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Is there a need for a bisphosphonate drug holiday?

Abstract

Data is very scanty with regards to the information to guide decision-making about the initiation and termination of "drug holiday". Bisphosphonates accumulates in bone & their residual benefit in terms of fracture reduction persists for some time after a 3-5 year course of bisphosphonate treatment. A 'drug holiday' refers to a temporary interruption of the osteoporosis treatment with BP, and then reintroducing it after a period of rest. Drug holiday may be considered for patients whose follow-up BMD reveal normal or osteopenic levels with low fracture risk probability. The "drug holiday" can be observed for 3-5 years or until there is a fracture or noticeable fall of BMD whichever comes first. In case of high fracture risk, treatment is given for 6-10 years. The "drug holiday" of 1-2 years can be taken or until there is significant decrease in BMD or the patient has a fracture, whichever comes first. Increase in bone turnover markers or fall in BMD should be considered as indicators to decide when to end a drug holiday.

Keywords: bisphosphonate, drug holiday, osteoporosis

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Introduction to osteoporosis

Normal bone growth and remodelling–a tightly coupled process of bone resorption and new bone formation. Osteoporosis-related bone loss occurs when bone resorption exceeds bone formation. Osteoporosis characterized by reduced bone mass, associated with microarchitectural changes in bone structure and increased skeletal fragility.[1]

World Health Organization Criteria for Classification of Osteopenia and Osteoporosis (Table 1) (Figure 1).[2]

Table 1 World Health Organization Criteria for Classification of Osteopenia and Osteoporosis[2]

Classification	BMD	T-score
Normal	Within 1 SD of the mean level for a young-adult reference population	T-score at -1.0 and above
Low Bone Mass (Osteopenia)	Between 1.0 and 22.5 SD below that of the mean level for a Young-adult reference population	T-score between -1.0 and -2.5
Osteoporosis	2.5 SD or more below that of the mean level for a Young-adult reference population	T-score at or below -2.5
Severe or Established Osteoporosis	2.5 SD or more below that of the mean level for a Young-adult reference population	T-score at or below -2.5 with one or more fractures

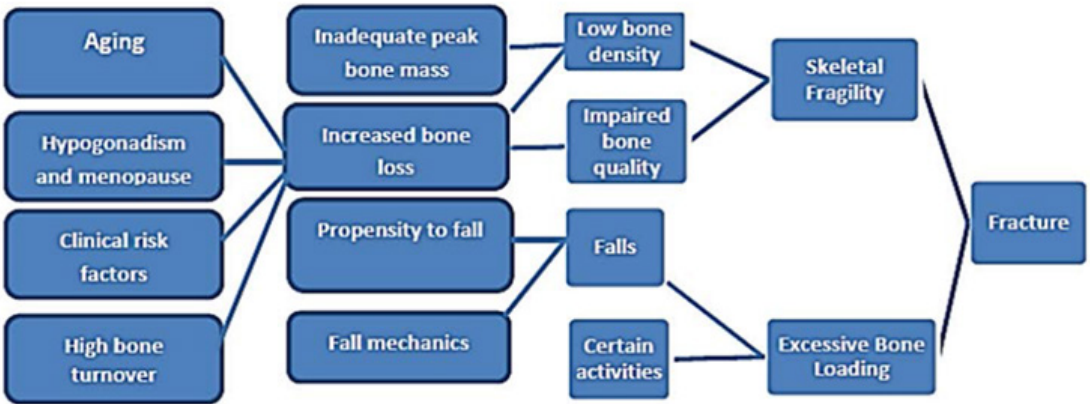

Figure 1 World Health Organization Criteria for Classification of Osteopenia and Osteoporosis[2]

Statistics & prevalence[3,4]

44 million people of ≥50 years have osteoporosis or low bone mass (IOF). Osteoporosis causes more than 8.9 million fractures annually. It results in osteoporotic fracture every 3 seconds. 1 in 3 women and 1 in 5 men aged over 50 years will experience osteoporotic fractures.[4]

Osteoporosis incidence increases with age: 37% of women between the ages of 50 and 59, 50% between the ages of 60 and 69, 75% between ages 70 and 79, 87% of women older than 80 years of age. Number of persons > 50 with osteoporosis will increase to 12 million by 2010 and to nearly 14 million by 2020. 1 out of 2 women; 1 out of 8 men will be affected by osteoporosis in their lifetime.[3]

Types of osteoporosis[3]

Primary Osteoporosis is result of aging and other risk factors and not associated with any other disease processes. Secondary Osteoporosis is result of underlying disease process, such as malabsorption syndromes or hyperparathyroidism (Figure 2).

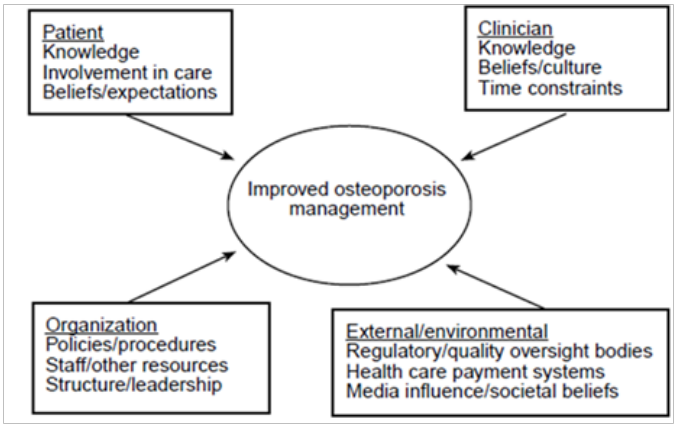

Figure 2 Factors Affecting Osteoporosis Management Improvement Initiatives[3]

FDA-approved options for osteoporosis[2]

Bisphosphonates (Alendronate, Ibandronate, Risedronate and Zoledronic acid), Calcitonin Estrogen Agonist/Antagonist (Raloxifene), Estrogens and/or Hormone Therapy, Tissue-selective Estrogen Complex (Conjugated Estrogens/Bazedoxifene), Parathyroid hormone 1-34 (Teriparatide) RANK ligand inhibitor (Denosumab).

Biochemical markers of bone turnover[2]

These include Resorption markers-serum Ctelopeptide (CTX), Urinary N-telopeptide (NTX), Serum bone specific alkaline phosphatase (BSAP), Osteocalcin (OC), Aminoterminal propeptide of type I procollagen (PINP).

Predict risk of fracture independently of bone density in untreated patients.

Predict rapidity of bone loss in untreated patients.

Predict extent of fracture risk reduction when repeated after 3-6 months of treatment with FDA approved therapies.

Predict magnitude of BMD increases with FDA-approved therapies.

The biochemical markers help determine adequacy of patient compliance and persistence with osteoporosis therapy & determine duration of 'drug holiday' and when and if medication should be restarted.

Bisphosphonates[1]

Structurally related to pyrophosphates which are incorporated in bone matrix. Inhibit osteoclast function & reduce osteoclast number by inducing apoptosis. Retained in skeleton for quite longer periods but its consequences, if any, are unknown. Mainstay of treatment for osteoporosis. Robust efficacy in preventing fractures in registration trials lasting 3 to 4 years. Having high affinity for bone and reduce bone resorption, thereby slowing bone loss. Bring about loss of osteoclastic resorptive function and accelerate osteoclast apoptosis. Inhibit farnesyl pyrophosphate synthase, an enzyme in the HMG-CoA reductase pathway.

History behind the concept of drug holiday

This is to minimize long term exposure and to avoid potential adverse effects. Always analyze the risk benefit ratio for a drug holiday. Maintain "some degree" of antifracture efficacy through antiresorptive activity of the residual bisphosphonate in the bone. The rank order for binding affinity is zoledronate > alendronate > ibandronate > risedronate.[6]

No data and may have a prolonged residual time in bone (and residual therapeutic effect after stopping), "bisphosphonate holidays" may be considered. As a result "Drug Holiday" concept has emerged as a break in bisphosphonate therapy. No guidelines on "drug holiday". Bisphosphonates accumulates in bone & their residual benefit in terms of fracture reduction persists for some time after a 3-5 year course of bisphosphonate treatment. A 'drug holiday' refers to a temporary interruption of the osteoporosis treatment with BP, and then reintroducing it after a period of rest. This has emerged as a break in bisphosphonate therapy; resets the clock for ONJ & AFF.[8]

Concept of bisphosphonates drug holidays[7]

There are no data providing information on how to monitor osteoporosis patients or guide decision-making about the initiation and termination of "drug holiday". It can be considered for patients whose follow-up BMD reveal normal or osteopenic levels with low fracture risk probability. It can also be suggested that repeat BMD measurement as well as 10-year fracture risk probability assessment be carried out 3-5 years of osteoporosis drug holiday.

No Guidelines on "Drug Holiday", following points to be considered1

No consensus on when to restart the treatment (or which drug). Treatment is given for 3-5years if fracture risk is considered mild & then discontinued. The "drug holiday" can then be continued until there is a fracture or noticeable fall of BMD whichever comes first. Bisphosphonate treatment is given for 5 years if fracture risk is considered moderate. The "drug holiday" can be observed for 3-5 years or until there is a fracture or noticeable fall of BMD whichever comes first. In case of high fracture risk, treatment is given for 6-10 years. The "drug holiday" of 1-2 years can be taken or until there is significant decrease in BMD or the patient has a fracture, whichever comes first. Increase in bone turnover markers or fall in BMD should be considered as indicators to decide when to end a drug holiday.

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Clinical trial evidences

This is to show how continuation of Bisphosphonate therapy is important (Table 2);

Table 2 Are there risks associated with bisphosphonate drug holidays?

Levels of evidence	Trail designs
Level	At least 1 property conducted randomized controlled trail, systematic review, or meta-analysis
Level	Other comparison trails; non randimized cohort, case-control, or epidemiologic studies; and prefereably more than 1 study
Level	Expert opinion or consensus statements

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 pre-treatment 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).

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 bisphosphonate administration or by high compliance to therapy.

When and for whom should bisphosphonate holidays be considered?

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 discontinue bisphosphonate therapy, and many who are at moderate risk might also be candidates for drug holiday.

Monitoring during the drug holiday

There are no data to suggest the most appropriate time to reinitiate 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.

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. Estimated fracture and fall risk, remaining life expectancy, and response and tolerance 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.

The 2010 Osteoporosis Canada guidelines state that "Individuals at high risk for fracture should continue osteoporosis therapy without a drug holiday [grade D]."

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Extension of the alendronate Fracture Intervention Trial: FLEX

Subjects who had 5 years of alendronate treatment in FLEX study → second 5-year study where subjects were randomized to either continue alendronate or start placebo.

What happens when alendronate is discontinued for up to 5 years??

On discontinuation of alendronate therapy, rates of change in BMD at the hip and spine resumed at the background rate→ anti-resorptive effect is slowly lost. At the lumbar spine (about 1.5% in 5 years). A slow and progressive loss of femur bone mineral density (BMD) (<3% in 5 years). Women who discontinued alendronate after 5 years showed a moderate decline in BMD and a gradual rise in biochemical markers. Higher fracture risk for clinical vertebral fractures.

Recommendation

Women at very high-risk of clinical vertebral fractures may help by continuing beyond 5 years.

The extension of the risedronate VERT-NA

1-year follow up of subjects who completed 3 years of blinded therapy with risedronate or placebo, then stopped their study medications.

What happens in the year off treatment??

BMD decreased in the former risedronate users, but remained higher than baseline and higher than in the former placebo subjects. Bone turnover markers increased and were no different from the former placebo subjects.

HORIZON In the 3-year extension of the zoledronate HORIZON pivotal fracture trial: subjects who had 3 years of zoledronic acid then went to placebo or zoledronic acid for another 3 years. There were significantly fewer morphometric vertebral fractures in the group that continued treatment compared with the placebo. Patients at high fracture risk may benefit from continued treatment.

Some other evidences

Meta-analysis by Brown et al. concluded that drug holidays should only be considered in low-risk patients and in select patients at moderate-risk of fracture after 3-5 years of therapy. Whereas, when BP is prescribed to patients at high-risk of fracture, their antifracture benefits considerably outweigh their potential for harm.

Adverse effects---but how many??

These include gastrointestinal effects, acute phase reactions, musculoskeletal pain, atrial fibrillation, Subtrochanteric or Diaphyseal fracture, Osteonecrosis of the jaw (ONJ), cutaneous hypersensitivity reactions and renal impairment.

Occurrences of subtrochanteric or diaphyseal fractures has been reported with long-term use of BP but is not substantiated by epidemiologic studies or prospective randomized controlled trials. Also, the possible mechanism of subtrochanteric or diaphyseal fractures it is unclear whether it is the effect of the drug or is due to underlying osteoporosis. Even though the risks of osteonecrosis of the jaw (ONJ) and atypical femur fractures (AFFs) may increase after 5 years of bisphosphonate therapy, the likelihood remains very low.

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.

ONJ

In osteoporosis, absolute risk of bisphosphonate-associated osteonecrosis of the jaw is approximately 1 case per 100 000 person-years. Canadian survey found: cumulative incidence of bisphosphonate-associated ONJ was 0.4% (400 in 100 000) for cancer patients but only 0.001% (1 in 100 000) for osteoporosis patients. Pathologic 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.

Atypical subtrochanteric and diaphyseal femur fracture

To date, there has been no direct causal evidence linking the use of bisphosphonates to the occurrence of AFF, case reports, case series, and cohort analyses demonstrating an association. Long-term clinical trial data: 10 years for alendronate, 7 years for risedronate, 6 years for zoledronic acid), have not demonstrated an increase in AFF incidence with prolonged bisphosphonate exposure. Pooled phase 3 clinical trials of bisphosphonates found no increased incidence of AFF.

Up to half of AFFs occur in people not exposed to bisphosphonates. AFF are more associated with presence of osteoporosis than with exposure to bisphosphonates. For every 100 or so reduction in typical femoral neck or intertrochanteric fractures, there was an increase of 1 subtrochanteric fragility fracture.

Risk vs Benefit

For every 100 reduction in typical femoral neck or intertrochanteric fractures, there was an increase of 1 subtrochanteric fragility fracture. Wang Z et al., 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 women. In a systematic review bisphosphonates in high-risk individuals decreases fracture risk by 20% to 50% over 3 years of therapy. Bisphosphonate Task force of ASBMR reported that bisphosphonates in high-risk patients (eg, with previous vertebral fracture), prevented 1000 non vertebral & 2300 clinical vertebral fracture per 100 000 person-years of treatment. For a moderate-risk population (femoral neck BMD T-score < -2.0) 700 non vertebral & 1000 clinical vertebral fractures prevented per 100 000 person-years with treatment. For 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 health canada concluded

Although the risk is higher with bisphosphonate use, it is still extremely small. The benefits of using bisphosphonate drugs in

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preventing fractures associated with osteoporosis outweigh the risk of an atypical femur fracture

Bisphosphonates for Osteoporosis — Where Do We Go from Here?

"Important Limitation of Use" statement: "The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis." To optimize the efficacy of bisphosphonates in reducing fracture risk, decisions to continue treatment must be based on individual assessment of risks and benefits and on patient preference.

Bisphosphonates — Where Do We Go From Here?

For purposes of comparison, proportions of patients with fractures in the core registration study are based on enrolment in the extension studies. Prove to be good candidates for discontinuation of bisphosphonate therapy after 3 to 5 years, whereas patients at increased risk for fracture (e.g., older patients with a history of fracture and a bone mineral density remaining in the osteoporotic range) may benefit further from continued bisphosphonate therapy. Clearly, given the potential for cumulative risk, caution should be exercised in switching between bisphosphonates and other potent antiresorptive medications. Further investigation into the benefits and risks of long-term therapy, as well as surveillance of fracture risk after discontinuation of bisphosphonate therapy, will be crucial for determining the best regimen of treatment for individual patients with osteoporosis.

The FDA review of the data focused on studies in which bisphosphonate drugs had been administered for at least 3 years and that had captured fracture data systematically and completely. We therefore focused on three long-term extension trials — the Fosamax Fracture Intervention Trial Long-Term Extension (FLEX), the Reclast Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly– Pivotal Fracture Trial (HORIZONPFT) extension, and the Actonel Vertebral Efficacy with Risedronate Therapy–Multinational Trial (VERT-MN) extension — in which the duration of treatment ranged from 6 to 10 years.

All three studies were extensions of the initial fracture registration trials that had enrolled postmenopausal women with baseline fractures, low bone mineral density T scores (−1.5 or less), or both. The FLEX and HORIZON-PFT trials used a randomized withdrawal design in which patients who had previously been receiving bisphosphonate treatment were enrolled in the extension periods and underwent repeated randomization to receive either placebo or continued bisphosphonate treatment. Unlike the registration trials, the extension studies used bone mineral density as the primary outcome measure.

Our analyses of the extension studies include both bone mineral density and fracture outcomes (which are limited to vertebral and nonvertebral osteoporotic fractures). Overall, findings with respect to all three bisphosphonates were remarkably similar in terms of mean treatment-related increases in bone mineral density through 5 years. Continuation of treatment beyond 5 years resulted in maintenance of bone mineral density in the femoral neck and further increases in bone mineral density at the lumbar spine.

Monitoring: How should it be done and is it possible??

If a drug holiday is advised, reassessment of risk should occur sooner for drugs with lower skeletal affinity, with a suggestion to reassess after 1 year for risedronate, 1–2 years for alendronate, 2–3 years for zoledronic acid. Decrease in BMD or an increase in bone turnover marker (BTM) might be used to decide when to end a drug holiday. Yet, there is lack of data on risk for fracture when these surrogate markers begin to change off bisphosphonates. There is no evidence that fracture risk is reduced if BMD is stable or BTM is low off treatment.

What was FDAs stand?

On 9 September 2011, the US Food and Drug Administration (FDA) held a hearing to review the long-term safety and efficacy of bisphosphonates. The majority of the advisory committee (17 to 6) voted that labelling for these drugs should further clarify the duration of use for bisphosphonates but there was a lack of panel consensus on label changes.[8]

FDA: There was consensus that the data did not support a regulatory restriction on the duration of drug. The FDA wrote their opinion on this perspective, suggesting re-evaluation of the need for continuing bisphosphonate therapy beyond 3–5 years in individual patients. The FDA suggested that a drug holiday may not be advisable in high-risk patients, but for patients discontinuing treatment, there were no concrete recommendations on what should be done (Table 3).

Table 3 Guidelines for bisphosphonate holiday

Fracture risk	Clinical profile and tests	Is a bisphosphonate holiday appropriate?
low (<10% 10-y risk)	No important clinical risk factors for fracture	Yes
		At low fracture risk, should be withdrawn from therapy
		Monitor at extended intervals (3-5y)
Moderate (<10%-20% 10-y risk)	Assess clinical risk factors for fracture	Maybe
	Assess femoral neck BMD	If vertebral fractures are found, stratify patient as high risk and continue bisphosphonate therapy
	Request lateral spine X-ray scan to investigate for any subclinical vertebral fractures	If there is no previous history of fragility fracture, a drug holiday can be considered if femoral neck BMD T-score is >-2.5 and there are no other important clinical risk factors
High (<20%-20% 10-y risk or previous fragility vertebral or hip fracture or > 1 fragility fracture after the age of 40 y)	NA	No
		Continue bisphosphonate therapy or switch to another proven agent such as teriparatide or denosumb

Abbreviations: BMD, bone mineral density; NA, not applicable.

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National Osteoporosis Guideline Group[9]

High risk patients include;

1. Post treatment T-score ≤ -2.5 with history of fragility fractures.
2. History of hip/vertebral/ or multiple fragility fractures (secondary prevention).
3. Continuing oral glucocorticoid therapy of ≥7.5mg/day prednisolone or equivalent.
4. Continuing high risk patients (frailty, frequent falls, and age ≥75).
5. Those who sustain low-trauma fracture(s) during treatment (exclude poor adherence to treatment and causes of secondary osteoporosis).

Recommendations

Bisphosphonates - alendronate and risedronate, reduce risk of non-vertebral and vertebral fractures in women with osteoporosis. Uncertainty on optimal duration of therapy, reports of rare but serious adverse events such as osteonecrosis of the jaw and external auditory canal and atypical femoral fractures. Decisions to stop or continue bisphosphonate treatment after 5 years (3 years for zoledronate) should be based on individual assessment of risks and benefits, following an informed discussion with the clinician and the individual patient. Patients require assessment using FRAX programme and BMD scan after 5 years to decide on appropriateness of on-going treatment:

a. If a total hip or femoral neck BMD T-score is <-2.5 or the patient is above the NOGG intervention threshold after 5 years then treatment should be continued.

b. If the total hip or femoral neck BMD T-score is > -2.5 and the patient is below the NOGG intervention threshold after 5 years then treatment withdrawal should be considered ('Drug Holiday').

A drug holiday should be viewed as a temporary, not permanent, suspension of active therapy. It should be remembered that discontinuing a bisphosphonate may not necessarily be a holiday from treatment, because persistence of the antiresorptive effect is expected for an undefined period of time. Patients have adequate levels of dietary calcium and vitamin D during treatment break. The situation with patients after a very long duration of treatment (e.g. > 10 years) is less clear. It may still be appropriate for 'high risk' patients to continue without a Drug Holiday, but the definition of high risk for these purposes should probably be more limited. The situation should be judged on a case by case basis and the current uncertainties of risk versus benefit discussed with patients where appropriate. Local opinion suggests that the majority of patients deemed 'high risk' after 10 years of treatment would benefit from a Drug Holiday.

Osteoporosis drug holiday guidelines for GPs10

Review indication for all patients prescribed bisphosphonates. Check treatment adherence after 3 months of initiating treatment. Re-assess patients at high risk of osteoporotic fracture every 5 years. Consider a treatment break (Drug holiday) for patients who have been on oral bisphosphonates for 5 years or in 3 years for Zoledronic acid (Patients should continue calcium & vitamin D supplementation).

Drug holiday duration –

Risedronic acid, Ibandronic acid - 2 years

Alendronic acid, Zoledronic acid - 3 years

Consider discontinuation of therapy for low risk patients. Reassess fracture risk after a new fracture regardless of when this occurs or at the end of drug holiday and re-continue treatment if indicated. The duration of treatment and the length of the 'holiday' should be tailored to individual patient circumstances and based on individual assessments of risk and benefit based on BMD monitoring and FRAX. The duration of the holiday should be based on clinical judgment.

Suggestions

FRAX (Fracture Risk Assessment) tool can be used to predict fracture probability in women currently or previously treated for osteoporosis, which may help in guiding the need for continued treatment or treatment withdrawal. In the higher-risk population treated for the right duration, bisphosphonates have an exceptionally high benefit/risk ratio. While lower-risk patients may be offered a 'drug holiday' after 3–5 years of use, higher-risk patients should be counselled on the greater risk for fracture if discontinuation is initiated. The strength of the evidence for fracture reduction in high-risk individuals and the rarity of long-term adverse effects indicate that the benefits of continued treatment outweigh the risks in individuals at high risk of fracture.

Conclusion

While amino bisphosphonates 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.

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Conflict of interest

The author declares there is no conflict of interest

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