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Osteoporosis (K Saag, Section Editor)

Bisphosphonate Drug Holiday and Fracture Risk: Reviewing the Evidence

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Abstract

Purpose of review This paper reviews evidence in support of or counter to the use of bisphosphonate (BP) drug holiday to minimize the occurrence of rare adverse events such as atypical femoral fracture, while maintaining the osteoporosis-related fracture prevention benefit conferred by the medication.

Recent findings Fracture prevention benefit achieved with 3–5 years of BP treatment appears to be maintained during holiday for women at low to moderate risk of fracture. Women with bone mineral density T-score < −2.5 or prior fragility fracture remain at high risk for fracture and continuation of therapy is advised. Additionally, evidence suggests that duration of BP use, level of adherence to therapy, and length of holiday may also influence fracture risk during holiday. There are few studies on AFF risk during drug holiday, but the limited evidence suggests a rapid decline in risk within the first 1–2 years of holiday.

Summary BP drug holiday appears to be a reasonable part of osteoporosis treatment strategy for women at relatively low risk of osteoporosis-related fracture as assessed after initial treatment, while higher risk women may benefit from continued therapy rather than a BP holiday. Greater understanding of the influences of BP treatment duration and holiday length, and their interaction, can inform more individualized treatment decision-making.

Introduction

Alendronate, a medication in the class of bisphosphonates (BPs), was approved for use in the USA for the treatment and management of osteoporosis in 1995. Other nitrogen-containing bisphosphonates were subsequently approved for use in osteoporosis: risedronate in 2000, ibandronate in 2003, and zoledronate in 2007. Bisphosphonates are currently the first-line medication for this condition and are used by millions of people around the world. Several clinical trials have established the efficacy of the bisphosphonates for reducing the occurrence of vertebral and hip fractures among men and women with osteopenia and osteoporosis, effectively reducing the morbidity and mortality associated with these osteoporosis-related fractures.

In 2005 and 2006, reports began appearing in the medical literature of femur fractures that were morphologically distinct from the "typical" osteoporosis-related hip and femur fractures occurring among people with osteoporosis. These distinctive fractures occurred below the lesser trochanter, often in the upper to mid-shaft region of the femur, and appeared to occur spontaneously, without trauma. Whereas hip fractures most frequently result from a fall, these new fractures, now called "atypical femoral fractures (AFF)," seemed to first break and then cause a fall.

As clinicians and researchers learned more about these fractures over the subsequent decade, a likely association with BP use became apparent. Beginning in approximately 2006, clinicians and patients with osteoporosis began hearing more about rare, adverse events associated with use of BPs, as a lawsuit was filed against Merck and Co, Inc., for osteonecrosis of the jaw (ONJ) in 2006, a published paper suggested an increased risk of atrial fibrillation with BP use (2008) [1], and ABC World News broadcast about alendronate and AFF (2010) [2]. Concurrently, after a decade of increasing use of BPs, steep declines in use began in about 2008–2009 [2]. Similarly, after years of declining incidence of hip fracture since 1995, age-adjusted rates began increasing again in approximately 2013 [3]. While the decline in BP usage is probably multifactorial, concerns about AFF certainly contribute as clinicians and/or patients elect to decline or delay treatment for osteoporosis in an attempt to avoid these concerning atypical fractures.

As the association between BP use, particularly longer-term use, and AFF became more clear, clinicians and researchers considered the use of a "drug holiday," a period of no treatment after a defined period of active treatment, as a way to minimize the risk of AFF while still maximizing the protective effect of BPs on major osteoporosis-related fractures (MOF). The main questions around the use of drug holiday include as follows: (1) do MOF risks increase during holiday and (2) does AFF risk decrease during holiday? Answers to these questions may change depending on the length of pre-holiday BP treatment, length of actual drug holiday, and the population of patients studied. It is important to understand whether there are subgroups of patients who should not be put on holiday. This review summarizes what is currently known about the answers to these questions about drug holiday and identifies important gaps in our knowledge about the use and effects of BP drug holidays.

Osteoporosis and bisphosphonate medications

Osteoporosis is a condition of bone where resorption outpaces formation, resulting in decreased bone mineral density (BMD) and increased risk for fractures due to bone fragility. Currently, the first-line medications for management and treatment of osteoporosis are the bisphosphonates (BPs), including alendronate, risedronate, ibandronate, and zoledronate. BPs are synthetic analogs of inorganic pyrophosphate, an endogenous inhibitor of bone mineralization via inhibition of the crystallization of calcium salts [4]. BPs strongly inhibit bone resorption at the bone surface and then remain

embedded in bone with a half-life of nearly 10 years [5, 6]. Decreased bone resorption, coupled with slowed bone formation, reduces the rate of overall bone turnover to that of premenopausal levels in women. Several randomized controlled trials (RCTs) have shown BPs to reduce vertebral fractures by approximately 35–70% and hip fractures by 35–50% [7].

Atypical femoral fractures

In 2005 and 2006, cases of unusual fragility fractures in the subtrochanteric and femoral shaft areas were reported in the literature [8, 9], and were soon followed by additional case reports and epidemiologic studies [10, 11]. These unusual fractures, now called atypical femoral fractures (AFFs), feature a morphological pattern distinct from other subtrochanteric and femoral shaft fractures. AFF characteristics include a transverse orientation and concomitant cortical thickening at the fracture site and seem to occur most commonly among women treated for osteoporosis with BPs, though AFFs have occasionally occurred among men and among women without BP exposure. Additionally, these fractures occur in the absence of trauma, unlike typical subtrochanteric and femoral shaft fractures typically resulting from high energy trauma such as motor vehicle crashes [11].

In 2010, the American Society for Bone and Mineral Research (ASBMR) published a Task Force Report on Atypical Femoral Fractures (AFF) reviewing the knowledge to date about the epidemiology and pathophysiology of these fractures and identifying areas of need for additional research [11]. Furthermore, the ASBMR Task Force proposed a case definition for AFF. The ASBMR Task Force published an updated report on AFF in 2014 [12] and included the latest information on the epidemiology, pathophysiology, and case management of these fractures. The 2014 ASBMR Task Force report also included a revised case definition of AFF, which now requires the following:

1. *Fracture location* — the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare.
2. At least 4 of 5 *major features* must be present:

    (a) The fracture is associated with minimal or no trauma.
    (b) The fracture line originates at the lateral cortex and is substantially transverse, though it may become oblique as it extends medially.
    (c) Incomplete fractures involve only the lateral cortex, while complete fractures extend through both cortices and may include a medial spike.
    (d) The fracture is non-comminuted or minimally comminuted.
    (e) Localized periosteal or endosteal thickening in the lateral cortex at the fracture site ("beaking" or "flaring") is observed.

3. *Minor features* may be observed as well, but are not required to be present for diagnosis:

    (a) Generalized increase in cortical thickness of the femoral diaphyses

(b) Prodromal pain or dull ache in the groin or thigh, either unilateral or bilateral
(c) Bilateral femoral diaphysis fractures, either incomplete or complete
(d) Delayed fracture healing

Since the initial reports of AFF appeared, several epidemiologic studies have attempted to quantify the potential association between AFF and BP use. Results have been somewhat mixed, partially due to differences in study design and the manner of ascertaining AFF (via radiograph review, ICD codes, or use of radiograph reports). Overall, the evidence suggests a strong relationship between BP use and the occurrence of AFF, though the magnitude of the association has varied across studies. A 2013 meta-analysis of 11 studies [13–23] estimated an overall pooled risk ratio of 1.70 (CI 1.22–2.37) [10], but also revealed that estimates of the association coming from the cohort studies [10, 13–15, 17, 18, 23] (RRs ranging from 1.03 to 2.41) tended to be systematically lower than those arising from the case–control studies [16, 19–22] (RRs ranging from 2.11 to 69.1). However, all of the cohort studies and one of the case–control studies [21] based their analyses on subtrochanteric/femoral shaft (ST/FS) fractures without x-ray verification that the fractures were AFF. It is likely that many of the fractures counted as outcomes in these studies were not AFF, which would dilute the association between BP and fracture, assuming that "typical" ST/FS fractures were not independently associated with BP use. The remaining case–control studies all used radiographically confirmed AFF as their outcome, which likely eliminated the dilution of effect. In the years after Gedmintas et al. [10] completed their meta-analysis, 4 other key epidemiologic studies looked at the BP and AFF association [24, 25•, 26], 3 of which used radiographically validated AFF as the outcome. Each of these 3 studies found elevated risk for AFF among BP users, whereas Abrahamsen found that risk was lower among more adherent BP users compared to less adherent users [24].

Duration of BP use also seems to be strongly associated with the occurrence of AFF. Dell et al. [27], in a cohort study with 142 radiographically adjudicated AFFs and BP exposure information from automated pharmacy data, observed incidence rates increased from an age-adjusted rate of 0.3 AFF/100,000 person-years at < 2 years of BP use to 38.9 AFF/100,000 person-years at 6.0–7.9 years of BP exposure. At ≥ 8 years of BP use, incidence of AFF increased steeply to 113.1/100,000 person-years. These findings were supported by later work by Schilcher et al. [26], though the magnitudes of risk at low levels of BP exposure were high, much greater than at each level of BP duration than those observed by Dell and were inconsistent with RCT evidence [28••].

Some of these initial studies also examined additional risk factors for AFF, above and beyond BP exposure, though findings have been mixed. Risk factors proposed have included age; race; activity levels; genetic factors; femoral characteristics like BMD, generalized cortical thickness, and femoral geometry; comorbidities such as diabetes mellitus and rheumatoid arthritis; and medication exposures such as glucocorticoids and proton pump inhibitors [28••]. In general, there does appear to be evidence of age, Asian ancestry, and glucocorticoid use all being associated with risk of AFF [11, 12, 28••].

Drug holidays

Being a chronic condition, osteoporosis treatment/management was originally expected to continue indefinitely once initiated. However, the apparent association between longer-term BP use and AFF risk prompted clinicians to consider ways to minimize AFF risk while still maximizing the fracture prevention benefit that BPs confer. Drug holidays, periods during when treatment with BP is temporarily suspended, are an attempt to do just that. Under the drug holiday framework, people would initially be treated with BPs for a period during which maximum fracture prevention benefit appears to be achieved. The optimal time length for pre-holiday BP treatment is debated, but current research suggests it might be somewhere between 3 and 5 years [29, 30••]. Following initial treatment, they then would stop taking the drug for a period of time, such as 1–3 years. Fracture risk assessments would be conducted prior to and periodically during the drug holiday with the patient restarting on BPs or other anti-osteoporosis agents when/if fragility fracture risk increased beyond a given threshold or other criteria were met.

Drug holidays are only a reasonable strategy, though, if the risk of major osteoporosis-related fragility fractures does not increase during the holiday period and if AFF risk decreases during holiday. Because of the relative rarity of AFF, any increase in risk of MOF would quickly counter any AFF risk reduction achieved with a drug holiday. Additionally, drug holiday may not be appropriate for all patients. Identifying those subgroups who should (or should not) be put on holiday is critical. So the key questions that needed to be addressed were as follows: (1) does BP drug holiday increase the risk of MOF during or after the holiday; (2) does AFF risk decrease during BP drug holiday; (3) how does the length of pre-holiday BP treatment and drug holiday itself influence answers to these questions; and (4) are there important subgroups of BP-treated patients who should not be considered for drug holiday?

Is fracture prevention benefit maintained during holiday?

Studies supporting maintenance of fracture prevention benefit

The initial evidence about retention or loss of fracture prevention benefit upon BP discontinuation came from early randomized controlled trials (RCTs) of BP efficacy and extensions of those trials (Table 1). In the Fracture Intervention Trial (FIT) Long-term Extension (FLEX) study, investigators found that after 5 years of alendronate treatment, an additional 5 years of treatment did not result in better prevention of non-vertebral fractures (NVF) when compared to women who ceased alendronate treatment after the initial 5 years [31]. That is, using alendronate for 5 years appeared to

Table 1 Summaries of studies addressing the effects of bisphosphonate drug holiday on risks of osteoporosis-related fractures

Study	Study design	Population	Sample size	Length of minimum pre-holiday BP use	Length of drug holiday	Conclusion	Limitations
Studies supporting maintenance of fracture prevention benefit							
Watts, 2008	RCT	Women, at least 5 years post-menopausal, younger than 85 years, and had either two or more vertebral fractures or one vertebral fracture and low spinal bone mineral density (T-score ≤ -2), average age 68 years	599	3 years	Up to 1 year	Risk reduction of new vertebral fractures remained in the year after treatment with risedronate was stopped. Did not observe a difference in the incidence of non-vertebral fractures in the extension period	The number of non-vertebral fractures in the extension period was low, so no clear conclusion can be drawn, whether this is an indication of a gradual loss of effect or rather a chance finding

Table 1 (continued)

Study	Study design	Population	Sample size	Length of minimum pre-holiday BP use	Length of drug holiday	Conclusion	Limitations
Adams, 2018	Observational retrospective cohort study	≥45 years who initiated oral or injectable BP medication between January 1, 1998, and December 31, 2008, and continued use for at least 3 years with ≥50% adherence in each of those years. Average age 71 years	39,502	≥3 years exposure to BP at least 50% adherence	≥12 months with no use, once categorized in drug holiday exposure patient remained in this group even with re-initiation of BP following holiday	Compared to the persistent use group, there was a slight reduction in overall osteoporosis-related fracture risk and no difference in hip fracture risk for the BP holiday group. A slight reduction in risk of vertebral fracture was observed. Compared to the non-persistent user group, the BP holiday group was at decreased risk for osteoporosis-related fractures, vertebral fractures, and hip fractures	Channeling bias — patients not randomly assigned to continue or discontinue, possible unmeasured confounding, data for some independent risk factors, such as functional status and frailty, were limited and did not have any information about the reasons for BP holiday or BP cessation

Table 1 (continued)

Study	Study design	Population	Sample size	Length of minimum pre-holiday BP use	Length of drug holiday	Conclusion	Limitations
Sølling, 2021	Observational retrospective cohort study	All individuals living in Denmark who had redeemed ≥ 2 alendronate prescriptions of any pack size between January 1, 1995, and September 1, 2017, above 50 years at first prescription. Average age 75 years	31,475	5 years with at least 80% adherence	Up to 5 years, but mean follow-up 1.8 for those with drug holiday, 2.5 years without. Patients in drug holiday group censored if they resumed BP	No difference in the risk of fractures in patients discontinuing versus continuing alendronate after 5 years	Patients not randomly assigned to continue or discontinue, possible unmeasured confounding, BMD and FRAX not available
Studies suggesting decrease in fracture prevention benefit							
Schwartz, 2010	Post hoc analysis of Black, 2006 (an RCT)	Postmenopausal women who had been randomized to alendronate in previous RCT, post hoc subgroups by vertebral fracture status and femoral neck (FN) T-score, average age 73 years	1099	3 years	Up to 5 years	Continuing therapy for 10 years instead of stopping after 5 years reduces NVF risk in women without prevalent vertebral fracture whose FN T-scores, achieved after 5 years of ALN, are − 2.5 or less	These analyses are limited by the small numbers of fractures in the FLEX Trial, so our ability to detect differences in subgroups is limited. Conclusions also must be tempered by the post hoc nature of these analyses

Table 1 (continued)

Study	Study design	Population	Sample size	Length of minimum pre-holiday BP use	Length of drug holiday	Conclusion	Limitations
Mignot, 2017	Observational retrospective cohort study	Patients with postmenopausal osteoporosis who had received a BP drug recommended in France as first-line treatment (alendronate, risedronate, ibandronate, and zoledronic acid) Mean age, 66.5 years	183	3–5 years, adherence not specified	3–36 months	After first-line BP therapy in postmenopausal women with osteoporosis, the risk of new clinical fractures was 40% higher in subjects who took a bisphosphonate drug holiday	Patients not randomly assigned to continue or discontinue, analyses based on number of fractures, so women with multiple fractures were counted multiple times. Results counting only one fracture per woman were not significant. Very small sample size, including only 35 patients on drug holiday

Table 1 (continued)

Study	Study design	Population	Sample size	Length of minimum pre-holiday BP use	Length of drug holiday	Conclusion	Limitations
Curtis, 2020	Observational retrospective cohort study	Women aged 65 years and above enrolled in fee-for service Medicare who had taken to alendronate, risedronate, or zoledronate. Average age 79 years	81,427	≥3 years with at least 80% adherence for≥3 years	>2 years, patients censored if they resumed BP	Discontinuing alendronate beyond 2 years was associated with increased risk of hip, humerus, and clinical vertebral fractures	Patients not randomly assigned to continue or discontinue, possible unmeasured confounding. The discontinuers and continuers were not balanced on several characteristics on the index date (CCI score, medication, previous fractures), did not have any information about the reasons for BP holiday or BP cessation, or BMD score

Table 1 (continued)

Study	Study design	Population	Sample size	Length of minimum pre-holiday BP use	Length of drug holiday	Conclusion	Limitations
Studies with mixed results regarding fracture prevention benefit							
Black, 2006	RCT	Postmenopausal women who had been randomized to alendronate in previous RCT, average age 73 years	1099	3 years	Up to 5 years	Women who discontinued alendronate after 5 years showed no higher fracture risk other than for clinical vertebral fractures compared with those who continued alendronate	Study not powered to detect moderate-modest differences in fracture risk, resulting in wide confidence intervals
Curtis, 2008	Cohort study	Women aged 60–78 years with medical and pharmacy benefits who were new users of alendronate or risedronate between 1/1998 and 7/2005 with at least 2-year discontinuation. Excluded for prior hip fracture, malignancy, HIV, and Paget's disease	9063	2 years	Any length of discontinuation, sensitivity analysis at 0–6, 6–12, and >12 months since discontinuation	The rate of hip fracture was increased among women compliant with bisphosphonate therapy for 2 years who subsequently discontinued, suggesting that discontinuation is not advisable under these conditions. This association was attenuated with higher compliance and a longer duration of previous bisphosphonate therapy	Patients not randomly assigned to continue or discontinue, possible unmeasured confounding. Small number of hip fractures in primary analysis, likely underpowered, wide Cis. did not have any information about the reasons for BP holiday or BP cessation, or BMD score

Table 1 (continued)

Study	Study design	Population	Sample size	Length of minimum pre-holiday BP use	Length of drug holiday	Conclusion	Limitations
Cosman, 2014	RCT	Postmenopausal women who participated in the core trial who have received 3 annual ZOL infusions and had hip BMD measured at the end of the core study. Mean age was 75.5 years and the ages ranged from 68 to 90	1233	3 years	Up to 3 years	After 3 years of ZOL, in women who have a TH t-score above −2.5, no recent incident fracture and no more than one risk factor (almost 55% of the population), risk for subsequent fracture (over three additional years) is low if treatment is discontinued	Powered for BMD outcome and there were relatively few patients and fractures to explore fracture outcome. Due to small sample size and wide CIs, cannot be sure of lack of treatment effect
Pfeilschifter, 2020	Interview-based prospective observational cohort	Men aged ≥ 59 years and postmenopausal women with DXA t-score of ≤ −2.0 (lumbar spine, femoral neck, or total hip) OR one moderate or severe low-trauma prevalent vertebral fracture (PVF) OR multiple low-trauma PVFs	1973	4 years at 80% adherence	Any period of time without osteoporosis pharmacotherapy beyond the completion of the last dosing interval of a preceding BP treatment, last follow-up day 24 months, based on patient self-report	No significant difference in fracture risk between holiday and ongoing BP use up to 25 months, but presence of prevalent vertebral fracture may increase relative risk of major osteoporotic fractures associated with longer BP holiday	Small sample size resulting in wide CIs. Fracture rates and timing of BP discontinuation depended on self-reported data, information on prior BP use provided by physicians

confer similar protection against NVF to that achieved by continuing alendronate for a total of 10 years.

Additionally, in another RCT of women randomized to either risedronate or placebo for 3 years, Watts et al. [32] found that after 1 year off drug, the risedronate group remained at reduced risk for morphometric vertebral fractures compared to the placebo group (RR 0.54, CI 0.34–0.86), suggesting that the fracture prevention benefit was retained over the course of a short holiday.

In 2014, Cosman and colleagues [33] used data from the 3-year extension of the HORIZON study of zoledronate and found that after discontinuation, low-risk women (those with hip T-score > − 2.5 and no recent incident fracture) had no additional risk for either NVF or morphometric vertebral fractures compared to women who continued zoledronate.

Additional evidence about associations between BP drug holiday and risk of fracture have come from several observational studies. In a large cohort study conducted using administrative data from a US healthcare organization, Curtis et al. [34] observed that for women who had used BPs with good compliance for at least 2 years, changes in hip fracture risk varied during holiday based on duration of pre-holiday BP use, BP adherence levels, and duration of holiday. After 2 years of use, cessation of BP for up to 1 year was not associated with any increased risk of hip fracture compared to continuing users of BP. They also observed that greater adherence (≥ 80% MPR) and longer pre-holiday use of BP (≥ 3 years) maintained fracture reduction benefit even among higher risk women.

Another cohort study conducted among members of 5 regional locations of a large, integrated healthcare system included 39,502 women who had used BP (mostly alendronate) for at least 3 years and then compared the occurrence of new MOF among those who subsequently went on holiday (> 12 months with no BP use) to those who did not have a drug holiday [35]. The holiday group had similar hip and spine fracture risk compared to the non-holiday group.

Pfeilschifter et al. [36•], in a prospective cohort study of 1973 men and women who had used BPs for at least 80% of the time for ≥ 4 years, and who also had BMD T-score ≤ − 2.0 (lumbar spine, femoral neck, or total hip) or had a vertebral fracture prior to BP initiation, found no difference in fracture risk for up to 25 months among the subjects without a prior vertebral fracture.

Most recently, Sølling and colleagues conducted a cohort study of 31,475 women and men in Denmark who used alendronate continuously for ≥ 5 years prior to taking a drug holiday [37•], and found no increased risk associated with drug holiday for any fracture, nor for vertebral, hip, radius/ulna, humerus, or other fractures.

Finally, a recent systematic review estimated summary hazard ratios (HR) for hip fracture and any clinical fracture from the observational studies reporting those outcomes, finding an HR of 1.09 (CI 0.87–1.37) for risk of hip fracture and an HR of 1.13 (CI 0.75–1.70) for any clinical fracture for persons on drug holiday compared to BP continuers [38]. This and other reviews have concluded that the sum of the evidence supports the assertion that fracture risk does not increase to any important degree with drug holiday [38, 39].

Studies suggesting decreases in fracture prevention benefit

Findings in both in RCTs and observational studies have not universally demonstrated maintenance of fracture prevention benefit during off-drug periods. Black et al. found that while 5 years of alendronate treatment had similar fracture reduction effects as 10 years of alendronate, there was evidence that cessation of alendronate at 5 years did increase the risk of clinical vertebral fractures, but not morphometric vertebral fractures, compared to the women who continued alendronate [31]. Additional *post hoc* analyses of FLEX data demonstrated that continuation of alendronate beyond 5 years appeared to reduce risk of NVF among women with femoral neck T-score ≤ − 2.5 at baseline [40]. Similarly, in a study of zoledronate, NVF risk appeared to be higher for zoledronate discontinuers with hip T-score ≤ − 2.5 compared to those who continued zoledronate, and regardless of hip T-score value, having a prior NVF or morphometric VF was associated with higher fracture risk after discontinuation compared to continuers [33].

In a small observational cohort study conducted in France, Mignot et al. [41] retrospectively assessed the occurrence of any clinical fracture among 183 postmenopausal women who had been treated with BP therapy for 3–5 years, comparing those who discontinued therapy to those who continued. They found that the women who discontinued BP were at 40% increased risk of having a new clinical fracture during follow-up (HR 1.40, CI 1.12–1.60). It is worth noting, though, that the only hip fractures observed were in the continuation group and the groups were similar for new vertebral fractures if the number of involved women was counted instead of the number of fractures.

In an observational cohort study, discontinuation of BP for longer than 1 year was associated with 2–3 times increased risk of hip fracture among women with adherence of ≥ 66% medication possession ratio (MPR) over 2 years of BP use, although this increased risk was attenuated among women with higher baseline adherence (≥ 80% MPR) and with longer use of BP (3 years) prior to holiday [34]. For patients with a prior vertebral fracture, MOF risk appears to also increase with holidays > 1 year in duration [36•]. Additionally, Curtis et al. [42•] found that BP drug holiday > 2 years increases the risk of all types of MOF among all patients. These studies strongly suggest that duration of holiday may play an important role in maintenance or decline of fracture prevention benefit above and beyond the influence of pre-holiday treatment duration and level of adherence to treatment.

Comments on variations in study methods

Though the early RCTs had the benefits of randomization to minimize bias, these studies were powered to detect changes in BMD, not moderate-modest differences in fracture risk [31]. This resulted in wide and often overlapping confidence intervals for fracture outcomes, or even insufficient events to estimate differences in NVF [32]. Results from these studies suggested no difference in fracture risk during drug holidays, with the possible exception of women with

femoral neck T-score ≤ −2.5 at baseline, but researchers could not be certain that the trials were just not powered to detect these differences [31, 33, 40]. This in turn also limited potential subgroup analyses of interest or examination of risk differences based on differing lengths of drug holiday. RCTs powered for rare outcomes such as NVF would require large enrollment and follow-up times which are cost prohibitive.

Observational studies have mitigated some of these problems with larger sample sizes, but also introduced new challenges, since the decision to go on or off BPs is not randomly assigned. This could be why some studies observed that drug holidays offered a small protective effect against subsequent fractures [35]. Subsequent studies could attempt to further mitigate this bias by using propensity score methods [43] to better account for differences in measured baseline characteristics for those who decide to go on drug holidays, or to consider using the target trial framework to better emulate an RCT [44]. Observational studies summarized above have also used different analysis populations in terms of age range, sex, definitions of medication adherence, and drug holiday lengths, making it difficult to parse out why they may be arriving at different results [35, 37•]. If these definitions could be better aligned, perhaps considering a range of important combinations of medication adherence and drug holiday lengths, it may be easier to understand whether a consistent relationship exists. Observational studies where BP use is self-reported [36•] or where outcomes are not assessed at the patient level [41] provide less useful evidence. Since race/ethnicity is also associated with fracture risk, further studies including diverse populations are also extremely important [35].

Does risk of AFF decline during and/or after drug holiday?

Evidence for the decreasing incidence of AFF with drug holiday is sparse. AFFs are extremely rare and few research groups have sufficient numbers of AFF cases to make valid inference. Schlicher and colleagues, studying a large Swedish population observed that after cessation of BP use, risk of AFF declined by 70% each year since last BP use (OR 0.28, CI 0.21–0.38) [22, 26]. In a large racially/ethnically diverse population in Southern California, Black and colleagues also found that rates of AFF decreased with time since BP discontinuation. Current BP users had an overall rate of 4.5 AFF/10,000 person-years, which then dropped to 1.8/10,000 person-years between 3 and 15 months after discontinuation, and further dropped to 0.5/10,000 person-years after 15 months of holiday [25•]. While the physiological mechanism for the rapid decline in risk has not yet been explained, the existing evidence does seem to suggest that rapid decline of AFF risk is possible upon discontinuation of treatment.

Comments on study methods

As mentioned previously, the extreme rarity of AFFs makes RCTs infeasible, and even limits inference in observational studies with large populations.

Schlicher [22, 26] was able to show risk of AFF declined with each year of drug holiday, using all AFFs in the Swedish population in a case–control study with controls having ordinary shaft fractures. However, the small number of AFFs and the homogenous Swedish population did not allow for analyses by important subgroups like race/ethnicity. Black et al. were able to improve on this by looking at AFFs in a more diverse population and comparing AFFs caused with hip fractures averted for a more complete risk–benefit analysis [25•]. Since women who sustain AFFs tend to be younger and less frail than those who experience hip fracture, statistical methods listed previously to reduce the effect of confounding in observational studies may provide additional value in addressing the question of AFF reduction with drug holiday.

Summary of findings: who should have a drug holiday?

Findings of several RCT and observational studies generally support the maintenance of fracture reduction benefit during drug holidays or periods of discontinuation for finite periods, though there are a few studies with findings of increasing risk as duration of holiday lengthens. Even among the studies supportive of holiday, some groups for which holidays may be detrimental have emerged. In particular, those with hip BMD < – 2.5 after 3–5 years of oral BP therapy or 3 years of IV BP therapy remain at high fracture risk and should continue BP or switch to another agent [45]. Additionally, evidence suggests that BP drug holiday may be riskier and/or avoided entirely for people with a fracture prior to or during therapy, hip BMD < – 2.0, older age, or poor compliance with the medication [46, 47]. Therefore, risk of MOF should be evaluated at the time holiday is being considered and, if a holiday is initiated, risk should be re-evaluated periodically during the holiday, with particular attention paid to the development of any new risk factors for fracture that may suggest a return to treatment.

Future directions

Addressing some additional questions could inform and improve decision-making around the use of BP drug holidays. Current evidence suggests that both duration of BP use prior to a holiday and the duration of the holiday itself may affect the risk of fractures after BP discontinuation [42•, 48]. Further details on the interaction of treatment duration and holiday length and effects on subsequent fracture risk would provide information clinicians could use to further personalize recommendations around continuation of therapy vs. employment of a drug holiday. In addition, MOF risk and AFF risk both vary based on factors such as age and race/ethnicity, though they vary differently from each other. More detailed understanding about how age and race/ethnicity may modify the risk of MOF during drug holiday and the risk of AFF while on therapy would also facilitate more personalized treatment

recommendations. How risks for MOF and AFF change upon resumption of treatment after drug holiday has also not been well studied.

Declarations

Conflict of Interest

Annette L. Adams reports grants from Radius Health, grants from NIH, grants from Amgen, and grants from Merck, outside the submitted work. Denison Ryan declares no competing interests. Anna Lawless declares no competing interests. Heidi Fischer declares no competing interests.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

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