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Bisphosphonate Drug Holidays in Primary Care: When and What to do Next?

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Abstract

Purpose of Review—This review describes the rational for bisphosphonate holidays, summaries key evidence to support the concept, and provide a roadmap to help clinicians initiate, monitor and discontinue a bisphosphonate drug holiday

Recent Findings—Randomized trials and data from large observational studies are available to determine the short and long-term bisphosphonate benefits (prevention of fracture) and harms (principally atypical femoral fractures and osteonecrosis of the jaw). Mounting evidence points towards a causal relationship between bisphosphonate use and AFF and ONJ, particularly with >5 years of use. Multiple studies now confirm the risk of AFF falls rapidly after BPs are discontinued.

Summary—Osteoporosis patients without previous hip, vertebral or multiple non-spine fractures who are successfully treated with oral bisphosphonates for 5 years (3 years if intravenous), should be offered a 3–5 year drug holiday, particularly if hip BMD T-score is >−2.5. Bisphosphonates should only be continued beyond 10 years (6 years if parenteral) in patients at very high risk of fracture.

Introduction

In virtually all high functioning health care delivery systems, primary care providers are responsible for efficiently managing multiple chronic conditions in their aging patients, including osteoporosis. The concept of stopping or changing anti-fracture treatment after a period of treatment with bisphosphonates is now well known to primary care providers, but many questions about the exact purpose, timing, and effectiveness remain. The purpose of this review is to summarize, from a primary care perspective, the most recent published data relevant to the concept of a bisphosphonate drug holiday and to suggest a simplified approach to be consider in clinical practice. This review will not cover osteoporosis

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Compliance with Ethical Standards

Conflict of Interest

Douglas C Bauer declares no conflict of interest.

Bo Abrahamsen reports grants and personal fees from UCB, grants from Novartis, personal fees from Amgen, personal fees from Pharmacosmos, grants and personal fees from Kyowa-Kirin, outside the submitted work

Human and Animal Rights and Informed Consent

Informed consent was obtained for all studies performed by the authors

pathophysiology, basic epidemiology, screening or initial pharmacologic treatment, all of which have been extensively discussed elsewhere [1].

What is a Drug Holiday and Who Recommends Them?

For the purposes of osteoporosis therapy, drug holidays can be defined as the temporary or possibly permanent discontinuation of effective anti-fracture therapy following some period of continuous use. Several professional organizations have issued practice guidelines supportive of drug holidays, including the American Society of Bone and Mineral Research (ASBMR) [2], the Endocrine Society[3], the European Menopause and Andropause Society (EMAS) [4], the American Association of Clinical Endocrinology (AACE) [5], and the International Osteoporosis Foundation (IOF) [6].

Why Consider a Drug Holiday?

The decision to initiate or continue any effective osteoporosis treatment should depend upon an informed assessment of the potential benefits and potential risks, preferably based upon high quality, long-term randomized trials with fracture and common side effect endpoints. After several such trials were published in the 1990s, as with other chronic conditions there was an expectation that the substantial antifracture benefits observed in short-term trials would be extended over decades of use. Furthermore, the relative paucity of serious BP side effects in those early trials, other than GI irritation which could be easily managed in most cases, suggested that long-term and perhaps lifelong BP therapy would be possible. Unfortunately, the increasing reports of rare but potentially serious BP side effects, particularly atypical femoral fractur (AFF) and osteonecrosis of the jaw (ONJ), have mandated additional consideration of long-term BP efficacy, safety and risk mitigation stratifies.

Evidence of short-term BP benefits

There is now substantial evidence from multiple placebo-controlled BP trials confirming the anti-fracture benefits of both oral and intravenous BPs given for 3–5 years, with only a handful of studies beyond 5 years. In general, oral and parenteral BP use is associated with a 40–50% reduction in incident vertebral fracture and a 20–30% reduction in non-spine fractures [7]. Importantly, hip fracture risk is reduced by about 50% with BP treatment. For example, in the Fracture Intervention Trial (FIT) among older women with low BMD (femoral neck T-score between −1.7 and −3.0), 5 years of oral ALN reduced vertebral fracture risk by about 50% in those with and without existing vertebral fracture. Among women with existing vertebral fracture, 3 years of ALN reduced all clinical and hip fracture risk by 28% and 51%, respectively [8, 9]. Conversely, among those in FIT without exiting vertebral fractures, after 5 year of ALN the risk of any clinical fracture was reduced but did not reach statistical significance (RH = 0.86 95% CI: 0.71 to 1.01)[9]. Subsequent post hoc analyses suggested that 5 yr of ALN reduced clinical fractures among those women with baseline femoral neck BMD T-scores <−2.5 [10]. Several studies of intravenous zoledronic acid, including the placebo-controlled Horizon study, have found similar risk reductions for vertebral, non-spine and hip fracture regardless of vertebral fracture status [1, 11].

Evidence of long-term BP benefits vs stopping

As with the assessment of short-term efficacy, the best evidence to establish the long-term benefits of prolonged osteoporosis therapy should be generated from prolonged (10 years or more) placebo-controlled trials. Unfortunately, such trials do not exist, and as with other chronic conditions such as HTN and DM, long-term placebo-controlled trials are unlikely to be done in the future due to ethical concerns about leaving patients at increased fracture risk untreated when effective treatments are available. Although there are a number of open-label extensions of completed BP trials beyond 3–5 years, these studies may be biased if those who continue during the extension differ substantially from those who do not.

Randomized discontinuation studies, where participants who receive an effective active treatment in a completed trial are re-randomized to either continue active treatment or switch to placebo without unblinding, also provide high-quality evidence about the benefits of long-term therapy. Two such trials exist for bisphosphonates, the Long-Term Extension of the FIT (FLEX) and the Horizon Extension trial. In FLEX, 1099 women who had been initially randomized to oral ALN for 5 years, were re-randomized to either continue ALN or switch to placebo for an additional 5 years [12]. In the Horizon extension study [13], 1233 postmenopausal women who had been initially randomized to yearly zoledronic acid infusions for 3 years were re-randomized to either continue zoledronic acid for an additional 3 years or switch to a placebo infusion. Both studies found that vertebral fractures were about 50% higher in those who discontinued BP therapy compared to those who continued BP therapy. Although both studies demonstrated gradual hip bone loss in those switched to placebo, neither study found evidence of an increased risk of non-spine or hip fracture. However, such findings must be considered exploratory as neither FLEX nor the Horizon Extension study were adequately powered for non-spine or hip fracture outcomes. Another important limitation is that results of the FLEX and Horizon-PFT Extension studies may not be applicable to other commonly used BPs, such as risedronate.

Large cohort studies describing the fracture experience among individuals who received prolonged BP therapy compared to those who received short-term treatments are also available [14–17]. As such observational analyses are susceptible to bias and confounding and therefore less reliable than randomized study designs, it is not surprising that published cohort studies are inconsistent. For example, using longitudinal data from 39,000 Kaiser Permanente patients, Adams et al. [15] found that after at least 3 years of continuous BP use, compared to those who continued treatment, those who discontinued BPs had similar hip fracture outcomes (RH = 0.95, CI: 0.83 to 1.10) and the risk other fractures was slightly lower in those who discontinued (RH= 0.92, CI: 0.84 to 0.99). Conversely, using longitudinal BP use data from Medicare, Curtis et al. [16] found that after at least 3 years of continuous alendronate, risedronate or zoledronic acid, compared to those who continued treatment those who discontinued BPs had a 27–55% increased risk of hip fracture and 22–59% increased risk of vertebral fracture. Importantly, neither of these studies was able to assess the reason for BP discontinuation, and both were performed well before the 2016 publication and dissemination of major drug holiday guidelines in the US [2]. Therefore, in these observational studies it is unclear how the decision to interrupt or stop treatment

was made, and specifically if these discontinuations were intended drug holidays or due to comorbidities, adverse events or other unspecified reasons.

Evidence of short and long-term BP side effects

As with the benefits of therapy, in principle the side-effect profile of a chronic medication is best assessed by high quality blinded placebo-controlled trials that focus on the collection of potential adverse experience. The efficacy trials discussed above confirmed that approved oral and intravenous BPs have relatively few common side effects, and those that are likely to be seen in clinical practice, such as GI irritation, can be managed by temporary discontinuation, concurrent acid suppression therapy or switching to another BP. On the other hand, two rare side effects, AFF and ONJ, are sufficiently serious that they have clearly influenced both patient and provider decisions about the use of BPs [18]. Unfortunately, these rare side effects are very difficult to study in RCTs for the simple reason that very few events may occur even with prolonged study in large RCTs. For example, as newly identified disease entities, neither AFF nor ONJ were detected with routine surveillance in a meta-analysis pooling the FIT, FLEX and Horizon randomized trials [19] which included over 14,195 bisphosphonate-treated women followed for up to 10 years.

Atypical Femoral Fractures (AFF)

Because they are often bilateral, occur with little or no trauma and require surgical repair, AFFs are the most serious potential side effect of long-term bisphosphonate use. First described in case series in 2005 [20], these radiographically distinct fractures located in the subtrochanteric and femoral shaft have been increasingly reported among individuals with high dose BP dosing for oncologic purposes and, much more infrequently, among those receiving standard BP dosing for fracture prevention. Fortunately, a widely accepted case definition has been developed and refined by an ASBMR task force (Table 1) [21]. Although the exact pathophysiology remains uncertain, many experts believe that AFFs are stress fractures exacerbated by impaired bone repair from prolonged exposure to anti-remodeling drugs [22].

Since only a handful of AFFs have been observed in RCTs, the best data about incidence, risk factors and clinical presentation come from large cohort studies with radiographic review and confirmation of AFFs, again with the caveat that such observational studies are at risk of bias and confounding compared to RCTs. To date, several prospective population-based studies have been published (Table 2), including 1 using Swedish national healthcare data and 4 using Kaiser HMO data [23–27]. The population studied, comparator and covariate adjustment for each cohort studied differed somewhat, and in these studies the relative risk of AFF among BP users ranges from 2 to 40. Conversely, the absolute risk of AFFs among BP users has been similar and remarkably low (Table 2) ranging from 0.3–0.7 AFFs/100,000 person-years among those who report little or no BP use, and increasing to 39–110 AFFs/100,000 person-years with 6–8 years of use and 112–139 AFFs/100,000 person years with >8 years of use.

Atypical femur fractures are very rare compared with osteoporotic fractures. Hence, an extremely important point for both patients and providers is that in almost all circumstances these risks compare extremely favorably to the number of fractures that will prevented by several years of BP use. For example, Black et al.[1]have estimated that for a hypothetical group of 1000 65 year old Caucasian females of average risk for fracture, 3 years of BP therapy prevents approximately 71 vertebral and 29 non-spine fractures (including 11 hip fractures). In that same group of 1000 women, assuming the relative risk for BP use and AFF ranges from approximately 2 to 12, the number of AFFs caused during that same 3 year period ranges from 0.08 to 1.25. Although far less impactful than prolonged BP use, other notable risk factors for AFF including Asan ancestry, rheumatoid arthritis and prolonged exposure to oral corticosteroids or proton pump inhibitors, but low bone mass and diabetes do not appear to be independent risk factors for AFF [22].

Relevant to the decision about initiation of a drug holiday, both the Swedish and Kaiser Southern California cohorts found that after discontinuation of BP, the risk of AFF fell rapidly. For example, both Black et al. and Schilcher et al. [23, 26] reported that among BP users who discontinued, the risk of AFF fell by 70% or more over the following year.

Osteonecrosis of the Jaw (ONJ)

ONJ is a very rare complication of bisphosphonates given for osteoporosis but is more common among cancer patients receiving higher doses of anti-resorptives, typically for myeloma, breast cancer or prostate cancer. ONJ is defined as exposed bone in the maxillofacial region that does not heal within 8 weeks in a patient with exposure to an antiresorptive agent who has no history of radiation therapy to the craniofacial region [28]. For osteoporosis patients, the incidence of ONJ is generally reported as less than 1 case in 10,000 patient years [28]. Most cases are mild and can be managed conservatively but the clinical spectrum is broad with some patients requiring extensive jaw and face surgery. A Danish national database analysis [29] found an incidence rate of surgically treated ONJ among alendronate users of 2.5 per 10,000 patient years. The risk increased two-fold in patients who received alendronate for five years or longer, with no difference between five and ten years of use. Other potential risk factors include chronic diseases such as COPD, diabetes, rheumatoid arthritis, poorly fitting dentures and use of proton pump inhibitors [28]. The higher rates of surgically treated ONJ in Danish alendronate users with more than five years of exposure suggest that drug holidays could perhaps reduce the risk of this already rare adverse effect in patients treated for osteoporosis.

Specifics of Drug Holidays in Primary Care: Who, When, How?

Given the concerns about iatrogenic AFFs (and to a lesser extent ONJ) with long term BP use and the expectation that benefits can be sustained for some time after pausing treatment, after a successful 3–5 year course of BP treatment clinicians and patients should discuss the potential benefits and risks of a drug holiday [2].

Drug Holiday Timing

Based upon the existing evidence from randomized discontinuation trials of alendronate and zoledronic acid, the vertebra fracture benefits continue but the non-spine fracture benefits of treatment appear to plateau or wane slightly after 5 of alendronate and 3 years zoledronic acid use. Little data exist for other BPs. Furthermore, the risk of AFFs appears consistently across studies to increase significantly after 5–7 years of BP use. Factoring the increase risk of AFF with the diminishing anti-fracture benefits, most guidelines recommend consideration of a BP drug holiday after 5 years of oral BP use and 3–6 years of zoledronic acid use.

Selecting Drug Holiday Candidates and Screening for AFFs

After discontinuation of 5 years of alendronate in the FLEX study, the only factors associated with off-therapy fracture were lower BMD and advanced age at the time of discontinuation [30]. Risk factors for fracture after discontinuation of zoledronic acid in the Horizon-PFT Extension were similar [31], but also include previous fractures and their recency. Thus, ideal candidates for initiation of a drug holiday are younger individuals (<65–75) who have successfully completed 3–5 years of BP treatment without fracture and whose BMD is no longer in the osteoporotic range (T-score > −2.5)(Table3). Those with previous hip fracture or multiple vertebra fractures, or any new on-treatment fracture, are not good candidates for a drug holiday and most should continue to receive BP treatment for up to 10 years. Older individuals >65, those with previous fracture other than hip or vertebral, and those with BMD T-scores remain in the osteoporotic range may be offered a drug holiday with informed decision making and the recognition that fracture risk remains elevated.

Among treated individuals, periodic monitoring for incipient AFFs using full-leg DXA imaging after 3–5 years of BP use has been suggested as a method to reduce the burden of AFF [32]. Although the technology is widely available for clinical use and can indeed identify cortical bone abnormalities consistent with early AFFs, there are few prospective data about the utility of such imaging or evidence that AFFs can be effectively identified or prevented. Given the relative infrequency of AFFs in clinical practice, even after 5 year of BP use, concerns about false positive leg scans and concerns about false reassurance after a negative leg scan must be addressed before widespread use in primacy care settings can be recommended.

Follow-up and Monitoring During a Drug Holiday

During a drug holiday periodic follow-up to assess clinical status and reinforce preventative measures is critical, but once an individual has discontinued BP treatment there are no validated approaches to assessing fracture risk. Periodic monitoring with DXA or measurements of biochemical markers of bone turnover have been advocated by some, but there is no empiric evidence that such monitoring is helpful. In fact, the FLEX study found that during the first 1–3 years following alendronate discontinuation, serial BMD or measurement of serum bone specific alkaline phosphatase (BAP) and urine N-telopeptide crosslinks of the type 1 collagen (NTX) (biochemical markers of bone formation and resorption, respectively) were not associated with the subsequent risk of fracture [30]. Nonetheless, acknowledging that BMD strongly predicts fracture in untreated individuals,

repeating DXA measurements 3 or more years after BP discontinuation may reassure both patients and providers and might be justifiable to identify rare unexpected instances of dramatic bone loss (>5%).

Stopping a Drug Holiday

After discontinuation of alendronate in the FLEX study participants, during the 5 year follow-up period there was no increase in non-spine fracture risk, and results were similar in the Horizon extension study after 3 years of intravenous zoledronic acid. As noted above, observational studies of fracture outcomes during drug holidays have been inconsistent. Nonetheless, individuals who fracture during a drug holiday, particular those with incident hip, vertebral or multiple non-spine fractures, should be fully evaluated for secondary causes of osteoporosis (such as myeloma, hyperparathyroidism, sprue, hyperthyroidism, etc.) or unintended drug side effects (PPI, steroids, aromatase inhibitors, etc) and treated appropriately.

Re-initiation of therapy following a drug holiday should be individualized, but there are essentially no data to guide clinical care. Expert opinions suggest those who have successfully completed a 5-year drug holiday should be assessed clinically, and BMD should be assessed if not previously done. Although not developed or validated for treated individuals, risk stratification with FRAX may be helpful to determine 10-year risk of hip and major osteoporotic fractures as the risk profile of the patient may have worsened [33]. Depending upon the clinical circumstances, restarting oral or parenteral BPs (for up to a total of 10 years of BP exposure), or switching to another anti-resorptive agent (such as denosumab or a SERM) may be appropriate. Anabolic agents should be considered for those with severe osteoporosis and multiple fractures. In this setting, referral to an osteoporosis specialist is also reasonable.

Other situations to consider

An important caveat to this discussion is that drug holiday guidelines only apply to BPs and not other anti-resorptives. In particular, the pharmacokinetics of denosumab differ greatly from BPs and discontinuation of denosumab is associated with rapid bone loss and an increased risk of multiple vertebral fractures [34]. Similarly, the drug holiday approach outlined here does not apply to anabolic treatments, including PTH-based therapies or mixed anabolic/anti-resorptive therapies such as romosozumab.

Summary

The decision regarding the long-term use (>5 years) of anti-fracture treatments, particularly bisphosphonates, should weigh the known benefits versus the possible side effects if the medication if continued. Although a number of high-quality fracture endpoint trials of 3–5 years duration exist, large long-term placebo-controlled trials do not and the benefits and risks must be inferred from other forms of evidence. Randomized discontinuation trials and cohort studies suggest BP use for more than 5 yr reduces the risk of vertebral but not non-spine fractures. Although the overall risk of BP-related side effects after 5 years of use, particularly AFF, are very rare compared to the number of fractures prevented, multiple

studies confirm that the risk of AFF increases with prolonged use (particularly after 7 years). Fortunately, at least two studies have confirmed that after prolonged use of BP, the risk of AFF falls dramatically (>70%) in the first year after discontinuation, providing an additional strong argument in favor of drug holidays.

Thus, until additional studies improve our ability to identify individuals who will benefit from prolonged use as well as those who are more likely to be harmed with prolonged BP treatment, drug holidays after 3–5 years of BP are currently recommended for many younger patients and some older patients. Those who remain at high risk after an initial course of BPs likely benefit from continued BP treatment for up to 10 years and possibly longer. The role of switching to other effective treatments, such as denosumab, anabolic agents or newer agents such as romosozumab, remains controversial.

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Table 1.

ASBMR 2014 Criteria for AFF [21]

To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare.

Additionally, **at least four of the five Major Features must be present**. None of the Minor Features is required but have sometimes been associated with these features.

Major Criteria *	
1	The fracture is associated with minimal or no trauma, as in a fall from standing height or less.
2	The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur.
3	Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex.
4	The fracture is noncomminuted or minimally comminuted.
5	Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site. (“beaking” or “flaring”).
Minor features	
A.	Generalized increase in cortical thickness of the femoral diaphysis.
B.	Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh.
C.	Bilateral incomplete or complete femoral diaphysis fractures.
D.	Delayed fracture healing.

* Excludes fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (e.g., Paget disease, fibrous dysplasia).

Table 2.

Risk of Radiographically-confirmed AFFs in Population-Based Prospective Cohort Studies

Study	Author (Date)	Population	Total Sample	AFFs	AFF Age (mean ±SD or %)	Primary analysis	Any BP Use and AFF risk (AFFs/100k)	AFF Risk by BP Duration (AFFs/100k)	Effect of Stopping	AFFs w/out BP use
Kaiser S. Cal	Dell (2012) [24]	Men and Women >45	1.8 million	142	69±9	Age-adjusted	1.8	No use: 0.3 1–2 yr:1.8 6–8 yr: 39	NR	10%
Kaiser NW	Feldstein (2012) [25]	Women >45, Men >65	98k/yr over 13 yr	75	77±12	Unadjusted	5.9	NR	NR	70%
Sweden	Schlicher (2015) [26]	Men and women >55	2.9 million	172	76±8	Unadjusted	Women 50 Men 16	>4yr: 110	70% fall after 1 yr	22%
Kaiser N. Cal	Lo (2019)	Women 45–90	94k	107	74±8	Age-adjusted	NR	<2 yr: 6 6–8 yr: 93 >8 yr: 112	NR	Only sampled BP users
Kaiser S. Cal	Black (2020) [23].	Women ≥50	1.1 million	277	50–64: 13% 65–75: 45% >75: 42%	Unadjusted	17	<0.25: 0.7 0.25–3 yr: 6 6–8 yr: 60 >8 yr: 131	79% fall after 1.25 yr	10% (not included in analysis)

NR = not reported

Table 3.

Suggested Approach to Bisphosphonate Drug Holiday in Primacy Care Settings

Completed 3–5 years of BP therapy for osteoporosis	**During a planned 5 year drug holiday**	**After completing 5 year drug holiday**
Proceed with holiday with yearly re-evaluation:	Continue holiday with yearly assessment:	Continue off osteoporosis medication with yearly assessment:
• <65–75 • No recent fracture (<2yr) • No hip or vertebral fracture • Femoral neck BMD T-score >−2.5 • Understands potential benefits and risks of stopping	• No new fractures • No new or worsening risk factors for fracture [+] • Compliant with non-pharmacologic therapy	• Repeat femoral neck BMD T-score after 5 years of holiday remains >−2.5 • No new fractures • No new or worsening risk factors for fracture [+] • Compliant with non-pharmacologic therapy
Continue bisphosphonate without holiday for up to 10 yr:	Stop holiday and restart bisphosphonate or other treatment:	Restart bisphosphonate or other treatment:
• None of the above • Understands potential benefits and risks of continuing	• New fractures • New or worsening risk factors for fracture [+] • Repeat femoral neck BMD T-score after ≥3 years of holiday is <2.5 AND shows >5% bone loss [*]	• Repeat femoral neck BMD after 5 years of holiday is <2.5 AND shows >5% bone loss • New fracture after successful holiday • New or worsening risk factors for fracture [+]

[+] new weight loss, medical condition (RA, Parkinson's, CVA, renal insufficiency, hyperthyroidism, frailty) or use of medications (steroids, PPI, AI, chemotherapy) associated with fracture risk

[*] Repeat BMD measurements during drug holidays are optional, but if done should be performed on the same DXA machine.