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CHAPTER

c0079 # 79

Long-term bisphosphonate treatment: continuation and interruption

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Abbreviations

s0010

AACE	American Association of Clinical Endocrinologists
ALN	alendronate
ALP	alkaline phosphatase
ASBMR	American Society for Bone and Mineral Research
AFF	atypical femoral fractures
BMD	bone mineral density
BP	bisphosphonate
BTM	bone turnover marker
CTX	C-telopeptide of Type 1 Collagen cross-links
CPG	clinical practice guideline
Dmab	denosumab
DXA	dual-energy X-ray absorptiometry
FNIH	Foundation for the National Institutes of Health
FLEX	Fracture Intervention Trial Long-term Extension
FDA	Food and Drug Administration
FRAX	fracture risk assessment tool
HT	hormone therapy
HRT	hormone replacement therapy
IBAN	ibandronate
NOGG	National Osteoporosis Guideline Group
NTX	urinary N-telopeptide cross-links
ONJ	osteonecrosis of the jaw
PINP	N-terminal propeptide of type I procollagen
PTH	parathyroid hormone
RIS	risedronate
RRR	relative risk reduction
SERM	selective estrogen receptor modulator
TPTD	teriparatide
ZOL	zoledronic acid

79.1 Introduction: osteoporosis as a chronic disease

s0015

Osteoporosis is a chronic disorder and a major health problem, with an estimated 2 million osteoporotic fractures every year in the United States, and over 3.5 million in Europe. As life expectancy increases in many parts of the world, the annual incidence of osteoporotic fracture is destined to rise, and more people will be potential candidates for treatment. p0260

Peak bone mass is attained in the third decade of life, and thereafter bone mass decreases. In women the decrease is accelerated by the loss of estrogen at the time of menopause. It is clear, however, that bone mass does not fully explain the age-related increase in fracture risk. If two people, ages 55 and 75 years, have the same bone mass as reflected by dual-energy X-ray absorptiometry (DXA), the older patient will have a much higher fracture risk than the younger ones. This difference is ascribed to decrease in bone quality, frailty, and tendency to fall [as best expressed in the age-dependent hip fracture incidence in the fracture risk assessment tool (FRAX) calculator] but yet still difficult to directly measure. Nonetheless, it can be stated that aging is a major risk factor for fracture and getting older increases fracture risk for the population overall. p0265

Marcus and Feldman's Osteoporosis.
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For those individuals with low bone density by DXA and other risk factors, as covered in other chapters, fracture risk continues to escalate.

p0270 Currently, no treatment cures osteoporosis. All existing treatments lower fracture risk to some extent, but none can eliminate it. Hence, osteoporosis can be classified as a chronic treatable but not curable disease. Management should be aimed at lowering fracture risk and containing related morbidities and costs to individuals and society as much as possible. Osteoporosis may require management for 20 or 30 years or more, and in most settings, bisphosphonates (BPs) are the first-line osteoporosis treatment class. Yet the longest placebo-controlled osteoporosis pharmacologic study lasted 10 years and was too small to adequately assess positive and negative outcomes, as well as predictors of such outcomes. Therefore the clinician must base treatment choices on relatively limited data. In this chapter, we will discuss how long-term treatment with BPs can decrease fracture risk, conduct a risk–benefit assessment of the positive impact of BPs and their potential side effects, and provide a proposed approach to the chronic treatment of osteoporosis with BPs.

79.2 Long-term bisphosphonate studies

s0020

p0275 There are many reasons why the BP class of medication is the single most commonly used category of drugs for the treatment of osteoporosis in adults. Modern treatment of osteoporosis began in the mid-1990s with the approval of alendronate (ALN), the first nitrogen-containing BP approved by regulatory agencies for human osteoporosis. Details of the studies assessing the efficacy and safety of ALN, risedronate (RIS), ibandronate (IBAN), and zoledronic acid (ZOL) are beyond the scope of this chapter. In general, the data show that all US Food and Drug Administration (FDA)–approved BPs lower the risk of vertebral fracture by about half [1]. In addition, ALN, RIS, and ZOL reduce hip fracture by about 30%–40%. The efficacy of nonvertebral fracture risk reduction is more modest. The registration trials for ALN, the earliest approved nitrogen-containing BP, did not provide evidence of any major side effects. Only later, when hundreds of thousands of patients were treated with BPs, did important risks such as osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFFs) become recognized. Longer term treatment and surveillance are necessary because no treatment cures osteoporosis. With the use of BPs for many years, and with long treatment duration, more reports of ONJ and AFF became apparent, leading to dramatic decreases in prescriptions for these drugs [2]. Indeed, it has been reported that 1 year after starting an oral BP, only half or fewer of treated patients remain adherent to therapy [3–5].

p0280 Thus the clinician and patient face a dilemma. Osteoporosis is a chronic disease with worsening fracture risk as the patient ages. Chronic treatment is needed, but BPs, the most commonly prescribed osteoporosis medications, are associated with risks of ONJ and AFF. Although such adverse events are rare and by far outweighed by substantial benefits in terms of fracture risk reduction in high-risk patients, they are clearly problematic in lower risk individuals. There may be other serious side effects. How does the clinician decide to prescribe BPs, to continue or interrupt therapy, and engage the patient in shared decision-making? Risk stratification, absolute risk prediction, and a risk–benefit assessment are crucial to such decision-making. To try to answer these questions, there are only two long-term randomized controlled trials on which some recommendations have been made. These two trials, a 10-year trial with ALN and a 9-year trial with ZOL, will be reviewed in detail.

79.2.1 Alendronate (FIT/FLEX)

s0025

p0285 The first study of long-term BP therapy for osteoporosis, the FLEX trial (Fracture Intervention Trial Long-term Extension), was reported in 2006 by Black et al. [6]. Over 3000 women who had participated in the FIT trial [7] of ALN versus placebo and had received active drug were assessed for potential inclusion in the extension trial. With an open-label year or more, subjects eligible for FLEX had been treated for 4–5 years. Eventually, 1195 were screened for inclusion in FLEX and 1099 were randomized to ALN 5 mg daily, ALN 10 mg daily, or placebo. All subjects were offered a supplement containing 500 mg of calcium and 250 U of Vitamin D. The FLEX study lasted 5 years with more than 95% included in the primary analysis. The randomization and block stratification were successful because the only baseline variable different among the three groups was the slightly older age of the placebo group (73.7 years) than the two ALN groups (72.7 and 72.9 years). The two ALN groups were pooled for analysis. Bone density results differed by region of interest. In the spine, bone density increased in subjects on ALN, while it did not change in the placebo group. Conversely, hip bone density was maintained in subjects taking ALN, but it declined 2.36% in the placebo subjects [6]. Of the 437 analyzed placebo subjects, 23 suffered a clinical vertebral fracture, compared to only 16 of 662 subjects assigned to ALN. There was no difference in the incidence of morphometric spine

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fractures or other clinical fractures, and no imbalance in serious adverse events between the groups. The conclusion from the FLEX trial was that 10 years of ALN led to fewer clinical vertebral fractures than 5 years of ALN followed by 5 years of placebo (relative risk 0.45, confidence interval 0.24–0.85) [6].

s0030 79.2.2 Zoledronic acid (HORIZON)

p0290 The other long-term treatment study was the HORIZON extension trial in which women who had received three annual infusions of ZOL were rerandomized to receive either 3 more years of ZOL or three placebo infusions [8]. Of the 2629 women who received 3 years of active drug, 1233 underwent rerandomization. Of the 616 allocated to receive three more ZOL infusions, all but three women received at least one additional infusion. Three annual doses were received by 451 women, but 44 did not complete the follow-up. The final bone mineral density (BMD) analysis included 451 women who received at least one additional dose, and the final X-ray analysis included 469 who received at least one additional dose. For the group rerandomized to placebo infusions, the corresponding numbers available for DXA and X-ray were 470 and 486, respectively. Bone density in the hip tended to decrease in the placebo group compared to the group that received three more ZOL acid infusions, but the difference between them was just over 1%. Spine bone density increased in both placebo and active drug groups but was greater by 2% in the group that received the second 3-year set of ZOL infusions. Interestingly, at year 6, there was very little difference in a bone resorption marker, C-telopeptide of type 1 collagen cross-links (CTX), between the two groups, suggesting that the first three infusions of ZOL had a lasting impact on bone resorption. While there were no differences in clinical fractures between the two groups, there were fewer morphometric vertebral fractures in the women who received six infusions of ZOL compared to those who only received three [8].

p0295 In addition to the first extension of HORIZON, 190 women who had received six annual infusions of ZOL met inclusion criteria and agreed to be randomized once more to either the more active drug or 3 placebo infusions [9]. About two-thirds had bone density measurements at the end of the trial. Interestingly, hip bone density tended to decrease slightly in both groups, with no significant difference between them. Again CTX was also the same in the two groups, again suggesting a long-term effect of prior ZOL infusions. There was a small imbalance in cardiac arrhythmias in those women who received nine ZOL infusions compared to six, although there was no difference in arrhythmias as serious adverse events. The study was too small to observe any differences in fracture incidence [9].

p0300 In a recent post hoc analysis, bone density and bone formation markers were compared at 3 years after BP discontinuation in FLEX and the HORIZON Extension Trial [10]. The purpose of this study was to determine the impact of a drug holiday, after the recommendation that one be considered after 5 years of oral treatment, similar to the FLEX study or 3 years of intravenous treatment, similar to the HORIZON trial. At the start of the extension studies, there were some differences in-between the women in FLEX and the women in HORIZON. The subjects in the former group were significantly younger (73.7 vs 75.5 years) and had fewer prevalent vertebral fractures (34.3% vs 63.2%) and higher hip bone density (T-score −1.8 vs −2). Three years after the start of the extension period, more subjects previously on ALN had a significant decrease in total hip bone density compared to those previously treated with ZOL (25.2% vs 18.7%, $P < .01$). This may again suggest a long-lasting effect of ZOL [9].

p0305 Other studies confirm the extended impact of ZOL infusions. In 2009 McClung et al. [11] randomized 581 postmenopausal women (average age about 60 years) to two annual infusions of ZOL, one infusion of ZOL at baseline and a placebo infusion at 1 year, or two annual placebo infusions. At 2 years, total hip had increased 2.91% in the first group and 2.28% in the second but decreased 1.45% in the placebo group. The pattern was similar in the femoral neck. Serum CTX declined markedly in the first group with a slow rise toward the end of month 12. With the second ZOL infusion the CTX decreased again. In contrast, a single ZOL infusion at baseline was followed by a gradual increase of CTX, although it never reached the baseline level. The placebo group had no change in CTX over the 2-year study. Greenspan et al. reported on the 2-year impact of a single ZOL infusion versus placebo in older women (average age about 85 years) [12]. At 2 years, total hip bone density increased by 2.6% in the active drug group and decreased by 1.5% in the placebo women. However, in these older women, improvement in femoral BMD neck at 1 year was not sustained to 2 years, although the absolute value was still higher than the placebo group. In older women the ZOL-induced drop in CTX was sustained for 2 years.

p0310 Grey et al. administered one infusion of varying doses of ZOL acid to women in their mid-sixties [13]. Comparing those that received the standard 5 mg dose to placebo, total hip BMD was still above baseline 5 years after the infusion and 5.4% higher than that of the placebo subjects. Also, at 5 years after the single

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infusion, CTX was 27% lower in the active drug group compared to placebo. Recently, Reid et al. reported the impact of four infusions of ZOL (5 mg each) over 6 years compared to placebo in osteopenic women aged about 71 years [14]. Total hip BMD was almost 4% higher at 6 years in the active drug group, whereas it had decreased almost 4% in the placebo group. There were 37% fewer fragility fractures in the ZOL group, compared to placebo. The conclusion from the cited studies is that the impact of ZOL on surrogates for fracture, BMD, and bone turnover markers (BTMs) lasts longer than 1 year. Thus a patient treated with three annual infusions of ZOL has evidence of continued effect beyond 3 years and may be eligible for an interruption in treatment. It has also been suggested that the interval between ZOL infusions could be lengthened such that a patient would have three infusions over 5 years [15], similar to the four infusions in 6 years as reported by Reid et al. [14]. Having all BP-treated patients take 5 years of treatment—either oral for 5 years or three infusions spread over 5 years—simplifies management for the busy clinician, but studies of the efficacy of the latter regimen on fracture risk reduction are lacking.

s0035 79.2.3 Risedronate and ibandronate

p0315 There is much less information about long-term treatment with RIS or IBAN. Eastell et al. reported on subjects who had 5 years of blinded RIS treatment (5 mg/day) followed by a 2-year open-label continuation of the same dosage [16]. The subjects then stopped RIS and were assessed at 6 and 12 months after discontinuation. Urinary N-telopeptide (NTX) rose toward baseline at the two time points. BMD was measured at the 1-year discontinuation visit. While lumbar spine and femoral neck BMD were maintained, total hip BMD decreased back to the about the original (year 0) level. In an earlier study, subjects discontinuing RIS after 3 years of treatment remained at lower risk for morphometric vertebral fracture compared to subjects who had been on placebo for 3 years followed by the 1-year extension [17]. In an extension trial [18], women on various regimens of IBAN for 2 years were randomized to monthly IBAN in doses of 100 or 150 mg. Over the next 3 years, spine BMD rose modestly in both groups (no difference) and total hip was maintained. There was no placebo group; thus information on treatment interruption is lacking.

s0040 79.2.4 Observational data

p0320 Observational studies have provided some information on long-term treatment and interruption of treatment. However, such studies have serious limitations, including confounding by indication and by low persistence with BP treatment. In a recent systematic review, persistence with BP treatment ranged from 17.7% to 74.8% at 1 year and 12.9% to 72.0% at 2 years [19]. At 3 years the medication possession ratio varied from 27.2% to 46%. Tracking of BP use is often complicated by patients stopping and restarting treatment. For example, Balasubramanian et al. used data from the Truven commercial insurance database in the United States [20]. They found that by 2 years, 70% of women had discontinued oral BP treatment. Almost half of women who discontinued treatment restarted it; those women who were hospitalized or were older were less likely to reinitiate BP therapy. The two largest observational studies are from the population-based Kaiser Permanente and Medicare databases. The Kaiser report included over 39,000 women, age 45 and above, who took BPs for more than 3 years compared to women who went on a drug holiday [21]. Fracture risk was lower in the drug holiday group suggesting that in that group, BP discontinuation was due to a lower risk profile. Conversely, a Medicare database report included over 160,000 highly compliant older women, [22] and showed a RR of hip fracture of 1.22 (1.11−1.34) at a median of 2.7 years post drug interruption, a risk that increased with the duration of the drug holiday. In countries with medication registries, it may be easier to determine real-world effectiveness of treatment. Strom et al. reported that the longer adults stayed on BP treatment, the less likely they would be hospitalized for a fracture [23]. These findings are compatible with the conclusions of the IOF Epidemiology/Quality of Life Working Group that discontinuation of BPs leads to increased risk of fracture [24].

79.2.5 Side effects of bisphosphonates s0045

p0325 A full discussion of BP's side effects is beyond the scope of this chapter. Two side effects, however, ONJ and AFF, play a major role in long-term BP treatment because the fear of such side effects and their sensational reporting in the general media have had a profound impact on osteoporosis evaluation, diagnosis, treatment, and adherence, despite their low incidence. ONJ is defined as at least 8 weeks of exposed bone in the maxilla or mandible, despite appropriate therapy. Most definitions also require that there has been no radiation to the jaw or metastatic disease in the area [25]. BP-associated ONJ was described as early as 2003 in patients with metastatic disease receiving high and repeated doses of the intravenous BPs, pamidronate, or ZOL. Although patients may be asymptomatic, many have pain, swelling, and in severe cases a fistula. Risk factors include smoking, poor oral hygiene, diabetes

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mellitus, glucocorticoid therapy, and invasive dental procedures. Current estimates for BP-associated ONJ in patients on BP for osteoporosis range from 1/10,000 to 1/100,000 [25]. A recent review from Denmark found the incidence of surgery for ONJ to be about 2.53 per 10,000 patient-years in patients on ALN [26]. There was an increased risk for recent, long-term, and adherent users of this most commonly used BP for osteoporosis. The increased risk with long-term use is consistent with findings from an early series [27]. In another recent study the number of women in the United Kingdom who were admitted to hospital because of ONJ was tracked over 8.2 years [28]. In women without cancer the incidence of hospitalization for ONJ was 1.38 per 10,000 patient-years in oral BP users compared to 0.18 per 10,000 patient-years in never users. In patients with osteoporosis the course is usually self-limited and can be treated conservatively [25]. These studies are good examples of a serious but unusual side effect that, nevertheless, has led to fewer patients initiating or adhering to BP treatment for osteoporosis. In the 2015 International Task Force report on ONJ, Khan et al. cited the highest incidence of ONJ in the oncology patient population (1%−15%), where high doses of these medications are used at frequent intervals, in contrast to an incidence of 0.001%−0.01% in the osteoporosis patient population, an incidence that is marginally higher that in the general population (<0.001%) [29].

p0330 Even more worrisome in the general population is the risk of AFF. The idea that a drug taken to reduce fracture risk might cause a particularly serious fracture was reported widely in popular media [30]. AFFs, as defined by the American Society for Bone and Mineral Research (ASBMR) Task Force, are located on the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare and must have four of five major characteristics: minimal trauma at most, a start at the lateral cortex, and be mostly transverse, if complete will have a medial spike (incomplete will be in lateral cortex only), no or minimal comminution, and the lateral cortex will have a localized reaction that shows "beaking" or flaring [30,31]. While such fractures have been reported in patients never exposed to BP (or other antiresorptive drugs) and in patients with genetic bone disorders not treated with BPs [32], there is no doubt about an association with BP treatment, with increased risk with longer duration and a decrease in risk with treatment cessation. An observational study from Italy provides perspective on the incidence of AFF versus typical osteoporotic fractures in a 7-year analysis (almost 1.4 million patient-years) of a major hospital [33]. During this time, there were 4003 fractures of the femur, of which 3335 were low trauma and in the femoral neck or trochanteric region. There were 308 low trauma fractures that were subtrochanteric or in the femoral shaft. Of these, only 22 were atypical (13 patients on BPs). Of the non-AFF in the subtrochanteric or shaft area, 20 of 286 patients were on BPs. Other epidemiologic studies have confirmed the fact that osteoporotic fractures of the proximal femur are much more common—and can be decreased by BPs—than AFF caused by BPs. A recent review made several estimates of benefits versus harms of AFFs [34]. In a 3-year period, they estimated that for every 10,000 patients treated, 1000 fractures would be prevented and just under 1 atypical fracture would be caused. However, treatment is almost always for longer than 3 years, and there is good evidence that duration of BP treatment increases the risk of AFF. In the widely cited Kaiser Permanente Study, the rate of AFF rose from 22 per 100,000 patient-years for patients on BPs from 4 to 5.9 years to 34.5 per 100,000 patient-years in those who took BPs for 10 or more years [35]. Other studies have confirmed the increased risk of AFF with time on BP treatment [36,37]. The impact of duration has led to suggestions that drug holiday or interruption of treatment might have a beneficial effect (see next). It has been difficult to determine which BP-treated patients are at highest risk for AFF, in addition to those on treatment for extended periods of time. Potential risk factors for AFF include the use of chronic glucocorticoids, proton pump inhibitors, and diabetes mellitus [38]. In the United States, people of East Asian ancestry have been found to be at higher risk [39]. Bowing of the femur, a shorter angle between the femoral neck and shaft, and varus alignment of the lower extremity suggest that the geometry of the pelvis and femur may increase the amount of tension on the lateral cortex of the femur. In practice, thigh or groin pain and possibly single energy images of the femur at the time of DXA testing may provide evidence of impending fracture [39]. The 2019 ISCD official positions for adults recommend the use of femur DXA images to detect abnormalities in the spectrum of AFF and scanning methods that generate bilateral full-length femur images [40].

p0335 Regardless of the low incidence of AFF compared to typical proximal femur fractures, concern about AFF has been trumpeted by news media, leading to patients stopping or never starting BP therapy. Not on the news have been studies suggesting that BPs have a salutary effect on mortality, including a recent large well-designed prospective cohort study [41].

79.3 Bisphosphonate interruption (holiday) s0050

79.3.1 Pharmacokinetics of bisphosphonates s0055

p0340 A comprehensive review of the pharmacokinetics and pharmacodynamics of ALN, RIS, IBAN, and ZOL

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is well beyond the scope of this chapter. In addition, there remain major questions to be answered. From reviews of this subject [42–44], it can be concluded that oral BPs are poorly absorbed in the gastrointestinal tract, but both oral and intravenous BPs are mostly incorporated into bone. The retention time is measured in months to years, and the impact on BTMs is also measured in months to years. A study of urine measurements of ALN and RIS in women who stopped treatment is emblematic of the long terminal half-life [45]. Postmenopausal women who took ALN (mean 51 months) or RIS (53 months) were assessed after they had discontinued treatment for 13–14 months. Using an HPLC method, the authors detected urinary ALN in 41% of the women who had taken ALN, but no RIS was found in the urine of previous RIS users. These data can inform the potential impact of discontinuation of osteoporosis treatment.

s0060 79.3.2 Placebo groups from FLEX and HORIZON

p0345 Review of the placebo subjects in the two main long-term osteoporosis trials provides prospective blinded data on the impact of BP discontinuation [46]. As described earlier, in the FLEX trial, subjects previously on ALN but rerandomized to placebo had no change in spine BMD over the 5-year extension, but the total hip BMD decreased 2.8% [6]. In the HORIZON trial extension after 3 years of annual ZOL infusions, spine BMD rose similarly in those women receiving three more annual active drug infusions or three placebo infusions [8]. In the hip, there was little change in the 3-year extension. In FLEX, placebo women had more clinical vertebral fractures than those continuing ALN, whereas in the HORIZON extension, placebo women had more morphometric vertebral fractures. In neither study were there enough nonvertebral fractures to determine the impact of the discontinuation of active BP on fractures at these skeletal sites.

s0065 79.3.3 Observational studies of drug interruption (holiday)

p0350 Observational studies may have unmeasured confounders, but advantages of this study design include the potential for longer term follow-up and larger numbers of study subjects, including people who may not qualify for randomized controlled trials. In a small study of women and men who discontinued oral treatment for a mean of 6.5 years or intravenous BP for 3.6 years, there were minimal decreases in spine BMD at 24–30 months [47]. However, total hip and femoral neck BMD decreased almost 3%. There was only one wrist fracture observed as well as 2 foot fractures, and interestingly a majority of the patients restarted osteoporosis treatment. Another observational study reported that in a follow-up period averaging about 2.5 years, the chance of fracture was 40% higher in women who discontinued BP treatment compared to those who remained on treatment [48]. In a somewhat larger study, 62 of 401 women who stopped treatment for 5 years developed a fracture [49,50]. Higher age and lower BMD were associated with greater chance of fracture. The largest observational study was from Kaiser Permanente, which is a closed system with excellent pharmacy records. Women who had taken BPs for at least 3 years were assessed [21]. Those women who had maintained at least 50% adherence were considered persistent. Those who adhered less than 50% of the time or discontinued for a period of less than 1 year were considered nonpersistent. A drug holiday was considered if the patient discontinued treatment for more than 1 year (average length 3.1 years). The fracture rate (per 1000 person-years) during the study period was 32.8, 43, and 28.8 for the persistent, nonpersistent, and drug holiday groups, respectively. Thus this large observational study suggested that intermittent intake of BP led to most fractures. While the three groups were similar in many ways, it is quite possible that unmeasured factors were important in determining who fractured.

p0355 Three systematic reviews of osteoporosis treatment and discontinuation have been recently published. Fink et al. concluded that continuing treatment beyond the first conventional treatment period may lower vertebral fracture risk but may increase the risk of rare adverse effects [46]. Based on the placebo groups of the long-term studies discussed earlier, Fink et al. also concluded that taking ALN for 10 compared to 5 years was associated with lower risk of clinical vertebral fracture and having six rather than three infusions of ZOL was associated with fewer morphometric vertebral fractures. Nayak and Greenspan concluded that women with low BMD at the end of the conventional initial treatment period were likely to benefit from continued treatment [51]. Discontinuation of treatment should be considered for women with higher BMD (i.e., T-scores > -2.5) at the end of the initial treatment period. Conversely, based on their analysis of the existing evidence, Dennison et al. disagreed with the concept of drug holidays being always offered to patients on long-term BPs [24]. Tailoring the decision for drug interruption is best based on each individual patient's risk–benefit profile from long-term therapy.

p0360 After osteoporosis treatment discontinuation, BTMs are likely to change sooner than BMD. Naylor et al. studied women who had been treated with IBAN, ALN, or RIS for 2 years [52]. Fifty-seven women with

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T-scores better than −2.5 completed the 2-year no-treatment extension, and 50 had BTM data measured. Two-thirds had changes in CTX beyond the least significant change, and almost the same number had levels above the reference range. Almost three-fourths had significant increases in P1NP. Interestingly, those women with the greatest change in BTMs had the largest decrease in total hip BMD off therapy (for CTX, $r = -0.58$ and for P1NP, $r = -0.41$). These data suggest that BTMs could serve as a tool for following patients after discontinuation. However, the FLEX trial showed that follow-up measurements of BTM were not associated with fracture incidence off therapy [53]. Using a different BTM, urinary deoxypyridinoline cross-links (uDPD), in an observational study, Liel et al. found that most patients on ALN had a substantial rise in this marker after the withdrawal of treatment. In about one-quarter of these women, the uDPD increased to above the upper limit for premenopausal women. However, a clinically useful tool for determining when to restart osteoporosis treatment is not clear from these studies [54]. Elevation of a BTM beyond the normal range might be a reasonable target, but it is likely that even within the normal range, BTM increases may signal return of increased fracture risk [10]. In a recent study, Kim et al. compared changes in BMD and BTMs 3 years after switching to placebo from ALN in the FLEX study and 3 years after switching to placebo from ZOL in the HORIZON extension study. Subjects in the former study had greater loss of hip BMD and were more likely to have a significant rise in P1NP. The authors concluded that the offset of medication effect from ZOL was longer than from ALN. In clinical practice, BTM levels can be affected by many factors [10].

79.4 Guidance for patients on long-term bisphosphonate therapy

The worrisome reports of serious adverse events in patients on long-term BP in the literature several years after their drug release on the market culminated in three consecutive FDA safety-related announcements; the first on ONJ in 2005, the second on atrial fibrillation in 2007, and the third on AFF in 2010. Finally, in September 2011, after a hearing to review the long-term safety and efficacy of BPs, the FDA recommended that physicians reassess the indication for continued BP therapy beyond 3–5 years, [55,56] but noted that drug discontinuation may not be advisable in high-risk patients. Currently, all FDA-approved BPs for the treatment of osteoporosis specify "Important Limitation of Use: The optimal duration of use has not been determined. All patients on BP therapy should have the need for continued therapy reevaluated on a periodic basis."[57].

The consecutive FDA warnings and intense media coverage about potential risks from prolonged BP therapy were paralleled by a series of spikes in internet search activity on ALN quantified by Google Trends [2]. This was followed by a steep decline in BP use over the following years, including high-risk populations, such as patients with hip fractures, in the United States [2] and worldwide [58]. This development led several organizations to examine the evidence to provide the best possible guidance to their constituencies. A risk–benefit analysis, risk stratification, and the concept of drug "holiday" became a common approach incorporated by all organizations in their guidance on therapy continuation in patients on long-term BPs. Therapy interruption or suspension may be more appropriate terms, but holiday is the term most commonly used in the literature over the years.

79.4.1 American Society for Bone and Mineral Research 2016 Task Force Report: managing osteoporosis in patients on long-term bisphosphonate treatment

In 2013 the ASBMR convened a multidisciplinary Task Force on "Managing Osteoporosis Patients after Long-Term BP Treatment." Osteoporosis experts in epidemiology, endocrinology, geriatrics, and drug surveillance served on the Task Force. The main charges were set by the ASBMR Professional Practice Committee (PPC), approved by Council, and subsequently slightly modified by Task Force members to address complementary themes. These were to

- "Provide guidance on duration of BP therapy in patients with postmenopausal osteoporosis, developing an algorithm that incorporates risk assessment (efficacy).
- Determine how potential harms may affect duration of therapy (safety), with a risk/benefit perspective.
- Discuss how the algorithm may apply to men and to glucocorticoid-induced osteoporosis."

Three parallel systematic literature searches using Medline, EmBASE, Cochrane, and PubMed were implemented on the following: randomized controlled trials with long-term BPs, BPs and drug holidays, and BPs and guidelines. The FLEX and HORIZON extension studies provided the evidence to develop the algorithm. Other topics thoroughly reviewed by the Task Force members included BP benefits, harms, differential effects, their resolution upon drug discontinuation, monitoring on and off therapy, alternative therapeutic options, and patient adherence and

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preferences. Case studies were included to illustrate applicability of the proposed care pathways to challenging clinical scenarios. The Task Force work spanned 2 years, the ensuing report was reviewed and endorsed by the ASBMR PPC, and it underwent peer review by the JBMR editorial board prior to publication [59,60].

p0400 The derived management algorithm was based on post hoc analyses from FLEX and HORIZON extension, registration trials exclusively conducted in postmenopausal women and thus pertaining to this specific population. For postmenopausal women who have been on oral BP therapy for 5 years, or intravenous ZOL for 3 years, but less than 10 years, the Task Force suggested that oral BP therapy be continued for up to a total of 10 years for ALN, and 6 years of ZOL, in the highest risk stratum, namely, patients who had experienced a hip, spine, or multiple other osteoporotic fractures prior to therapy or those who experienced a major osteoporotic fracture (spine, hip, humerus, or forearm) on therapy. For the latter subgroup an evaluation for causes of secondary osteoporosis, appearance of new risk factors, vitamin D deficiency, and assessment of medication adherence was recommended. In addition, switching to alternative therapies was a possible option, but there were no adequate studies then to evaluate the efficacy of such an approach. The optimal length of therapy for the patient who suffers a fracture while on treatment also could not be defined, and clinical judgment was called on to address such cases. In individuals who have not experienced a fracture, other variables that can signal high fracture risk were recommended to inform decisions on therapy continuation. These were based on post hoc analyses from FLEX and HOROZON, and included low *T*-score (≤ -2.5) and older age ($>70-75$ years). Other variables deemed indicative of high risk included a high fracture risk based on country-specific risk assessment tools, medication use (e.g., aromatase inhibitors, glucocorticoid therapy), or a new diagnosis of a disorder associated with secondary osteoporosis. If based on the above criteria the patient remained at high fracture risk, the Task Force suggested that BP treatment be continued for another 2–3 years, with periodic reassessment. Alternative antifracture therapy, with teriparatide (TPTD) or denosumab (Dmab) as first options, then raloxifene, could be considered for those patients remaining at high risk for fracture. For those women who are not considered to be at high fracture risk, a drug holiday of 2–3 years was to be considered, with monitoring and risk assessment every 2–3 years (possibly earlier for women on RIS). Tools to identify patients who will fracture off therapy and for monitoring are limited, and therefore the Task Force report suggests reinitiation of therapy, using BPs or alternative therapies, if a patient's *T*-score drops below −2.5, or additional risks appear [59]. Although the report did not support routine measurement of bone remodeling markers, it noted that some experts would resume therapy in patients when they exceed the lower half of the premenopausal range, off therapy [61]. The report also examined data in men and subjects on glucocorticoids and concluded that the algorithm would probably be applicable to men and patients with glucocorticoid-induced osteoporosis, with some modifications, such as raising *T*-score thresholds for risk stratification in patients on steroids.

p0405 In its risk–benefit assessment the report compared the incidence of ONJ and AFF and that of typical osteoporotic fractures, as well as that of other important outcomes and serious events. BP therapy for up to 5 years will prevent approximately 175 hip fractures, 1470 vertebral fractures, and 945 wrist fractures (2590 total/100,000) for 16 AFFs/100,000 associated with treatment. This would equate into a total of 162 fractures of the spine, hip, or forearm prevented/AFF potentially caused. For longer treatment, there are insufficient data to derive similar estimates [59].

p0410 The Task Force report underscored several limitations to the evidence available and thus to its approach, in its abstract, main text, and conclusion. The algorithm reflected data from clinical trials in which the majority of subjects were Caucasian women (from Europe and America). It was based on limited evidence and applies only to vertebral fracture reduction, mostly in white postmenopausal women (from Europe and America), and not necessarily to other BPs. Furthermore, the reduction in vertebral fractures differed between FLEX and HORIZON. The reduction was in clinical vertebral fractures with 10 years of ALN (compared to 5 years of ALN and 5 years of placebo) and for morphometric vertebral fractures with 6 years ZOL (compared with 3 years ZOL and 3 years of placebo). Finally, the report outlined that country-specific thresholds and those for non-Caucasian women vary for initial treatment and therefore this may also affect thresholds for continuation or reinstitution of therapy. In view of all previously limitations the report therefore used the terms guidance rather than guideline, "suggested approach," and verbs such as "may" and "would" rather than should, consistently in the document. The abstract reads "It is obvious that there is relatively little evidence on which the Task Force can base recommendations, and indeed we have presented management suggestions based on limited data and clinical experience." A call for clinical judgment was made and for the ultimate decision to continue long-term BP therapy beyond 5 years to take into consideration previously limitations, patients' values, and preferences, to enable an individualized approach.

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Its approach was incorporated in the algorithm proposed by the Endocrine Society in its clinical practice guideline (CPG) on "Pharmacologic Management of Osteoporosis in Postmenopausal Women."

79.4.2 Endocrine Society 2019 Clinical Practice Guideline: pharmacological management of osteoporosis in postmenopausal women

s0080

p0415 In 2016 the Endocrine Society convened an international panel of experts with the main objective to formulate a CPG for the pharmacological management of osteoporosis in postmenopausal women [62]. The committee included endocrinologists and osteoporosis experts from Canada, the United States, and Europe and a methodology expert. It commissioned two systematic reviews, one to quantify the evidence for the efficacy of various pharmacologic interventions to reduce vertebral, hip, and nonvertebral fractures and the other to assess patients' preferences in a qualitative approach. The first systematic review and metaanalysis included 107 trials (193,987 postmenopausal women; mean age of 66 years; 55% Caucasian; median follow-up of 28 months). It reiterated the established efficacy of HRT (hormone replacement therapy) and SERMs (selective estrogen receptor modulator) [RRR (relative risk reduction) 40%–44%, tibolone, raloxifene], BPs [(RRR 31%–56%), ALN, RIS, ZOL, and IBAN], Dmab (RRR 68%), anabolics (RRR 74%–87%, TPTD, abaloparatide) in reducing the risk of vertebral fractures. Similarly, BPs (ALN, RIS, ZOL), Dmab, HRT (estrogen with or without progestogen), and a calcium/vitamin D combination reduced the risk of hip fractures by 40%. BPs (ALN, RIS, ZOL), Dmab, TPTD, abaloparatide, hormone therapy (HT), tibolone, calcium or vitamin D, romosozumab, and bazedoxifene reduced the risk of nonvertebral fractures by 17%–46%. The second systematic review revealed that women gave equal weight to effectiveness and adverse events, followed by the convenience of taking the drug. Cost and duration of treatment were less important factors for decision-making. The CPG committee developed an approach regarding BP drug holidays based on risk stratification. Low risk included subjects with no prior hip or spine fractures, a BMD *T*-score at the hip and spine both above −1.0, and 10-year hip fracture risk <3%, or 10-year risk of major osteoporotic fractures <20%; moderate-risk subjects with no prior hip or spine fractures, a BMD *T*-score at the hip and spine both above −2.5, or 10-year hip fracture risk <3%, or risk of major osteoporotic fractures <20%; high-risk subjects as those with a prior spine or hip fracture, or a BMD *T*-score at the hip or spine ≤ −2.5, or 10-year hip fracture risk ≥3%, or risk of major osteoporotic fracture risk ≥20%; and very high risk includes multiple spine fractures and a BMD *T*-score at the hip or spine equal to or below −2.5 [62]. The guidelines recommended BPs as first-line therapy to treat postmenopausal women at high risk (high-quality evidence), and for those taking BPs, that fracture risk be reassessed after 3–5 years, and that women who remain at high risk of fractures to continue therapy, while those who are at low-to-moderate risk of fractures to be considered for a "BP holiday (low-quality evidence)." BP holiday was defined as a temporary discontinuation of the drug for up to 5 years, possibly longer depending on BMD and clinical scenario. The guidelines recommend reassessment of fracture risk every 2–4 years and consideration of osteoporosis therapy reinitiation earlier than the 5-year holiday maximum, in the event of an interim fracture, a significant decline in BMD, or increased clinical risk status. The CPGs also underscored that fracture risk stratification should be determined using country-specific assessment tools to guide decision-making. Its derived cutoffs were based on FLEX and HORIZON extension studies that consisted mostly of Caucasian subjects, and the *T*-score cutoff and thresholds specified and may not be applicable to other populations.

79.4.3 American Association of Clinical Endocrinologists 2019: clinical practice guideline for the diagnosis and treatment of postmenopausal osteoporosis

s0085

p0420 American Association of Clinical Endocrinologists (AACE) issued their original set of recommendations for the management of postmenopausal osteoporosis in 2010. The original document suggested a drug holiday after 4–5 years of BP treatment in patients at moderate risk of fractures, and after 10 years for high-risk patients, but the terms high and moderate risk were not defined [63]. The update includes an additional risk stratum: very high-risk patients [64]. In the 2019 update, AACE refined risk stratification as follows: Recommendation 23. Patients at very high fracture risk include those with a recent fracture (e.g., within the past 12 months), fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), very low T-score (e.g., <-3.0), high risk for falls or history of injurious falls, and very high fracture probability by FRAX® (fracture risk assessment tool) (e.g., major osteoporosis fracture >30%, hip fracture >4.5%) or other validated fracture risk algorithm. Patients, who have been diagnosed with osteoporosis but are not at very

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high fracture risk, as defined above, are considered high risk (Grade B; BEL 1; downgraded due to limited evidence). With regard to drug holidays in patients on BPs, the 2019 update recommends the following: Recommendation 36 [65]. For BPs, consider a BP holiday after 5 years of oral treatment, or 3 years of intravenous treatment, if fracture risk is no longer high (*T*-score > -2.5, no fractures, etc.), but continue treatment if fracture risk remains high (Grade B; BEL 2): Recommendation 37. For oral BPs, consider a BP holiday after 6–10 years of stability in patients with very high fracture risk and continue treatment if fracture risk remains high (Grade B; BEL 2): Recommendation 38. For ZOL, consider a BP holiday when fracture risk is no longer high, but continue treatment when fracture risk is high (Grade A; BEL 1): Recommendation 39. The ending of a BP holiday should be based on individual patient circumstances such as an increase in fracture risk, a decrease in BMD, or an increase in BTMs (Grade A; BEL 1). For information on grading of the evidence, please refer to Table 79.1 [64].

t0010 **TABLE 79.1** 2010 AACE protocol for production of clinical practice guidelines.

2010 AACE protocol for production of clinical practice guidelines
2004 AACE criteria for grading recommendations

Recommendation grade	Description
A	Homogeneous evidence from multiple, well-designed, randomized controlled trials with sufficient statistical power
	Homogeneous evidence from multiple, well-designed, cohort-controlled trials with sufficient statistical power
	≥1 Conclusive level 1 publications demonstrating benefit ≫ risk
B	Evidence from ≥1 well-designed clinical trial, cohort- or case-controlled analytic study, or metaanalysis
	No conclusive level 1 publications; ≥1 conclusive level 2 publications demonstrating benefit ≫ risk
C	Evidence based on clinical experience, descriptive studies, or expert consensus opinion
	No conclusive level 1 or 2 publications; ≥1 conclusive level 3 publications demonstrating benefit ≫ risk
	No conclusive risk at all and no conclusive benefit demonstrated by evidence
D	Not rated
	No conclusive level 1, 2, or 3 publications demonstrating benefit ≫ risk
	Conclusive level 1, 2, or 3 publications demonstrating risk ≫ benefit

t0010

2010 AACE update: mapping evidence levels to recommended grading

BEL	Subject factor impact	Two-thirds consensus	Mapping	Recommended grading
1	None	Yes	Direct	A
2	Positive	Yes	Adjust up	A
2	None	Yes	Direct	B
1	Negative	Yes	Adjust down	B
3	Positive	Yes	Adjust up	B
3	None	Yes	Direct	C
2	Negative	Yes	Adjust down	C
4	Positive	Yes	Adjust up	C
4	None	Yes	Direct	D
3	Negative	Yes	Adjust down	D
1,2,3,4	NA	No	Adjust down	D

1, Strong evidence; 2, intermediate evidence; 3, weak evidence; 4, no evidence. Starting with the left column, BEL, subjective factors, and consensus map to recommendation grades in the right column. When subjective factors have little or no impact (none), then the BEL is directly mapped to recommendation grades. When subjective factors have a strong impact, then recommendation grades may be adjusted up ("positive" impact) or down ("negative" impact). If a two-thirds consensus cannot be reached, then the recommendation grade is D. NA = not applicable (regardless of the presence or absence of strong subjective factors, the absence of a two-thirds consensus mandates a recommendation grade D). *BEL*, Best evidence level.
Reproduced with permission from Camacho PM, Petak SM, Binkley N, Clarke BL, Harris ST, Hurley DL, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2016. Endocr Pract. 2016;22(Suppl. 4):1–42.

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s0090 ## 79.4.4 National Osteoporosis Guidance Group 2017: clinical guideline for the prevention and treatment of osteoporosis

p0425 The UK National Osteoporosis Guideline Group (NOGG) developed a care path algorithm that suggests a drug holiday in individuals who have no history of fracture, whose FRAX risk falls below the NOGG intervention threshold, and whose hip BMD *T*-score is above −2.5; in such patients, repeating FRAX with BMD in 1.5–3 years was recommended [66–68]. The NOGG guidance was updated in 2017. It recommends continuation of BP treatment beyond 3–5 years (3 years for ZOL and 5 years for ALN, IBAN, and RIS) in high-risk individuals (Evidence level IIb, Grade of recommendation B). Individuals at high risk were defined as 75 years or older, with a previous history of a hip or vertebral fracture, who experience one or more low trauma fractures on therapy (after excluding poor treatment adherence and ruling out causes of secondary osteoporosis) or on current treatment with oral glucocorticoids (≥7.5 mg prednisolone/day or equivalent). If treatment is discontinued, the document recommends to reassess fracture risk after a new fracture regardless of when it occurs and after 18 months to 3 years in the absence of fractures (Grade C recommendation). The authors also state that treatment review should be performed after 5 years of treatment with ALN, RIS, or IBAN and after 3 years of treatment with ZOL (Grade C recommendation). Reassessment of fracture risk in treated individuals can be performed using FRAX with femoral neck BMD (Grade B recommendation). The NOGG intervention thresholds can then be used to guide the decision as to whether treatment can be stopped for a period of time. If the hip BMD *T*-score is ≤ −2.5, resumption of treatment should be considered regardless of FRAX-derived fracture probability. If markers of bone turnover indicate relapse from suppressed bone turnover and BMD has decreased following withdrawal, resumption of treatment should be considered (Grade C recommendation). For information on grading of the evidence, please refer to Table 79.2 [68].

s0095 ## 79.4.5 Calculations of benefit and risk by experts

p0430 In addition to the work of various organizations, osteoporosis experts have reviewed the evidence and provided estimates of the osteoporotic fractures saved by treatment compared to the number of atypical

t0015 **TABLE 79.2** Grading of recommendations.

Levels of evidence for studies of intervention are defined as follows:

Ia from metaanalysis of RCTs
Ib from at least one RCT
IIa from at least one well-designed controlled study without randomization
IIb from at least one other type of well-designed quasiexperimental study
III from well-designed nonexperimental descriptive studies, e.g., comparative studies, correlation studies, case–control studies
IV from expert committee reports or opinions and/or clinical experience of authorities

The validity of candidate risk factors is also assessed by an evidence-based approach:

Ia systematic reviews or metaanalysis of level I studies with a high degree of homogeneity
Ib systematic reviews or metaanalysis with moderate or poor homogeneity
Ic level I studies (with appropriate populations and internal controls)
IIa systematic reviews or metaanalysis of level II studies
IIb level II studies (inappropriate population or lacking an internal control)
IIIa systematic reviews or metaanalysis of level III studies
IIIb case–control studies
IV evidence from expert committees without explicit critical scientific analysis or that based on physiology, basic research, or first principles

The quality of the guideline recommendations is similarly graded to indicate the levels of evidence on which they are based:

Grade A evidence levels Ia and Ib
Grade B evidence levels IIa, IIb, and III
Grade C evidence level IV

Risk factors can also be categorized according to evidence for reversible risk:

Grade A validated by use as inclusion criteria in randomized controlled trials
Grade B do not adversely affect fracture outcomes in randomized controlled trials
Grade C untested or adversely affect intervention outcomes

RCTs, randomized controlled trials.
Data from NOGG: Clinical guideline for the prevention and treatment of osteoporosis, Available from: <https://www.sheffield.ac.uk/NOGG/NOGG%20Guideline%202017.pdf>; 2017 [accessed 28.10.19]

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fractures associated with treatment. Black and Rosen estimated that many more typical osteoporotic fractures would have happened over 3 years if patients had not taken BPs, compared to the few AFF that would have occurred if the patients had adhered to BP treatment [69]. In estimates from a later detailed review of atypical fractures, 1000 osteoporotic fractures would be prevented by 3 years of BP treatment compared to 0.8 atypical fractures caused by the drugs [34]. Importantly, of the 1000 prevented, 110 were estimated to be hip fractures and 710 were estimated to be vertebral fractures. Given the excess mortality noted with these important fractures, the article concluded that benefits of BP treatment of osteoporosis clearly outweigh the risks. As summarized in the review (and described in Chapter 75), there are clinical characteristics that are associated with increased risk for AFF. Such characteristics are used in the clinical judgment recommended by the guidelines and approaches described previously.

79.4.6 Summary

s0100

p0435 The various approaches summarized earlier are all based on data provided by the FLEX and HORIZON extension studies. They unanimously recommend risk assessment after 5 years of oral BP and 3 years of IV BP and continuation of therapy in high-risk individuals (with some variation in risk definition). Two recent systematic reviews and metaanalyses confirm that the only two trials to develop care pathways regarding long-term therapy with BPs and drug holidays are the FLEX and HORIZON extension studies [46,51].

p0440 Therapy continuation for up to 6 years with IV ZOL and 10 years with ALN reduces the risk of morphometric and vertebral fractures, respectively, with no consistent evidence on nonvertebral fractures. The feared serious adverse events of AFF and ONJ are real and have to be put in the context of a risk–benefit analysis as outlined by the ASBMR and detailed previously [59]. There is no evidence to guide the management of patients on long-term BP beyond 10 years for oral ALN and 6 years for intravenous ZOL; and recommendations after such durations will have to be made by experts.

p0445 It is highly unlikely that there will ever be randomized controlled trials of sufficient size and duration to provide the evidence needed for a definitive strategy for long-term therapy in patients with osteoporosis. Thus the ASBMR Task Force guidance/algorithm remains current today (Fig. 79.1). Additional evidence regarding the effect of offset of treatment post drug discontinuation, combination, and sequential therapy, as well as the approval of two new anabolic therapies, abaloparatide and romosozumab, may affect the selection of alternative therapies in the event of BP discontinuation.

79.5 Suggested approaches to long-term treatment

s0105

p0450 Risk stratification remains the basis of shared decision-making with patients on long-term BPs with regard to initiation, continuation of drug therapy, or institution of drug holidays, as outlined in the recommendations by the various major organizations in preceding section. Age, BMD, and prior fractures remain the most consistent predictors of future fracture prior to therapy initiation, and probably so on therapy and while on drug holiday [24,59]. Risk calculators are also gaining increasing attention [70,71]. However, the current evidence is rather limited, based on trials conducted in large part in Caucasian women, limiting their generalization worldwide, and provided by implementing multiple simultaneous comparisons that were not corrected for multiplicity of testing.

p0455 Notwithstanding these limitations, we herein summarize the evidence as available today.

79.5.1 Surrogate end points for fracture on therapy

s0110

p0460 The Foundation for the National Institutes of Health (FNIH) Bone Quality project aims to collect subject level data from all placebo-controlled randomized trials to identify surrogate end points for fractures that can be used for new therapeutic drugs, namely, BMD and bone markers. The investigators conducted a metaregression based on 38 placebo-controlled trials of 19 therapeutic agents, inclusive of 6 BPs (20 trials), 4 SERMs (5 trials), calcitonin, estrogen compounds (2 trials), tibolone (1 trial), anti-RANK Ligand antibody (2 trials), parathyroid hormone (PTH) [1–84] (1 trial), 2 PTH analogs (4 trials), antisclerostin antibody (1 trial), and a cathepsin K inhibitor (1 trial), [72]. The analyses of BMD change and vertebral fracture included 111,183 subjects and 4557 fractures, and of BMD change and hip fracture included trials with 94,469 subjects enrolled and 882 hip fractures. They revealed that 2% or 6% improvements in total hip BMD on therapy were associated with a 28% or 66% reduction in vertebral fracture risk and a 16% or 40% reduction in hip fracture risk, respectively [72]. Regression models for the largest BMD changes at the total hip of 6% had r^2 of 0.56 and 0.48 for vertebral and hip fracture reduction estimates, respectively. Conversely, BMD

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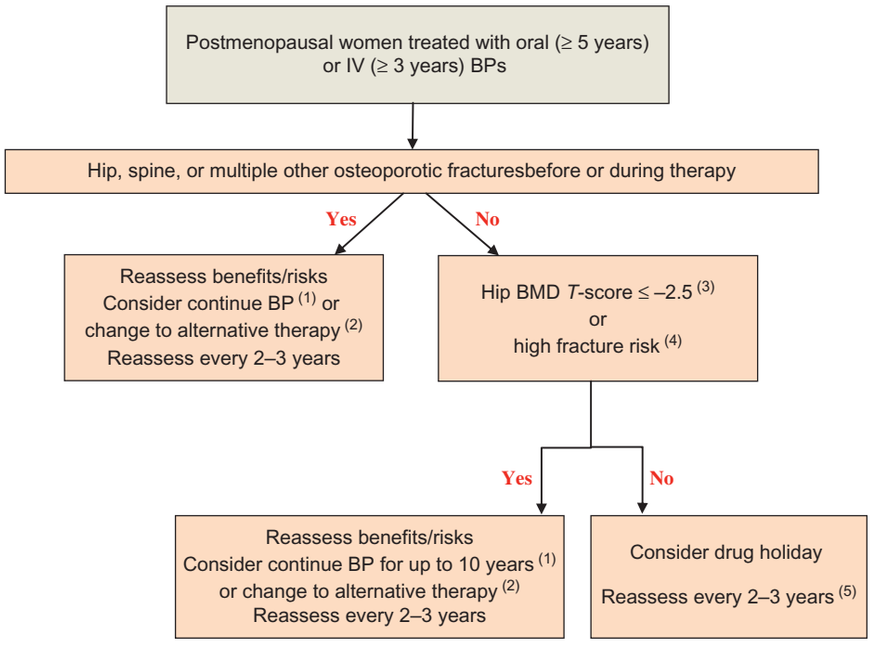

f0010 **FIGURE 79.1** Approach for management of postmenopausal women on long-term bisphosphonate therapy. *Source: Figure reproduced with permission, Wiley Inc. Adler R, El-Hajj Fuleihan G, et al. JBMR 2016;31(10):1910. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA, et al. Does osteoporosis therapy invalidate FRAX for fracture prediction? J Bone Miner Res 2012;27 (6):1243–51.*

(1) From the registration trials, the benefits of 5 years of therapy clearly outweigh the risks.For treatment up to 10 years with oral bisphosphonates (FLEX extension) and 6 years with intravenous bisphosphonates (HORIZON extension), estimates of benefits and risks are based on much weaker data. For patients who fracture on therapy, assess adherence and rule out secondary causes of osteoporosis. Management of high-risk patients is discussed in the text.
(2) The benefits of switching to an alternative anti-fracture therapy after prolonged bisphosphonate treatment have not been adequately studied.
(3) Based on FLEX and HORIZON extension study (Caucasian women), may not apply to other populations.
(4) High fracture risk: defined by older age (70–75 years), other strong risk factors for fracture, or FRAX fracture risk score that is above country-specific thresholds. The use of FRAX in patients on therapy was only assessed in the Manitoba observational cohort.(1)
(5) Reassessment includes clinical evaluation, risk assessment, including risk factors and may include bone density measurement by DXA. The monitoring interval with DXA should be based upon changes that are detectable and clinically significant. Reassessment may be necessary at less than 2 years in patients with a new fracture, or in light of anticipated accelerated bone loss (e.g., institution of aromatase inhibitor or glucocorticoid therapy).

increments were not predictive of nonvertebral fractures between treatment and reduction in nonvertebral fractures, possibly because such a relationship, even for the most effective agents, is generally much weaker [72]. The study findings are consistent with similarly conducted metaregressions evaluating the relationship between BMD and vertebral fractures and nonvertebral fractures albeit with a smaller number of total participants [73,74]. Limitations of the FNIH metaregression include the heterogeneity in study duration and definition of fractures between trials, and the fact that only BMD changes obtained at the end of the study, and not earlier, were correlated with fracture efficacy. Most importantly, the significant findings were achieved with regression curves derived from a very large number of subjects ($>100{,}000$) and may not necessarily apply to an individual patient on therapy in terms of predicting treatment response.

p0465 Investigators on the FNIH at project also analyzed study-level data from 28,000 participants enrolled in 11 BP and 3 SERMs placebo-controlled fracture end point trials. Changes in bone alkaline phosphatase (ALP) and N-terminal propeptide of type I procollagen (PINP) were available for over 16,000 and 10,000 participants, respectively. There was a strong relationship between treatment-related bone ALP or PINP changes and vertebral fracture risk reduction [$r^2 = 0.82$ ($P < .001$) and $r^2 = 0.75$ ($P < .011$), respectively]; but the relationships were weaker and no longer statistically significant for nonvertebral and hip fractures. Analyses limited to BP trials gave similar results. For all fracture types, relationships with all fracture types

were weaker and nonsignificant for bone resorption markers, namely, NTx/Cr and sCTX [75]. Noteworthy, not all trials measured all four markers, assays and fasting status of individuals varied, and cross-calibration between the various assays was not available. The findings do not apply to anabolic therapies, and most importantly, the findings do not apply to individual subjects. The conclusions are, however, consistent with previously published analyses from smaller and shorter studies conducted at the individual level [53,76–81]. It is possible, but not established yet, that early BTM monitoring may eventually be useful to identify treated individuals demonstrating a suboptimal treatment response.

s0115

79.5.2 Surrogate end points for fracture off therapy

p0470 In the FLEX study the only significant predictor(s) of fracture risk reduction was for nonspine fractures in women with an FN *T*-score ≤ -2.5 and no vertebral fracture at study baseline, if subjects continued ALN for 10 years compared to a similar subgroup who discontinued ALN after 5 year (1/12 subgroup analyses that turned out significant) [82]. In addition, femoral neck and total hip *T*-scores, entered as tertiles at study extension, predicted a threefold increase in the risk of any clinical fracture after ALN discontinuation in subjects who were randomized to placebo [53]. Similarly, age (entered as a continuous variable) and hip BMD *T*-score (lowest vs other two tertiles) at time of holiday initiation predicted clinical vertebral fractures during the 5 years extension [53]. In the HORIZON extension, subjects with an FN or total hip *T*-score ≤ -2.5 at entry into the extension, had an increased risk of morphometric vertebral fractures by three- to fourfold, if randomized to placebo [83]. Similarly, on univariate analyses, hip *T*-score entered as a continuous variable, prevalent vertebral fractures, and incident nonvertebral fractures in the core study predicted the risk of nonvertebral fractures, in subjects assigned to placebo in the extension [83]. BTM measurements, while having some promise, and used by some experts, cannot be recommended for risk stratification at the individual level at this time [59]. For an overview of the clinical utility of BTMs in untreated or treated individuals, please refer to a recent clinical review [84].

s0120

79.5.3 Alternative therapies after long-term bisphosphonates

p0475 Switching to alternative therapies in high-risk patients on long-term BPs, as opposed to continuation with a BP, is a consideration (Fig. 79.1, ASBMR algorithm). The switch could be to a more potent antiresorptive (Dmab) or to anabolic treatment. The evidence to-date consists of RCTs with BMD data as outcome [85–87] and is summarized in Table 79.3 (switch to Dmab) and Table 79.4 [88–93] (switch or add on to TPTD), as compared to BP continuation. The trials were relatively small (less than a hundred to few hundreds per arm), included subjects in mid–late 1960s, on prior BP treatment on the average for 1.5–3 years, with the exception of the study by Miller et al. (6.3 years), and only lasted 1 year, for studies switching to Dmab (Table 79.3), and 2–5 years for studies switching to TPTD (Table 79.4), with a follow-up for up to 2 years. Lag time or washout periods between switch was zero, undefined, or relatively short being less than a month for the most part (Tables 79.3 and 79.4). Switching to Dmab, as opposed to BP continuation, consistently resulted in slightly larger increments in total hip BMD by a mean of 0.9%–1.6% (Table 79.3 and Fig. 79.2) [94–97], increments that are modest.

p0480 However, such modest changes have been demonstrated to result in reductions in the risk of vertebral and nonvertebral fractures in metaregression analyses [98,99]. Conversely, switching from BP to TPTD consistently resulted in an early loss of BMD in the first 6–12 months, a loss that ultimately reversed by 18 months (Table 79.4 and Fig. 79.3) [88–91].

p0485 These early decrements led some investigators to recommended bridging the switch to TPTD with continued BP treatment for a few months, but the optimal duration for such overlap is unclear [89]. Such decrements early after switch to TPTD come in sharp contrast to the increments in bone mass at several skeletal responses in treatment naïve subjects. In one recent study, switching to a newer anabolic agent, romosozumab, did not lead to a short term decrease in hip BMD [100]. It is important to note that Dmab, TPTD, abaloparatide, and romosozumab therapy are associated with rapid bone loss postdiscontinuation. Thus consolidation of achieved gains with a potent BP is required [85,87]. However, it is unclear whether such losses after discontinuation of Dmab or TPTD do take place, to the same extent or at all, in patients previously treated with long-term BPs [101]. Equally unclear is the treatment efficacy of the previously described treatment alternatives in patients who were previously on long-term BP, as is their optimal treatment duration.

79.6 Conclusion

s0125

p0490 The chronic nature of osteoporosis mandates a lifelong management approach. Once the diagnosis is made, treatment decisions and drug selection are based on fracture risk assessment and drug efficacy

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t0020 **TABLE 79.3** Randomized trials investigating change in bone mineral density 1 year after switching to denosumab (Dmab) versus continued bisphosphonate (BP) therapy.

Study/entry criteria	Drug group/ study duration	Arm/ total sample size	Age (years, mean ± SD)	*T*-score total hip	History of fracture N (%)	Previous BP duration Mean (± SD) Median (Q1, Q3) months[a]	Lag/washout period	% Changes in total hip BMD 12 months
Simultaneous therapy								
Kendler et al. [94]/ Postmenopausal women ≥55 years − 4 ≤ *T*-score ≤ − 2 LS or HipALN 70 mg/week for at least 6 months	→ Dmab 60 mg every 6 months	253/ 504	66.9 ± 7.8	− 1.79 ± 0.82	Osteoporotic: 117 (47%)	36.0 (6, 133)	Subjects received open-label, branded ALN 70 mg once weekly for a month prior to randomization	1.9[b]
	→ALN continuation 70 mg once weekly	251/ 504	68.2 ± 7.7	− 1.81 ± 0.74	Osteoporotic: 134 (53%)	34.5 (6, 192)		1.05
Recknor et al. [95]/ Postmenopausal women ≥55 years − 4 ≤ *T*-score ≤ − 2 LS or hipDiscontinued BP therapy 1 month or more prior to screening or had insufficient adherence	→Dmab 60 mg every 6 months	417/ 833	67.2 ± 8.1	− 1.8 ± 0.7	Osteoporotic:132 (31.7) Nonvertebral: 121 (29) Vertebral: 23 (5.5)	16.7 (4.8, 51.7)	Discontinued BP therapy 1 month or more before screening	2.3[b]
	→IBN 150 monthly	416/ 833	66.2 ± 7.8	− 1.8 ± 0.7	Osteoporotic: 121 (29.1) Nonvertebral: 105 (25.2) Vertebral: 23 (5.5)	16.8 (4.0, 57.4)		1.1
Roux et al. [96]/ Postmenopausal women ≥55 yearsReceiving ALN ≥1 month prior to screening Stopped ALN before the screening or had insufficient adherence	→Dmab 60 mg every 6 months	435/ 870	67.8 ± 7.0	− 1.6 ± 0.9	Osteoporotic:151 (34.7)	20.0 (5.7, 52.5) 133 were still receiving ALN at study entry	No wash out period: subject must have either stopped oral ALN therapy before the screening visit, or was still taking oral ALN therapy	2[b]
	→RIS 150 mg once monthly	435/ 870	67.7 ± 6.8	− 1.6 ± 0.8	Osteoporotic:150 (34.5)	27.2 (8.9, 64.0) 126 were still receiving ALN at study entry		0.4
Miller et al. [97]/ Postmenopausal women ≥55 years ≥2 years oral BP therapy before screening *T*-score ≤ − 2.5 LS, TH, FN	→ Dmab 60 mg SC every 6 months	321/ 643	68.5 ± 7.1	− 1.93 ± 0.74	Any: 169 (52.6) Osteoporotic:120 (37.4) Nonvertebral: 109 (34) Vertebral: 24 (7.5)	6.2 ± (3.8) years	Oral BP therapy for 2 years or longer immediately before screening No lag period	1.9[b]
	→ ZOL 5 mg IV every 12 months	322/ 643	69.5 ± 7.7	− 1.93 ± 0.80	Any: 159 (49.4) Osteoporotic:121 (37.6) Nonvertebral: 106 (32.9) Vertebral: 28 (8.7)	6.4 ± (3.7) years		0.6

[a] *Months unless mentioned otherwise.*
[b] *Significant difference in % change in hip BMD between the two arms, P < .05.*
ALN, Alendronate; *BMD*, bone mineral density; *Dmab*, denosumab; *IBN*, ibandronate; *RIS*, risedronate; *ZOL*, zoledronic acid.

t0025 **TABLE 79.4** Randomized trials investigating change in bone mineral density after switching to or adding teriparatide.

Study/entry criteria	Drug group	Arm/ total sample size	Age (years, mean ± S)	Total hip *T*-score	History of fracture *N* (%)	Previous BP duration Mean (± SD) Median (Q1, Q3) months	Lag/washout period	% Change in total hip BMD			
								6 months	12 months	18 months	24 months
Ettinger et al. [90]/ Women 60–87 years of age Prior LS or TH *T*-score ≤ −2.5 on ALN 10 mg/day or RLX 60 mg/day for 18–36 months before study entry.	ALN→TPTD	33/59	71.2 ± 7.65	−2.3 ± 0.8	–	29.3 ± (5.2)	NA	−1.8%[a]	–	0.3%[a]	–
	RLX→TPTD	26/59	68.8 ± 5.6	−2.1 ± 0.5	–	29.0 ± (5.5)		0.5%	–	1.8%	–
Boonen et al. [88]/ Postmenopausal women ≥55 years LS (L1–L4), FN, or TH *T*-score < −2.5 and ≥1 preexisting clinical vertebral or nonvertebral fragility fracture within the last 3 years before enrollment Use of BP (ALN, RIS, or etidronate) >12 months with <3 months of any other BP Use of non BP > 12 months with <3 months of any BP	ALN→TPTD	107/ 245	70.3 ± 6.9	–	–	29.2 (19.2, 52.3)	Median (Q1, Q3): ALN: 28.0 (17.0, 38.0) days RIS: 26.0 (14.0, 41.0) days	−1.2%	−0.6%	+0.6%	+2.1%
	RIS→TPTD	59/245	68.9 ± 7.1	–	–	23.4 (19.2, 29.7)		−1.6%	−0.4%	+0.9%	+2.9%
Miller et al. [91]/ Postmenopausal women with osteoporosis LS or TH *T*-score ≤ −2.0 and ≥1 prevalent osteoporotic fracture Received either ALN 10 mg daily or 70 mg weekly or RIS 5 mg daily or 30–35 mg weekly for at least 24 months	RIS→TPTD	146/ 292	69.3 ± 7.4	−3.1 ± 0.6	Fragility fracture: 101 (69.2%)	37.2 ± 10.3	1–2 weeks	−1.2%	−0.3%[a]	–	–
	ALN→TPTD	146/ 292	67.7 ± 7.8	−3.1 ± 0.6	Fragility fracture: 100 (68.5%)	38.0 ± 11.1		−1.9%	−1.7%	–	–
Cosman et al. [89]/ Postmenopausal women ≥50 years Previous diagnosis of osteoporosis based on fracture history and/ or LS or TH *T*-score ≤ −2.0 On ALN 70 total mg/ week or RAL 60 mg/ day for at least 18 months	ALN→TPTD/ 18 months	50/102	69.1 ± 1.4	−2.0 ± 0.1	–	45.7 ± 3.1	No lag period mentioned women continued ALN and RAL treatments during the 2-month antiresorptive phase and then randomized (1:1) to either continue or discontinue their ALN or RAL treatments	−0.8%	–	+0.9%	–
	ALN + TPTD/ 18 months	52/102	67.8 ± 1.4	−2.0 ± 0.1	–	38.4 ± 3.0		+1.4%[a]	–	+3.2%[a]	–
	RAL→TPTD/ 18 months	49/96	68.6 ± 1.1	−2.1 ± 0.1	–	39.8 ± 3.0		+0.5%	–	1.8%	–
	RAL + TPTD/ 18 months	47/96	68.3 ± 1.1	−1.9 ± 0.1	–	46.3 ± 3.1		+1.8%[a]	–	+2.8%	–

[a]*Significant difference in % change in hip BMD between the two arms.*

ALN, Alendronate; *BMD*, bone mineral density; *RLX/RAL*, raloxifene; *RIS*, risedronate; *TPTD*, teriparatide.

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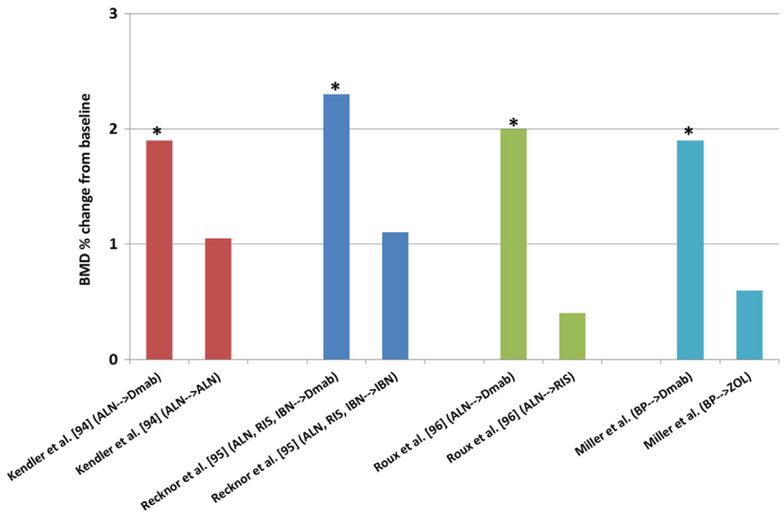

FIGURE 79.2 Change in hip BMD at 12 months with continued bisphosphonate versus switch to denosumab. * Indicates significant difference between groups, $P < .05$. *ALN*, Alendronate; *BMD*, bone mineral density; *BP*, bisphosphonate; *Dmab*, denosumab; *IBN*, ibandronate; *RIS*, risedronate; *ZOL*, zoledronic acid. f0015

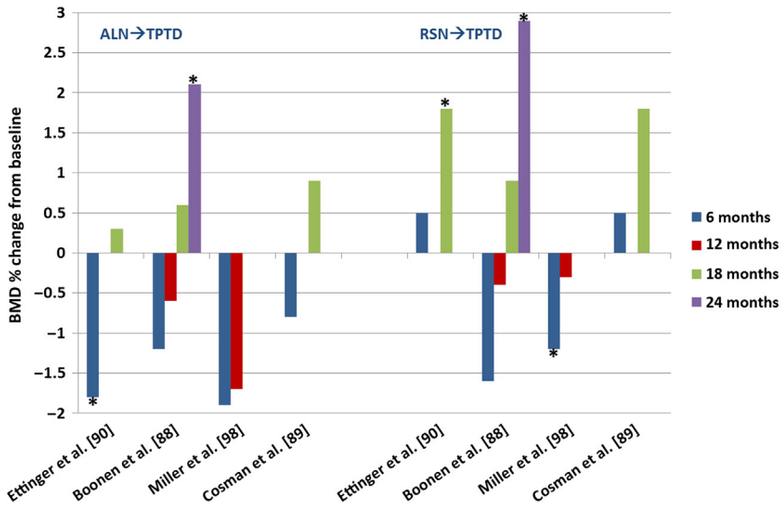

FIGURE 79.3 Change in hip BMD after switching from a bisphosphonate to teriparatide. * Indicates significant difference between groups, $P < .05$. *ALN*, Alendronate; *BMD*, bone mineral density; *RSN*, risedronate; *TPTD*, teriparatide. f0020

(taking into consideration the skeletal sites at the highest risk of fracture). The challenge is to determine the optimal duration of therapy taking into account fracture risk stratification (low, moderate, high, very high), its changing nature over time, patient adherence and preferences, pharmacokinetics/offset of efficacy of drug therapy, and a risk–benefit analysis. New drugs were approved based on registration trials similar to the ones for existing approved drugs, and no trials are anticipated to address sequential therapies over extended periods of time, in general, and following initial BP therapy in particular. Furthermore, there is also no evidence base to inform treatment decisions beyond 10 years. Therefore the management of such patients is based on expert opinion taking into account the patient's individual risk profile.

The ASBMR algorithm provides a framework for decision-making that is based on fracture risk assessment in patients on BPs for less than 10 years. While the recommendation to treat fragility fractures is universal, risk stratification in treatment naïve patients, who have not experienced a fracture, is quite variable worldwide [102]. Fracture risk assessment approaches in patients on long-term BPs are equally variable. They include clinical risk factors, comorbidities (steroids, frailty), *T*-scores, fracture risk calculators (both with variable cutoffs), or a combination of any of these. Concerns regarding the accuracy of risk assessment tools to predict future fractures in patients on therapy have been raised, but analyses from the Manitoba Canadian cohort suggest that at least in the case of FRAX they are feasible [103]. We concur with the p0495

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ASBMR approach on fracture risk assessment after 3 years of intravenous ZOL and 5 years of oral BP therapy, and on recommendations to continue BP therapy, for up to 6 years of intravenous ZOL, or up to 10 years for oral BPs, in high-risk patients. We consider individuals at high risk those who are older (>70–75 years), have comorbidities such as frailty or are on corticosteroids or sex-steroid ablation hormonal therapy, have a low BMD if Caucasians (*T*-score below −2 or −2.5 at the hip), exceed their country-specific fracture risk threshold, and those who suffer prevalent (spine or hip), or incident fractures on BP treatment (provided poor adherence and secondary causes of osteoporosis have been ruled out). Subjects at lower risk can be considered for a BP drug interruption or holiday, with periodic monitoring every 2–3 years, consisting of clinical evaluation, measurement of BMD, and possibly bone markers [59,72,75]. Consideration to resume drug therapy in patients on drug holidays is probably best based on incident fractures, bone loss (exceeding center-specific least significant change), high fracture risk score, and possibly high BTMs (exceeding lower third of premenopausal range). Importantly, it would be most desirable to refer patients on long-term BP to a bone expert, who can best describe benefits and risks to the individual patient, engaging him/her in the decision to reach a tailored individual decision and agreeable therapeutic plan.

s0130 ## Acknowledgment

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NON-PRINT ITEM

Abstract

Bisphosphonates (BPs) remain first-line treatment for osteoporosis; long-term management is based on registration trial extensions. In one, postmenopausal women after 5 years of alendronate (ALN) were rerandomized to 5 more years of ALN or placebo. In another, women receiving three annual zoledronic acid (ZOL) infusions were rerandomized to three more active or placebo infusions. Continuing ALN led to fewer clinical vertebral fractures; continuing ZOL led to fewer morphometric vertebral fractures. Fracture risk reduction must be weighed against risks of osteonecrosis of the jaw and atypical femoral fractures. The American Society for Bone and Mineral Research Task Force approach remains valid. Patients at high fracture risk after 5 years (oral) or 3 years (intravenous) BP should continue treatment with periodic reassessment. Treatment beyond 10 years is guided by clinical judgment, and new long-term studies are unlikely. Alternative treatments are an option, but bone loss resumes immediately after discontinuation of all osteoporosis medications other than BPs.

Keywords: Bisphosphonates; drug holiday; drug interruption; drug suspension; drug discontinuation; discontinued treatment; risk–benefit; fracture risk