with very rare but serious adverse complications such as atypical femoral fracture (AFF) and osteonecrosis of the jaw (ONJ).[7,8] Moreover, while extension trials indicate that long-term bisphosphonate therapy helps maintain bone density, the evidence supporting further fracture risk reduction with prolonged treatment is less convincing.[9-11] Regarding concerns about rare adverse effects and the attenuated benefit-to-risk ratio with long-term use, several professional organizations have issued guidelines suggesting bisphosphonate drug holidays.[4,11] This approach aims to minimize prolonged exposure and mitigate rare risks while preserving some residual anti-fracture benefits from the persistent drug in the skeleton.[4,11] Here, we review the role of bisphosphonate drug holidays in the long-term management of osteoporosis, the supporting evidence, recommended guidelines on treatment duration, along with key considerations for implementing a bisphosphonate drug holiday.

What Is a Drug Holiday and How Does It Apply to Bisphosphonates?

A drug holiday is defined as the deliberate interruption of pharmacotherapy for a defined period and for a specific clinical purpose.[12] Drug holidays are rarely recommended for chronic conditions since interruption of medical therapy can be harmful in such cases. However, bisphosphonates are unique in the management of osteoporosis. Although their half-lives in the plasma are short, after a baseline period of exposure, bisphosphonates have extended effects on the skeleton as they bind avidly with hydroxyapatite crystals of bone surfaces and become part of the bone matrix.[13] Consequently, bisphosphonates can remain stored in the bone for many years after stopping treatment, continuing to suppress osteoclast-mediated bone resorption. They are gradually released from the bone and reused, leading to a lasting though gradually diminishing anti-resorptive effect.[6,13] This distinct characteristic of bisphosphonates not only raises concerns about the potential risks of extended "over-suppression" of bone turnover, which can hinder bone remodelling essential for repairing skeletal microdamage, but also underscores their clinical effectiveness during a bisphosphonate drug holiday.

Differences in Bisphosphonates

Alendronate, risedronate, and zoledronic acid are potent nitrogen-containing bisphosphonates recommended as first-line pharmacotherapy for osteoporosis in Canada.[4] Oral bisphosphonates have been more widely used due to their ease of accessibility and low cost, whereas intravenous zoledronic acid has been typically used in settings of gastrointestinal intolerance or contraindications to oral bisphosphonates. While comparative head-to-head trials are lacking, a network meta-analysis suggests that the differences in effectiveness among these bisphosphonates in reducing the risk of vertebral, nonvertebral, and hip fractures are likely overall small.[5] However, these bisphosphonates differ in their pharmacokinetic properties in terms of their anti-resorptive potency on osteoclasts, as well as their binding affinity to bone, which may modify their duration of effects during a drug holiday.[6,13] Zoledronic acid has the highest binding affinity, followed by alendronate, then by risedronate.[6] As a result, the anti-fracture benefits may diminish more quickly after discontinuing risedronate compared to alendronate, while zoledronic acid is anticipated to have the longest lasting effects once treatment is stopped.

Evidence From Withdrawal Extension Trials

In line with the pharmacologic properties of bisphosphonates, evidence from 2 randomized withdrawal extension trials[9,10] evaluating the effects of continuing versus discontinuing bisphosphonate treatment, suggest that fracture risk reduction can be maintained for years after

stopping bisphosphonate treatment. These findings support the concept and safety of bisphosphonate drug holidays.

The Fracture Intervention Long-term Extension (FLEX) trial[9] randomized a subset of participants from the original Fracture Intervention Trial (FIT).[14,15] These participants had already received 3–4 years of alendronate and up to 1 year of open-label alendronate. They were assigned to either continue alendronate for 10 years or to discontinue alendronate for a drug holiday for the next 5 years. Comparing 10 years of continued alendronate versus an average of 5 years of alendronate followed by a drug holiday of 5 years, there was a gradual decline in bone mineral density (BMD) and a rise in bone turnover markers (BTMs) in the drug holiday group, though the BMD and BTMs did not return to their pretreatment levels.[9] Fracture risk reduction was an exploratory endpoint and there was no difference in all clinical, nonvertebral, or morphometric vertebral fractures in those who stopped alendronate after 5 years compared to those who continued therapy for 10 years.[9] However, there was a statistically significant lower rate of clinical vertebral fractures in the extended alendronate group (2.4%) versus those in the drug holiday group (5.3%). Subgroup analysis suggests that the greatest reductions in clinical vertebral fractures with extended alendronate occur in women with a T-score of ≤-2.5 at the femoral neck at FLEX baseline and in those with a baseline vertebral fracture.[9]

Similarly, the HORIZON extension trial[10] randomized a subset of participants from the original HORIZON-Pivotal Fracture Trial.[16] These participants had already received 3 annual intravenous (IV) infusions of zoledronic acid and were then assigned to either continue yearly zoledronic acid for an additional 3 years versus stop treatment for a drug holiday. A drug holiday of 3 years after annual zoledronic acid treatment for 3 years resulted in a mild decline in BMD and a slight rise in BTMs compared to ongoing therapy for 6 years. However, the BMD and BTMs were still better compared to pretreatment values. Fractures assessed as secondary endpoints showed no difference in all clinical, clinical vertebral, nonvertebral, or hip fractures in those who stopped zoledronic acid for a drug holiday after 3 years of therapy compared to those who continued therapy for 6 years. However, there were fewer new morphometric vertebral fractures in the extended treatment group (odds ratio = 0.51; p=0.035)[10]. A post-hoc subgroup analysis suggests that this benefit in reducing morphometric vertebral fractures with extended therapy is greatest in those with a total hip or femoral neck T-score of ≤-2.5 and in those with an incident morphometric vertebral fracture during the initial 3 years of zoledronic acid therapy.[17] A second extension of the HORIZON trial,[18] examining annual zoledronic acid for 9 years, versus annual zoledronic acid for 6 years followed by a drug holiday of 3-years, showed no differences in the rate of bone loss and no differences in fractures between the 2 groups.

In summary, evidence from withdrawal extension trials of alendronate and zoledronic acid suggest residual anti-fracture benefits for up to 3–5 years after stopping bisphosphonate treatment. Continuation of therapy does not appear to provide further benefit of reducing all clinical and nonvertebral fractures and may inconsistently reduce vertebral fractures. The reported mixed reduction of vertebral fractures should be interpreted with caution, especially considering that one trial showed a decrease in clinical vertebral fractures, but not morphometric vertebral fractures, while the other trial reported the opposite. Furthermore, it is important to note that a limitation of these extension trials is that bone density changes were the primary endpoint, while fractures were exploratory endpoints owing to small sample sizes.

Although the extension of the Vertebral Efficacy with Risedronate Therapy (VERT-NA) study showed that the risk of new morphometric vertebral fracture remains reduced 1 year after stopping risedronate following 3 years of treatment, despite decreases in BMD and a rise in BTMs,[19] there is no comparable withdrawal extension trial for risedronate.

Evidence from Real-World Studies

Real-world studies offer additional insight into the relative safety of bisphosphonate drug holidays observed in everyday clinical practice. A recent large systematic review that examined real-world studies evaluating bisphosphonate drug holidays found that even after adjusting for various clinical factors that may influence decisions regarding drug holidays, discontinuing bisphosphonate therapy after at least 3 years of treatment was generally safe with no significant rise in fractures during a monitoring period of up to 5 years.[20] These studies primarily included postmenopausal women, with a mean age of 69–75 years, and adherence rates

Years of Bisphosphonate Use	Incidence Rate per 10,000 person-yr
<0.25	0.1 (AFF=4)
0.25 to <3	0.6 (AFF=35)
3 to <5	2.5 (AFF=50)
5 to <8	6.0 (AFF=93)
≥8	13.1 (AFF=95)

Table 1. AFFs according to cumulative bisphosphonate exposure; *adapted from Black, DM, et al., 2020.*

Abbreviations: AFF: atypical femoral fracture

to oral or intravenous bisphosphonate treatments ranged from >50% to 80%. High adherence was recognized as a key factor in maintaining reduced fracture risk during a bisphosphonate drug holiday; while poor adherence, lower baseline BMD, previous fractures, and age >78 years were identified as risk factors for drug-holiday related fractures in the real-world studies.[20] Changes in BMD and BTM were more notable in those who stopped oral bisphosphonates versus IV bisphosphonates during drug holidays, with a suggested trend toward increased fractures in oral bisphosphonate users, particularly with risedronate.[20]

Impact on Rare Adverse Effects

While randomized controlled trials do not provide sufficient data about rare harms related to long-term bisphosphonate treatment, real-world observational studies clearly demonstrate the duration-dependent association between bisphosphonate use and AFF. A large prospective cohort study[7] indicates that although the absolute risk of AFF is very low compared to the higher number of osteoporotic fractures that are prevented by bisphosphonates, the frequency of AFF significantly increases with longer bisphosphonate use. The incidence rises from 2.5 AFFs per 10,000 person-years with 3–5 years of treatment, to 13.1 per 10,000 person-years after more than 8 years of exposure (**Table 1**). The risk of AFF was 5 times higher in Asian women compared to Caucasian women. However, the risk of AFF declines rapidly upon bisphosphonate discontinuation. Even a 1-year drug holiday leads to a significant reduction of AFFs, with the risk nearly returning to baseline levels of 0.6 per 10,000 person-years after 15–48 months off medication, despite the drug's long-term presence in the bone (**Table 2**). These data suggest that although the benefits of bisphosphonates outweigh the rare risk of AFF in the early stages of treatment, the balance becomes less certain for long-term users, particularly among Asian women. It also underscores the beneficial effect of a bisphosphonate drug holiday, even as short as 1 year, in reducing the risk of AFF.

ONJ is more commonly linked to higher-dose bisphosphonate regimens used in cancer treatment. However, the incidence is much lower with bisphosphonate dosing for osteoporosis, with an estimated risk of 2.5 cases per 10,000 patient-years.[8,21] While there seems to be a trend suggesting an increased risk of ONJ with longer cumulative bisphosphonate use, roughly doubling after more than 5-years of exposure,[8] the evidence supporting this is of low quality.[22] Additionally, no studies have yet examined the incidence of ONJ in patients at various points after discontinuing bisphosphonates for a drug holiday.

Suggested Approach to Bisphosphonate Drug Holidays

Several organizations have proposed approaches to bisphosphonate drug holidays in the long-term management of osteoporosis.[4,11] In light of limited evidence, it is unsurprising that guidelines vary on who should take bisphosphonate drug holidays, when they should be initiated, how long they should last, and the criteria for restarting

Months Since Discontinuation of Bisphosphonate	Incidence Rate per 10,000 person-yr
Not yet used	0 (AFF=1)
≤3	4.5 (AFF=200)
>3 to 15	1.8 (AFF=46)
>15 to 48	0.6 (AFF=18)
>48	0.5 (AFF=12)

Table 2. AFFs according to time since bisphosphonate discontinuation; *adapted from Black, DM, et al., 2020.*

Abbreviations: AFF: atypical femoral fracture

therapy. However, most guidelines emphasize the importance of individualizing the approach from a benefit-risk perspective, clinical factors, and patient preference.

The 2023 Osteoporosis Canada Clinical Practice Guideline[4] recommended considering bisphosphonate discontinuation for a drug holiday in all individuals after an initial treatment duration of 3–6 years (**Figure 1**). Individuals at higher risk for fractures, such as those with prior hip, vertebral, or multiple fractures, or those with new or ongoing active risk factors for accelerated bone or fractures should be treated for at least 6 years.

Suitable candidates for a bisphosphonate drug holiday include those who have adhered well to treatment and have shown a good response to the initial bisphosphonate course (e.g., stable/improved bone density and no fractures during treatment). It is suggested that after 3 years off bisphosphonate therapy, patients should be reevaluated for resuming treatment, based on updated BMD and clinical assessment of fracture risk (**Figure 1**). Treatment should be restarted for those who continue to meet the treatment threshold outlined in the guidelines.[4] However, an earlier reassessment than 3 years to resume treatment may be appropriate in those with a higher risk of fracture (such as prior hip or vertebral fracture, or a high Fracture Risk Assessment Tool [FRAX] score), secondary causes of osteoporosis, new fracture, or those with new clinical risk factors associated with rapid bone loss (**Table 3**). The decision to restart therapy sooner for a shorter drug holiday may also be influenced by the overall bisphosphonate exposure (e.g., shorter treatment duration or suboptimal adherence) and the specific bisphosphonate used, with risedronate having the shortest-lived protective effect in bone during a drug holiday (**Table 3**).[4,11] Current evidence does not support the use of BTMs in decisions about bisphosphonate drug holidays.[4,11,20]

A bisphosphonate drug holiday is not recommended if there are concerns about inadequate treatment response or ongoing substantial concern for fracture during the initial treatment period (**Figure 1**).[4] Inadequate response can be defined by the occurrence of new fractures or significant bone density decline (e.g., ≥5%) despite adherence to an appropriate course of bisphosphonate therapy.[4] Adherence to bisphosphonate therapy is consistently low in published studies[23,24] and should be ruled out when there are concerns about inadequate response. Substantial concerns for fracture may involve individuals with active risk factors such as steroid use, other secondary causes, or comorbidities linked to a high fracture risk, particularly in the very elderly.

If a bisphosphonate drug holiday is deemed inappropriate and not recommended, continuing bisphosphonate therapy or switching to an alternative medication is advised as the benefits of continued therapy likely outweigh potential rare harms in these patients (**Figure 1**).[4] Nonetheless, the decision to extend bisphosphonate treatment versus switching to a different class of medication should consider a patient's individualized risk for AFF and ONJ (**Table 4**). Continuing bisphosphonate therapy, including transitioning to IV bisphosphonate, may be a suitable option for individuals with a history of poor

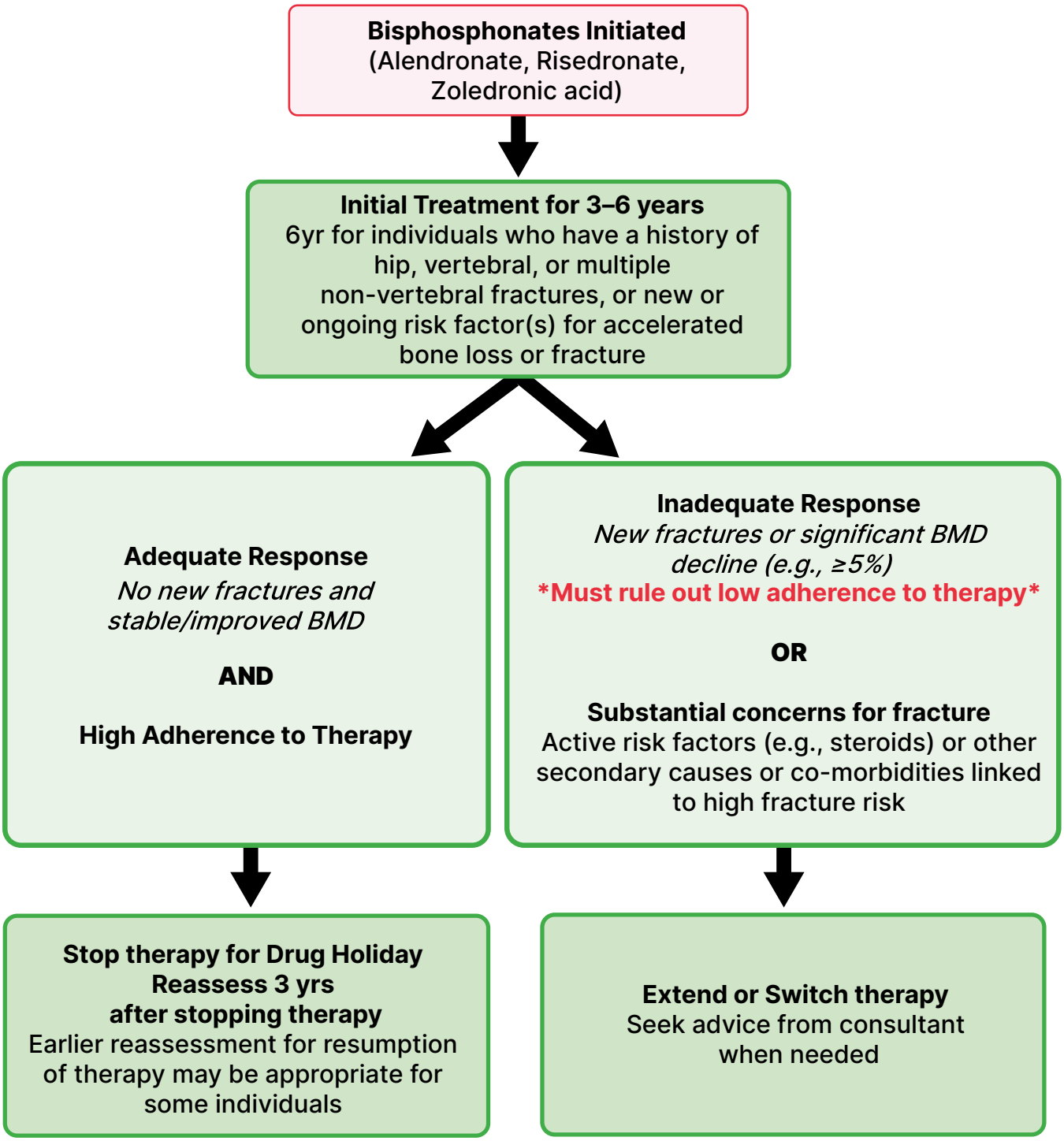

Figure 1. Suggested approach to bisphosphonate duration and drug holiday; *adapted from Morin, SN, et al., 2023.*

Abbreviations: BMD: bone mineral density

Factors that May Warrant a Shorter Bisphosphonate Drug Holiday[4,11]
• Prior hip or vertebral fracture(s)
• Very high fracture risk (e.g., high Fracture Risk Assessment Tool [FRAX] score with low bone mineral density [BMD] and older age considered)
• New fracture(s)
• New clinical risk factor(s) or active secondary cause(s) for osteoporosis or fracture (e.g. glucocorticoid use, aromatase-inhibitor therapy, androgen-deprivation therapy, falls)
• Shorter treatment duration or suboptimal adherence
• Use of risedronate (versus alendronate or zoledronic acid)

Table 3. Factors that may warrant a shorter bisphosphonate drug holiday.

Risk Factors for Rare Adverse Effects with Bisphosphonate Therapy[4,7,8,21]	
Atypical Femoral Fracture (AFF)	**Osteonecrosis of the Jaw (ONJ)**
Longer bisphosphonate duration> 5–8 years	Long-term bisphosphonate use >5 years
Asian ethnicity	Higher bisphosphonate dosing used in cancer
Shorter height, higher weight	Poor dental health, invasive dental surgery
Glucocorticoid use	Glucocorticoid use

Table 4. Key risk factors for bisphosphonate-related AFF and ONJ.

treatment adherence. For individuals at a higher risk of developing AFF or ONJ, switching to an anabolic agent may be a better option. Denosumab is also linked to the risk of AFF and ONJ.[4] Additionally, the challenges of implementing a drug holiday with denosumab, due to the risk of rapid bone loss and rebound vertebral fractures after discontinuation, should be taken into account when considering this treatment option.[4]

Conclusion

Osteoporosis is a chronic progressive disorder that requires long-term management. However, extended bisphosphonate therapy is linked to rare adverse effects, and, after a certain duration, further significant anti-fracture benefits are unlikely. Bisphosphonate drug holidays take advantage of the drug's unique durability in bone beyond their period of use. Extension trials and real-world studies demonstrate that in the vast majority of patients, a bisphosphonate drug holiday can be safely implemented after adherent therapy for 3–6 years, and the risk of AFF rapidly declines even after a 1-year drug holiday. However, the residual anti-fracture effects diminish over time, therefore; careful planning of treatment resumption is needed, particularly in those who remain at higher risk for fractures. Guidelines suggest an approach to bisphosphonate drug holidays but emphasize a tailored approach from a benefit-risk perspective, weighing clinical risk factors for both osteoporotic fractures and rare adverse effects. Further research on intermittent bisphosphonate treatment and sequential therapy may help identify improved long-term strategies for reducing fracture risk and minimizing harm.

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Financial Disclosures

S.K.: None declared.
A.L.: None declared.

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