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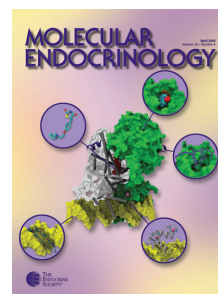
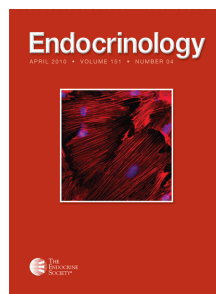
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Long-Term Use of Bisphosphonates in Osteoporosis

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Context: Bisphosphonates have been widely used in the treatment of osteoporosis. Uncommon side effects have emerged in postapproval use. Because bisphosphonates accumulate in bone and are released for months or years after treatment is stopped, it is reasonable to consider the clinical question of how long to treat.

Objective: In this personal perspective, we review the pharmacology and mechanism of action of bisphosphonates and the clinical studies that support their efficacy. We then review the literature for longer-term studies and reports of possible side effects that were not seen in clinical trials.

Results: Bisphosphonates have demonstrated antifracture efficacy in randomized, placebo-controlled trials of 3 and 4 yr duration and have been widely used since the initial release of alendronate in 1995. For zoledronic acid and risedronate, an early effect (fractures reduced within 6–12 months of starting therapy) has been shown. A sustained effect for risedronate has been shown through 5 yr and suggested through 7 yr. Ten-year data with alendronate and 8 yr data with risedronate indicated good tolerability and safety; it is unlikely that longer-term studies will be done. Side effects that emerged in clinical trials include esophageal irritation with oral administration and acute phase response with iv treatment or high-dose oral therapy. Uncommon side effects that have been noted with wide clinical use include osteonecrosis of the jaw, musculoskeletal complaints, and atypical fractures. The numbers of events are small, and a clear cause-and-effect relationship between these events and bisphosphonate treatment has not been established. Because bisphosphonates accumulate in bone, they create a reservoir leading to continued release from bone for months or years after treatment is stopped. Studies with risedronate and alendronate suggest that if treatment is stopped after 3–5 yr, there is persisting antifracture efficacy, at least for 1–2 yr.

Conclusions: Bisphosphonates are popular and effective for treatment of osteoporosis. Because they accumulate in bone and provide some residual antifracture reduction when treatment is stopped, we recommend a drug holiday after 5–10 yr of bisphosphonate treatment. The duration of treatment and length of the holiday are based on fracture risk and pharmacokinetics of the bisphosphonate used. Patients at mild risk might stop treatment after 5 yr and remain off as long as bone mineral density is stable and no fractures occur. Higher risk patients should be treated for 10 yr, have a holiday of no more than a year or two, and perhaps be on a nonbisphosphonate treatment during that time. (*J Clin Endocrinol Metab* 95: 1555–1565, 2010)

Bisphosphonates are made up of two phosphonic acids joined to a carbon plus two side chains designated R¹ and R² (Fig. 1) (1). They were discovered in the mid-1800s and to this day have wide commercial use as antiscaling

agents because of their physical-chemical property of complexing with divalent cations (*e.g.* calcium, magnesium, *etc.*). The P-C-P structure acts as a bone hook that causes these compounds to bind avidly to hydroxyapatite crystals

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Abbreviations: AF, Atrial fibrillation; BMD, bone mineral density; CCr, creatinine clearance; FIT, Fracture Intervention Trial; ONJ, osteonecrosis of the jaw.

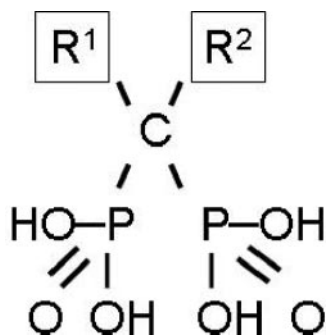


FIG. 1. Structure of pyrophosphate and geminal bisphosphonates. [Reproduced with permission from N. B. Watts: *The osteoporotic syndrome*, 4th ed. (edited by L. Avioli), Academic Press, San Diego, 2000, p 121–132 (1).]

on bone surfaces, particularly at sites of active bone remodeling. Because of their affinity for bone, bisphosphonates are used for nuclear bone scintigraphy. In the late 1960s, they began to be used for treatment of metabolic bone diseases including heterotopic ossification, fibrous dysplasia, osteogenesis imperfecta, Paget's disease of bone, hypercalcemia due to a variety of causes, bone loss due to a variety of causes, destructive arthropathy, and skeletal involvement with metastatic cancer or multiple myeloma.

Pharmacology, pharmacokinetics, and mechanism of action

Binding affinity and antiresorptive potency differ among the compounds. Although complex mechanisms are involved (2), the side chains (Fig. 1) influence the binding affinity (R^1 side chain) and the antiresorptive potency (R^2 side chain). Modification of these side chains allows for a variety of agents (Table 1).

Bisphosphonates can be given iv or taken by mouth. When taken orally, they must be taken after a prolonged fast (usually first thing in the morning), with water only, followed by 30–60 min with nothing else by mouth to allow for adequate absorption. Under ideal conditions, less than 1% of an orally administered dose is absorbed; taking a bisphosphonate with food or anything containing

divalent cations will completely block its absorption. There is no systemic metabolism. The half-life in plasma is short. Fifty percent of the absorbed dose binds to bone surfaces, mostly avidly at sites of active remodeling. The skeletal capacity is large and the binding sites are virtually unsaturable. The 50% or so that does not bind to bone is excreted rapidly by the kidneys.

In the environment of acid and enzymes beneath an active osteoclast, bisphosphonates are released from bone, entering the osteoclast and causing loss of resorptive function and accelerating apoptosis. There may be some effect of bisphosphonates on osteocytes as well.

The four bisphosphonates in common clinical use all contain one or more nitrogen molecules in the R^2 side chain. They differ in the strength of binding to bone. The rank order for binding affinity is zoledronate greater than alendronate greater than ibandronate greater than risedronate. Higher-affinity bisphosphonates will bind avidly to the bone surface but will spread through bone more slowly and have less access to the osteocytes network. Lower-affinity agents will be distributed more widely through the bone and also have a shorter residence time in bone if treatment is stopped (2). Clinically this could explain differences in speed of onset of antifracture effect and whether there is an effect on fractures at nonvertebral sites.

Bisphosphonates reduce osteoclastic bone resorption. The net result is a rapid and substantial decrease in bone turnover markers that is dose and compound dependent, with a maximum effect in 3–6 months that, with continued treatment, is maintained in a new steady state for 10 yr (3, 4) and perhaps longer. Treatment with bisphosphonates also results in a modest increase in bone mineral density (BMD). Non-nitrogen-containing bisphosphonates (*e.g.* etidronate, clodronate; see Table 1) inhibit osteoclastic activity by producing toxic analogs of ATP that cause cell death (5). Nitrogen-containing bisphosphonates (*e.g.* alendronate, risedronate, ibandronate, and zoledronate; see Table 1) inhibit an enzyme called farnesyl pyrophosphate synthase, an enzyme in the 3-hydroxy-3-methylglutaryl coenzyme A reductase pathway (2, 6). Inhibition of this enzyme interferes with a process called prenylation: preventing the addition of 15- and 20-carbon side chains that anchor GTP-binding proteins to the osteoclast cell membrane; this leads to reduced resorptive activity of osteoclasts and accelerated apoptosis (programmed cell death). The rank order of potency for inhibiting farnesyl pyrophosphate synthase is zoledronate > risedronate \gg ibandronate > alendronate, with the more potent heterocyclic bisphosphonates (zoledronate and risedronate) having a more optimal fit than the compounds with an alkyl side chain (alendronate and ibandronate).

TABLE 1. Structures of some of the bisphosphonates in clinical use

	R^1	R^2
Non-nitrogen-containing compounds		
Etidronate	OH	CH ₃
Clodronate	Cl	Cl
Tiludronate	H	SC ₆ H ₃ Cl
Nitrogen-containing compounds		
Pamidronate	OH	CH ₂ CH ₂ NH ₂
Alendronate	OH	CH ₂ CH ₂ CH ₂ NH ₂
Risedronate	OH	CH ₂ -3-pyridinyl
Zoledronate	OH	CH ₂ C ₃ N ₂ H ₃

Used with permission from N. B. Watts.

TABLE 2. Placebo-controlled studies with bisphosphonates that show antifracture efficacy

Bisphosphonate	Vertebral fractures	Hip fracture	Nonvertebral fracture
Alendronate	Black <i>et al.</i> (85) Cummings <i>et al.</i> (86)	Black <i>et al.</i> (85)	Black <i>et al.</i> (90) Pols <i>et al.</i> (91)
Risedronate	Harris <i>et al.</i> (92) Reginster <i>et al.</i> (87)	McClung <i>et al.</i> (88)	Harris <i>et al.</i> (92) McClung <i>et al.</i> (88)
Ibandronate	Chesnut <i>et al.</i> (93)	No effect demonstrated (93)	
Zoledronate	Black <i>et al.</i> (29)	Black <i>et al.</i> (29)	Black <i>et al.</i> (29)

Each bisphosphonate has a unique profile of binding affinity and antiresorptive potency that likely results in clinically meaningful differences in the speed of onset and offset of effect, the degree of reduction of bone turnover, uptake in cortical *vs.* trabecular bone and types of anti-fracture effect (vertebral *vs.* nonvertebral).

Clinical trials and experience with bisphosphonates

Bisphosphonates have proven efficacy for prevention of bone loss due to aging, estrogen deficiency, and glucocorticoid use and prevention of fractures in women with postmenopausal osteoporosis and women and men with glucocorticoid-induced osteoporosis. Etidronate was the first bisphosphonate approved in the United States (1977), followed by pamidronate (1991), but these drugs were never approved in the United States for use in osteoporosis. Alendronate was the first bisphosphonate approved in the United States for treatment of osteoporosis (1995), followed by risedronate (approved for Paget's disease in 1998 and for use in osteoporosis in 2000), zoledronic acid (approved for skeletal complications of malignancy in 2001 and for use in osteoporosis in 2007), and ibandronate (approved in 2005 for use in osteoporosis). Table 2 summarizes the placebo-controlled trials of nitrogen-containing bisphosphonates that show antifracture efficacy. Of all the agents approved in the United States for use in osteoporosis, only three bisphosphonates, alendronate, risedronate, and zoledronate, have evidence for reducing the risk of hip fractures. These same three agents have also been shown to reduce the risk of nonvertebral fractures as a composite end point (teriparatide, a PTH peptide that is not a bisphosphonate, also has evidence for reducing the risk of nonvertebral fractures). It is this broad-spectrum

antifracture efficacy that has established bisphosphonates as the agents of choice for most patients with osteoporosis. Table 3 shows the current indications for these agents and Table 4 shows the available dosing forms.

Side effects and safety issues

Orally administered bisphosphonates may irritate the esophagus and should not be used by patients who cannot remain upright, who have active upper gastrointestinal symptoms, or have delayed esophageal emptying (*e.g.* strictures, achalasia, or severe dysmotility). Up to a third of patients receiving their first iv dose or monthly oral dose of nitrogen-containing bisphosphonate experience acute-phase reactions (fever, myalgias, lymphopenia, *etc.*) (7–9), but these rarely recur with repeated administration. Hypocalcemia may occur but is usually mild and not clinically recognized (10). Iritis has been described with bisphosphonates (more with iv than oral) but is a rare occurrence.

The only route of elimination for bisphosphonates is renal excretion, but little information is available on dosing in patients who have impaired renal function. Renal toxicity may occur with rapid iv administration. Use is not recommended for patients with creatinine clearance less than 30–35 ml/min but may be safe under certain circumstances (11, 12). With rapid parenteral administration of bisphosphonates, hypocalcemia may occur; however, it is infrequent and usually mild. Disturbances of mineral metabolism should be corrected before initiating bisphosphonate therapy.

Since their approval and widespread use, a number of potential side effects have been identified but with no clear cause-and-effect relationship. Likewise, there are no data linking these potential side effects to the duration of treatment.

TABLE 3. FDA-approved indications for nitrogen-containing bisphosphonates

Drug	Postmenopausal osteoporosis		Glucocorticoid-induced osteoporosis		Men
	Prevention	Treatment	Prevention	Treatment	
Alendronate (Fosamax)	✓	✓		✓	✓
Risedronate (Actonel)	✓	✓	✓	✓	✓
Ibandronate (Boniva)	✓	✓			
Zoledronate (Reclast)	✓	✓	✓	✓	✓

TABLE 4. Available dosing forms of nitrogen-containing bisphosphonates in the United States

Drug	Oral Dosing			Intravenous
	Daily	Weekly	Monthly	
Alendronate (Fosamax)	5 and 10 mg	35 and 70 mg		
Risedronate (Actonel)	5 mg	35 mg	150 mg	
Ibandronate (Boniva)	2.5 mg		150 mg	3 mg every 3 months
Zoledronate (Reclast)				5 mg once a year

Osteonecrosis of the jaw (ONJ)

The first report linking bisphosphonate use and an apparently new condition called ONJ appeared in 2003 (13). All 36 patients in this series were being treated with high doses of iv bisphosphonates (~10 times higher than the doses used to treat osteoporosis) for skeletal complications of malignancy. Subsequent reports (14, 15) included patients receiving lower doses of bisphosphonates for treatment of osteoporosis, but well over 90% of reported cases have been in cancer patients. This subject was extensively addressed by a task force of the American Society for Bone and Mineral Research (16).

This condition received considerable public exposure in the New York Times (17) as well as other high-level publications (18) and broadcasts on radio (19). This led to misconceptions among medical and dental professionals as well as the public regarding the frequency and seriousness of this condition as well as decisions of patients to stop bisphosphonate treatment, although they were at high risk of fracture and low risk of ONJ.

ONJ is defined as exposed necrotic bone in the maxillofacial region, not healing after 6–8 wk, in patients with no history of craniofacial radiation (16). It appears as areas of exposed yellow or white hard bone with smooth or ragged borders. It often follows a dental extraction or other invasive dental procedures or occurs in patients with poorly fitting dentures or bony exostoses. Possible signs and symptoms include pain, swelling, paresthesias, supuration, soft tissue ulceration, intra- or extraoral sinus tracks, and loosening of teeth (15). ONJ may or may not be painful and may or may not be progressive. Many lesions do not heal or heal slowly, but healing has been reported (20). It has also been seen in subjects not using bisphosphonates, but the background incidence is not known.

ONJ was not identified prospectively in any of the clinical trials that included more than 60,000 patient-years in studies for osteoporosis or Paget's disease (21). In the HORIZON trial with iv zoledronate for osteoporosis, retrospective review identified two cases of ONJ: one in the treatment group and one in the placebo group (22).

It is estimated that there have been more than 190 million prescriptions in the United States for oral alendronate, risedronate, and ibandronate and more than 6 million patients treated with iv bisphosphonates for cancer world-

wide (1.9 million with pamidronate, 1.2 million with zoledronate, and 3.1 million with both) (23). Epidemiological data suggest an incidence of ONJ in oral bisphosphonate users ranging from 1:10,000 (from Australia and Israel) to 1:250,000 (from Germany) to 1:160,000 worldwide. These figures are rough approximations because of difficulties in case finding (not all cases of ONJ are reported and not all cases reported are really ONJ) and in knowing the number of patients at risk.

A causal link between bisphosphonate use and ONJ has not been established but seems likely. The small number of cases makes it difficult to sort out mechanisms. Possibilities include oversuppression of bone turnover (failure of osteoclasts to remove diseased necrotic bone), imbalance between osteoblasts and osteoclasts leading to overly dense bone (osteopetrosis), inhibition of T cell function, inhibition of angiogenesis, bony overgrowth blocking flow through the sublingual artery or vascular canals, and death of the mucous membrane overlying the bone due to accumulation of bisphosphonate in the bone of the jaw.

There is some evidence that bisphosphonates may be beneficial in treating avascular necrosis involving the ends of long bones (24, 25) and also may be helpful for preserving alveolar bone in the jaw in patients who have periodontal disease (26, 27).

Guidelines for dentists and oral surgeons have been published by the American Dental Association and American Association of Oral and Maxillofacial Surgeons (28). The American Society for Bone and Mineral Research Task Force performed a comprehensive review (16). Useful information for patients is available on the web site of the American Dental Association (www.ada.org). Patients who are starting or taking bisphosphonates should be informed that there are risks of treatment, including a low risk of ONJ. Regular dental visits and maintenance of good oral hygiene are important for everyone. Routine dental cleaning and restorative procedures should be strongly encouraged. Patients using bisphosphonates who are considering dentoalveolar surgery should be advised of the risks and alternatives. Invasive surgical procedures should be avoided, if possible, especially in patients receiving iv bisphosphonates for cancer. If dental treatment is needed, it should progress stepwise, if possible. Patients with periodontal disease should receive appropriate non-

surgical therapy. Patients starting oral bisphosphonates who need invasive dental procedures should have procedures done and healing complete before starting, if circumstances permit. Patients already taking a bisphosphonate may elect to take some time off therapy, although there is no evidence that this will improve outcomes.

Atrial fibrillation (AF)

The concern regarding AF and bisphosphonate use arose from the zoledronic acid HORIZON Pivotal Fracture Trial data in which a greater number of subjects had AF as a serious adverse event in the zoledronic acid group (1.3%) compared with the placebo group (0.5%) (29). This unexpected observation raised the question of whether this imbalance was related to the medication itself or whether this was a chance finding. This occurrence of AF did not seem to be associated with the timing of the infusion, the acute phase reaction after the infusion, or any acute electrolyte imbalance. No increase in the rate of AF was noted in the HORIZON Recurrent Fracture Trial, a smaller and shorter study, in which careful evaluation of AF and its serious adverse events was performed, (30), nor was an increase in AF noted in the oncology trials of zoledronic acid, using a dose approximately 10 times higher than is used to treat osteoporosis.

Regarding the potential for other bisphosphonates to increase the risk for AF, retrospective analysis of the alendronate Fracture Intervention Trial (FIT) showed a non-significant trend toward an increase in AF (1.5 *vs.* 1.0%, relative hazard 1.51, 95% confidence interval 0.97–2.40, $P = 0.07$) (31), but a similar review of the risedronate Vertebral Efficacy with Risedronate Therapy study showed no signal at all (32). A case-control study revealed that past, not current, use of alendronate was associated with a higher risk of incident AF (33). On the other hand, a large population-based matched case-control study from Denmark showed that the use of bisphosphonates, mainly alendronate and etidronate, was not associated with an increased risk of atrial arrhythmias compared with nonusers (34). Due to these conflicting results, a similar study was performed to evaluate rates of AF in fracture patients starting oral bisphosphonates based on a Danish database, concluding that there was an increased risk of AF in bisphosphonates users *vs.* nonusers, with the main risk factors for AF being old age and patients who are already at an increased cardiovascular risk (35). Two other large population studies, one using two U.S. databases and the other using a U.K. database, did not find an association between bisphosphonate therapy and AF (36, 37).

In a metaanalysis of the four aforementioned randomized trials, bisphosphonate exposure was significantly associated with risk of serious but not all AF adverse events

(38). There was no increase in the risk of stroke or cardiovascular mortality in an analysis of these trial data sets.

Thus, whereas there are some data potentially linking the past use of bisphosphonates with an increased risk of AF as a serious adverse event, the available information does not reveal a consistent association and the overall evidence does not support a causal relationship. Moreover, there is no convincing mechanism to account for this effect, which seems to be independent of the dose and duration of therapy. At the present time, the U.S. Food and Drug Administration (FDA) recommends that physicians not alter their prescribing patterns for bisphosphonates while it continues to monitor postmarketing reports of AF in such patients (39). In view of the above and the absence of more definitive data, the benefits of treatment for osteoporosis should outweigh the risks in the majority of patients from this perspective.

Esophageal cancer

Esophageal irritation has been a concern for patients using oral bisphosphonates. Over the past 2 decades, the FDA has received reports of 23 cases of esophageal cancer among patients receiving oral bisphosphonate therapy, described in a letter to the editor by Wysowski *et al.* (40). In addition, 31 cases of esophageal cancer from Europe and Japan have been reported in patients after using oral bisphosphonates (40). The median time from use to diagnosis was 1–2 yr (40). However, this report lacked information regarding risk factors for esophageal cancer in this group of patients and the expected incidence of esophageal cancer in this age group (41). Furthermore, it was limited by the lack of a control group, which makes the association between esophageal cancer and bisphosphonate use purely speculative (42). Two other reports, one using data from European national registries and the second from the U.S. Medicare database, have not shown an increased risk of esophageal cancer among individuals who were receiving oral bisphosphonates compared with those who were not (43, 44). Lastly, the time from exposure to diagnosis was brief and hence not consistent with a causal relationship (45, 46).

The theoretical rationale for a possible association of esophageal cancer and bisphosphonate use stems from the fact that this class of medications can cause erosive esophagitis, and esophageal biopsies of patients on alendronate have revealed crystalline material similar to this drug as well as persistent mucosal abnormalities (47, 48). Although further studies looking at the potential risk for carcinogenicity are clearly needed, the current data do not support a causal association between oral bisphosphonates and esophageal carcinoma.

Musculoskeletal pain

The prescribing information for all bisphosphonates lists musculoskeletal pain as a potential, albeit an uncommon, adverse effect. Between 1995 and 2005, the FDA received 117 reports of severe musculoskeletal pain (bone, joint, and/or muscle pain) developing in adults on bisphosphonates, described in a letter to the editor by Wysowski and Chang (49). This may occur at any point after starting bisphosphonate therapy. Although symptoms improved promptly in some patients after discontinuation of the offending drug, most patients experienced a gradual or incomplete resolution of symptoms (49). The mechanism for this adverse effect is not known, and evidence supporting a causal relationship between this and bisphosphonate use is lacking. Musculoskeletal pain is a common problem in this age group. Further studies are needed to evaluate the frequency and possible risk factors for this problem. Particularly severe musculoskeletal pain associated with bisphosphonate therapy has been described in patients with cystic fibrosis (50) and can be alleviated by prior glucocorticoid therapy (51). At present, the FDA recommends instructing patients to alert their physician if such symptoms occur for consideration of stopping the medication.

Renal safety

For treatment of osteoporosis, bisphosphonates have not been associated with renal adverse events in patients with creatinine clearances (CCr) above 30–35 ml/min, but the FDA product labeling states that it is not recommended to use these medications in patients with a lower CCr due to lack of experience in such patients (52, 53).

Attempts have been made to analyze data retrospectively and shed some light in this area. A *post hoc* analysis of subjects from nine randomized trials in the risedronate data set revealed that 7% had severe renal impairment (CCr < 30 ml/min) and 45% had moderate impairment (CCr \geq 30–50 ml/min) as estimated by the Cockcroft-Gault formula (11). Compared with placebo, there was no difference in the incidence of adverse events in the treatment groups regardless of renal function, and therapy was as effective in terms of preservation of BMD and reduction of fractures. A retrospective analysis of the FIT data revealed similar findings with the use of alendronate (12). It is important to note that none of these patients had intrinsic kidney disease or a CCr less than 15 ml/min.

In the iv bisphosphonate studies, both ibandronate and zoledronate appeared to be safe in patients with CCr above 30–35 ml/min if administered correctly (30, 54–56). Transient changes in renal function may occur in postmenopausal women after receiving iv zoledronate, but renal function returns to baseline in the long term (57).

Adverse effects on renal function seem to be primarily related to the peak concentration (determined by the dose and the infusion rate).

Thus, bisphosphonates appear to be safe and effective in individuals with modestly reduced renal function. The low risk of kidney damage in patients receiving iv bisphosphonates can be reduced further by adequate hydration and prolonging the infusion rate. No dosage adjustment is necessary in patients with mild or moderate renal impairment. However, there are inadequate data in patients with more severe chronic kidney disease and in end-stage renal failure, in which other forms of metabolic bone disease may be present (58). There are no data regarding the use of bisphosphonates in patients with stage 5 chronic kidney disease (CCr < 15 ml/min), although one expert opinion recommends treating patients suffering fragility fractures with half the usual dose of bisphosphonates for up to 3 yr, after the diagnosis of osteoporosis is confirmed by a bone biopsy (58, 59). This approach is mainly based on the known pharmacokinetics of bisphosphonates in subjects with normal renal function (60).

Atypical fractures

Although bisphosphonates reduce the rates of fractures due to osteoporosis, recent reports suggested a link between bisphosphonate use and the development of atypical insufficiency fractures. This is thought to be due to long term oversuppression of bone turnover leading to impaired bone remodeling, accumulation of microdamage in bone and increased skeletal fragility (61–64). A number of case reports have described unusual low-energy subtrochanteric femoral fractures and pelvic insufficiency fractures, which exhibited problems with healing, in patients on long term bisphosphonate therapy (65–72). These fractures are typically associated with prodromal pain in the region of the fracture and are frequently bilateral; characteristic radiographic findings include cortical hypertrophy, a transverse fracture pattern, and medial cortical spiking (Fig. 2) (73). Bone biopsies in such patients often show severely suppressed bone turnover (59–61), although we have seen a patient with one of these subtrochanteric fractures whose iliac crest biopsy was completely normal (Watts, N. B., personal communication). Several retrospective studies also suggested an association between bisphosphonate use and atypical fractures (74–76). On the other hand, a register-based national cohort study from Denmark showed that the ratio of classical to atypical hip fractures was identical in the alendronate-treated subjects *vs.* matched untreated controls (77), although exclusion of high-impact trauma fractures was not possible due to lack of rigorously stated trauma codes in their data set. This suggested that these atypical fractures

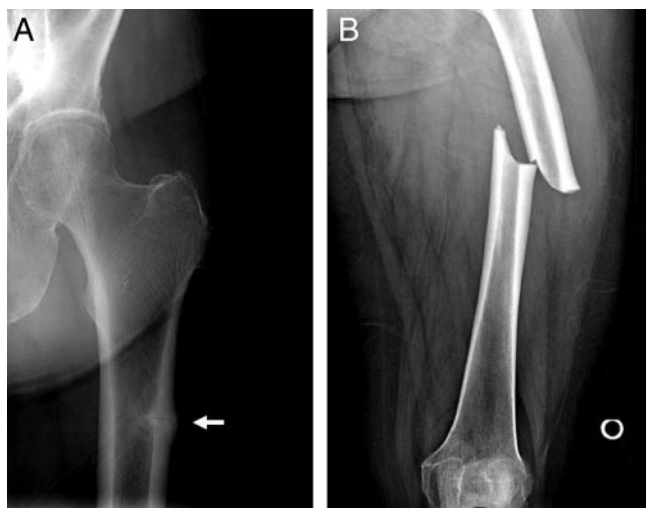


FIG. 2. X-rays showing an impending femoral shaft fracture (A) and a representative atypical diaphyseal femoral fracture (B) with thickened cortices and a beak or spike. [Courtesy of J. Lane and A. Unnanuntana, Hospital for Special Surgery, New York, NY.]

were more likely due to osteoporosis rather than the bisphosphonate therapy itself. The observed association between long-term bisphosphonate use and atypical fractures does not prove causality, and additional large-scale studies are needed to elucidate this issue further. More definitive data would be critical because this may influence decisions regarding duration of therapy in selected individuals (78), but concern about oversuppression of bone turnover resulting in atypical fractures should not lead to stopping bisphosphonate therapy in the vast majority of postmenopausal women at the present time (79, 80).

Long-term studies with bisphosphonates

Approval of bisphosphonates in the United States was based on studies of 3 or 4 yr duration. Some of these studies have been extended, with two alendronate cohorts followed up for 10 yr (3, 4) and risedronate cohorts followed up for 4 (81) and 7 yr (82). No new safety concerns have emerged. Although some have expressed concern about possible oversuppression of bone turnover, iliac crest biopsies after up to 10 yr of treatment have not shown oversuppression.

There has been considerable discussion about how long to treat with bisphosphonates. This does not come up with treatments for other silent diseases such as hypertension and hyperlipidemia because it is well known that benefits of treatment disappear fairly quickly when treatment is stopped. It is a reasonable question when considering bisphosphonate therapy, however, because these drugs accumulate in the skeleton, leading to a reservoir that continues to be released for months or years after treatment is stopped (83). As previously mentioned, the skeletal binding sites for bisphosphonates are virtually unsaturable, so

a considerable amount could be accumulated. Because release depends in part on the level of bone turnover, which is reduced by the presence of bisphosphonates, the actual amount released may be fairly small. Stopping alendronate after 10 yr of treatment at a dose of 10 mg daily (which should be the same as 70 mg weekly), the amount of alendronate released from bone over the next several months or years would be equivalent to taking one fourth of the usual dose (2.5 mg daily or 70 mg once a month) (84). Earlier studies suggested that lower-than-standard doses of bisphosphonates might reduce the risk of fracture [alendronate 5 mg daily (85, 86) and risedronate 2.5 mg daily (87, 88)]. When treatment is stopped, if there is continued presence of bisphosphonate in bone and continued release (and possible reattachment to bone), there might be some lingering antifracture effect after treatment is stopped.

The extension of the risedronate Vertebral Efficacy with Risedronate Therapy-NA study was a 1-yr follow-up of subjects who completed 3 yr of blinded therapy with risedronate 5 mg daily or placebo and then stopped their study medications (but continued calcium and vitamin D). In the year off treatment, BMD decreased in the former risedronate users (but remained higher than baseline and higher than in the former placebo subjects) and bone turnover markers increased (and were no different from the former placebo subjects); despite the apparent resolution of treatment effect on these intermediate markers, the risk of new vertebral fractures was reduced by 46% in the former risedronate users compared with the former placebo subjects (81).

In the extension of the alendronate Phase 3 study, when treatment was stopped after 5 yr, bone density in the hip remained stable but BMD in the hip sites decreased by approximately 2% over 5 yr (3), but clear fracture data were not available. The extension of the alendronate Fracture Intervention Trial enrolled subjects who had approximately 5 yr of alendronate treatment in the FIT into a second 5-yr study during which some subjects continued alendronate and others were changed to placebo. At the end of the Fracture Intervention Trial Long-Term Extension (FLEX), 5-yr fracture rates for new vertebral fractures were reduced by 55% in the subjects who had 10 yr of treatment compared with those who had 5 yr on/5 yr off. Although the published report suggested no differences in radiographic vertebral fractures or nonvertebral fractures, a subsequent analysis indicated that, among subjects with T-scores of -2.5 or below, nonvertebral fracture risk was reduced by 50% (89).

The data suggest to us that, although there is some residual benefit in terms of fracture reduction for some time after a 3- to 5-yr course of bisphosphonate therapy, continuing treatment for 10 yr is better for some patients.

TABLE 5. Suggested duration of bisphosphonate treatment and drug holidays

Patient's fracture risk	Suggested duration of treatment	Suggested duration of drug holiday ^a
Low	Treatment rarely indicated	NA
Mildly increased	Treat for approximately 5 yr	Stay off bisphosphonate until BMD decreases significantly or fracture occurs
Moderately increased	Treat for 5–10 yr	Stay off bisphosphonate for 2–3 yr (or less if BMD decreases or fracture occurs)
High	Treat for 10 yr	Stay off bisphosphonate for 1–2 yr (or less if BMD decreases or fracture occurs); alternate medication (e.g. raloxifene, teriparatide) may be given during the holiday from bisphosphonates

Duration is based largely on personal opinion.

^a Longer holidays might be appropriate for patients treated with bisphosphonates that bind most strongly to bone (*i.e.* zoledronic acid, alendronate), whereas shorter holidays might be considered for patients treated with compounds that bind less strongly (*i.e.* risedronate, ibandronate).

Although the risks of bisphosphonate therapy for osteoporosis are small, for patients at low risk of fracture, the risk to benefit ratio may be negative. For patients who were candidates for treatment, after a course of some years, treatment may be stopped for a drug holiday. Although it is difficult to find evidence to support the need for or clinical results of a course of treatment followed by a drug holiday (how long to treat, how long the holiday should be, when the holiday should be stopped, effectiveness of treatment after restarting), we believe there is logic to support the following clinical scenarios as shown in Table 5:

1. Low risk of fracture: treatment is not needed. If a bisphosphonate has been prescribed, it should be discontinued and not restarted unless/until the patient meets treatment guidelines. Example: 53-yr-old woman, menopause at age 50 yr, lowest T-score -1.6 , no risk factors, bisphosphonate therapy for 2 yr. Treatment was not indicated in the first place and can be discontinued.
2. Mild risk of fracture: treat with bisphosphonate for 3–5 yr and then stop. The drug holiday can be continued until there is significant loss of BMD (*i.e.* more than the least significant change as determined by the testing center) or the patient has a fracture, whichever comes first. Example: 65-yr old woman, menopause at age 52 yr, initial lowest T-score -2.6 , no risk factors, bisphosphonate treatment for 5 yr, BMD stable over that time. Treatment was indicated, but after 5 yr of treatment, a drug holiday might be considered.
3. Moderate risk of fracture: treat with bisphosphonate for 5–10 yr, offer a drug holiday of 3–5 yr or until there is significant loss of BMD or the patient has a fracture, whichever comes first. Example: 70-yr-old woman, menopause at age 49 yr, lowest initial T-score -2.7 , no risk factors, bisphosphonate therapy for 8 yr, BMD increased over that time so lowest T-score now is -2.3 . Treatment was indicated, but

after 8 yr of treatment, a drug holiday might be considered.

4. High risk of fracture: treat with bisphosphonate for 10 yr, offer a drug holiday of 1–2 yr until there is significant loss of BMD or the patient has a fracture, whichever comes first. A nonbisphosphonate treatment (*e.g.* raloxifene, teriparatide) may be offered during the holiday from the bisphosphonate. Example: 72-yr-old woman, menopause at age 43 yr, lowest initial T-score -3.8 , rheumatoid arthritis requiring ongoing corticosteroid therapy for 12 yr, 3-in. height loss and two vertebral fractures by VFA, treatment with bisphosphonate therapy for 10 yr. Treatment was indicated. After 10 yr, she remains at high risk of fracture. If a holiday from the bisphosphonate is considered, interval treatment with teriparatide or raloxifene would be prudent.

It has been suggested that a decrease in BMD or increase in bone turnover marker might be used to decide when to end a drug holiday, but the risedronate study showed that fracture risk remained reduced despite what appeared to be unfavorable changes in these parameters (81). Conversely, there is no evidence that, off treatment, fracture risk is reduced if BMD is stable or bone turnover marker is low.

Summary and conclusions

Bisphosphonates offer a safe and effective treatment to reduce fracture risk, with evidence for broad spectrum (*i.e.* spine, hip, and nonvertebral) fracture risk reduction not shown for other available agents. They can be administered orally (daily, weekly, or monthly) or iv (quarterly or yearly). Since their initial introduction in the United States in 1995, questions have been raised about their association with possible side effects (ONJ, musculoskeletal pain, atrial fibrillation, atypical fractures, esophageal cancer) that appear to be rare and may not be causally related. For most patients with osteoporosis, the benefits of treatment outweigh the risks.

Because bisphosphonates are avidly bound to bone, a reservoir of drug accumulates after years of treatment that is gradually released over months or years and appears to result in a lingering antifracture benefit for some time after therapy is stopped. This makes it possible to consider drug holidays [time off bisphosphonate therapy (but possibly on another agent)] and then resuming therapy. Although there is no strong science to guide us, we believe that some time off treatment should be offered to most patients on long-term bisphosphonate therapy. The duration of treatment and the length of the holiday should be tailored to individual patient circumstances, including the risk of fracture and the binding affinity of the particular bisphosphonate used.

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References

- Watts NB 2000 Bisphosphonate treatment for osteoporosis. In: Avioli LV, ed. The osteoporotic syndrome. San Diego: Academic Press; 121–132
- Russell RGG, Watts NB, Ebtino FH, Rogers MJ 2008 Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int* 19:733–759
- Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, Rodriguez-Portales JA, Downs RW, Gupta J, Santora AC, Liberman UA, for the Alendronate Phase III Osteoporosis Treatment Study Group 2004 Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* 350:1189–1199
- Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, Satterfield S, Wallace RB, Bauer DC, Palermo L, Wehren LE, Lombardi A, Santora AC, Cummings SR, for the FLEX Research Group 2006 Effects of continuing or stopping alendronate after 5 years of treatment. The Fracture Intervention Trial long-term extension (FLEX): a randomized trial. *JAMA* 296:2927–2938
- Frith JC, Mönkkönen J, Blackburn GM, Russell RG, Rogers MJ 1997 Clodronate and liposome-encapsulated clodronate are metabolized to a toxic ATP analog, adenosine 5' (β , γ -dichloromethylene) triphosphate, by mammalian cells *in vitro*. *J Bone Miner Res* 12: 1358–1367
- Rogers MJ, Frith JC, Luckman SP, Coxon FP, Benford HL, Mönkkönen J, Auriola S, Chilton KM, Russell RGG 1999 Molecular mechanisms of action of bisphosphonates. *Bone* 24:735–795
- Adami S, Bhalla AK, Dorizzi R, Montesanti F, Rosini S, Salvagno G, Lo Cascio V 1987 The acute phase response after bisphosphonate administration. *Calcif Tissue Int* 41:326–331
- Gallacher SJ, Ralston SH, Patel U, Boyle IT 1989 Side-effects of pamidronate. *Lancet* 2:42–43
- Zojer N, Keck AV, Pecherstorfer M 1999 Comparative tolerability of drug therapies for hypercalcaemia of malignancy. *Drug Saf* 21: 389–406
- Maalouf NM, Heller HJ, Odvina CV, Kim PJ, Sakhac K 2006 Bisphosphonate-induced hypocalcemia: report of 3 cases and review of literature. *Endocr Pract* 12:48–53
- Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE 2005 Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. *J Bone Miner Res* 20:2105–2115
- Jamal SA, Bauer DC, Ensrud KE, Cauley JA, Hochberg M, Ishani A, Cummings SR 2007 Alendronate treatment in women with normal to severely impaired renal function: an analysis of the Fracture Intervention Trial. *J Bone Miner Res* 22:503–508
- Marx RE 2003 Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 61:1115–1117 (Letter)
- Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL 2004 Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 62:527–534
- Woo SB, Hellstein JW, Kalmar JR 2006 Systematic review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 144:753–761
- Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DL, Shum L, Silverman SL, Van Poznak CH, Watts N, Woo SB, Shane E 2007 Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 22:1479–1491
- Kolata G 2006 Drug for bones is newly linked to jaw disease. *New York Times*, June 2, 2006;
- Rubin R 2005 Drug linked to death of jawbone. *USA Today*
- Knox R 2006 Side effects noted with bone-loss drugs. National Public Radio, broadcast April 23 (<http://www.npr.org/templates/story/story.php?storyId=5358285>)
- Triester N, Woo SB 2006 Bisphosphonate-associated osteonecrosis of the jaw. *N Engl J Med* 335:2348
- Bilezikian JP 2006 Osteonecrosis of the jaw: do bisphosphonates pose a risk? *N Engl J Med* 355:2278–2281
- Black DM, Boonen S, Cauley J, Delmas P, Eastell R, Reid I, Rosario-Jansen T, Caminis J, Zhang J, Hu H, Cummings S 2006 Effect of once-yearly infusion of zoledronic acid 5 mg on spine and hip fracture reduction in postmenopausal women with osteoporosis: the HORIZON pivotal fracture trial. *J Bone Miner Res* 21(Suppl 1):S16 (Abstract)
- IMS Health 2006 NPA Plus
- Agarwala S, Sule A, Pai BU, Joshi VR 2002 Alendronate in the treatment of avascular necrosis of the hip. *Rheumatology* 41:346–347
- Desai MM, Sonone S, Bhasme V 2005 Efficacy of alendronate in the treatment of avascular necrosis of the hip. *Rheumatology* 44:1331–1332; author reply 1332
- Jeffcoat MK 2006 Safety of oral bisphosphonates: controlled studies on alveolar bone. *Int J Oral Maxillofac Implants* 21:349–353
- Palomo L, Bissada NF, Liu J 2005 Periodontal assessment of postmenopausal women receiving risedronate. *Menopause* 12:685–690
- American Association of Oral and Maxillofacial Surgeons 2007 Position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 65:369–376
- Black DM, Delmas PD, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR, for the HORIZON Pivotal

- Fracture Trial 2007 Once-yearly zoledronic acid for treatment of osteoporosis. *N Engl J Med* 356:1809–1822
30. Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore KA, Lavecchia C, Zhang J, Mesenbrink P, Hodgson PK, Abrams K, Orloff JJ, Horowitz Z, Eriksen EF, Boonen S 2007 Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 357:1799–1809
 31. Cummings SR, Schwartz AV, Black DM 2007 Alendronate and atrial fibrillation. *N Engl J Med* 356:1895–1896 (Letter)
 32. Karam R, Camm J, McClung M 2007 Yearly zoledronic acid in postmenopausal osteoporosis. *N Engl J Med* 357:712–713; author reply 714–715
 33. Heckbert SR, Li G, Cummings SR, Smith NL, Psaty BM 2008 Use of alendronate and risk of incident atrial fibrillation in women. *Arch Intern Med* 168:826–831
 34. Sorensen HT, Christensen S, Mehnert F, Pedersen L, Chapurlat RD, Cummings SR, Baron JA 2008 Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population based case-control study. *BMJ* 336:581–592
 35. Abrahamsen B, Eiken P, Brixen K 2009 Atrial fibrillation in fracture patients treated with oral bisphosphonates. *J Intern Med* 265:581–592
 36. Bunch TJ, Anderson JL, May HT, Muhlestein JB, Horne JB, Crandall BG, Weiss JP, Lappé DL, Osborn JS, Day JD 2009 Relation of bisphosphonate therapies and risk of developing atrial fibrillation. *Am J Cardiol* 103:824–828
 37. Grosso A, Douglas I, Hingorani A, MacAllister R, Smeeth L 2009 Oral bisphosphonates and risk of atrial fibrillation and flutter in women: a self-controlled case-series safety analysis. *PLoS One* 4:e4720
 38. Loke YK, Jeevanatham V, Singh S 2009 Bisphosphonates and atrial fibrillation: systematic review and meta-analysis. *Drug Saf* 32:219–228
 39. Update of safety review follow-up to the October 1, 2007, Early communication about the ongoing safety review of bisphosphonates (<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm136201.htm>)
 40. Wysowski DK 2009 Reports of esophageal cancer with oral bisphosphonate use. *N Engl J Med* 360:89–90 (Letter)
 41. Siris ES, Oster MW, Bilezikian JP 2009 More on reports of esophageal cancer with oral bisphosphonate use. *N Engl J Med* 360:1791 (Letter)
 42. Shaheen NJ 2009 More on reports of esophageal cancer with oral bisphosphonate use (letter). *N Engl J Med* 360:1790–1791 (Letter)
 43. Abrahamsen B, Eiken P, Eastell R 2009. More on reports of esophageal cancer with oral bisphosphonate use. *N Engl J Med* 360:1789 (Letter)
 44. Solomon DH, Patrick A, Brookhart MA 2009 More on reports of esophageal cancer with oral bisphosphonate use. *N Engl J Med* 360:1789–1790 (Letter)
 45. Hofbauer LC, Mielke S 2009 More on reports of esophageal cancer with oral bisphosphonate use. *N Engl J Med* 360:1790 (Letter)
 46. Robins HI, Holen KD 2009 More on reports of esophageal cancer with oral bisphosphonate use. *N Engl J Med* 360:1790 (Letter)
 47. Ribeiro A, DeVault KR, Wolfe 3rd JT, Stark ME 1998 Alendronate-associated esophagitis: endoscopic and pathologic features. *Gastrointest Endosc* 47:525–528
 48. Abraham SC, Cruz-Correa M, Lee LA, Yardley JH, Wu TT 1999 Alendronate-associated esophageal injury: pathologic and endoscopic features. *Mod Pathol* 12:1152–1157
 49. Wysowski DK, Chang JT 2005 Alendronate and risedronate: reports of severe bone, joint, and muscle pain. *Arch Intern Med* 165:346–347
 50. Haworth CS, Selby PL, Webb AK, Mawer EB, Adams JE, Freemont TJ 1998 Severe bone pain after intravenous pamidronate in adult patients with cystic fibrosis. *Lancet* 352:1753–1754
 51. Haworth CS, Selby PL, Webb AK, Freemont TJ 1999 Oral corticosteroids and bone pain after pamidronate in adults with cystic fibrosis. *Lancet* 353:1886 (Letter)
 52. Recker RR, Lewiecki EM, Miller PD, Reiffel J 2009 Safety of bisphosphonates in the treatment of osteoporosis. *Am J Med* 122: S22–S32
 53. Miller PD 2005 Treatment of osteoporosis in chronic kidney disease and end-stage renal disease. *Curr Osteoporos Rep* 3:5–12
 54. Lewiecki EM, Miller PD 2007 Renal safety of intravenous bisphosphonates in the treatment of osteoporosis. *Expert Opin Drug Saf* 6:663–672
 55. Eisman JA, Civitelli R, Adami S, Czerwinski E, Recknor C, Prince R, Reginster JY, Zaidi M, Felsenberg D, Hughes C, Mairon N, Masanaukaite D, Reid DM, Delmas PD, Recker RR 2008 Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. *J Rheumatol* 35:448–497
 56. Miller PD, Ward P, Pfister T, Leigh C, Body JJ 2008 Renal tolerability of intermittent intravenous ibandronate treatment for patients with postmenopausal osteoporosis: a review. *Clin Exp Rheumatol* 26:1125–1133
 57. Boonen S, Sellmeyer DE, Lippuner K, Orlov-Morozov A, Abrams K, Mesenbrink P, Eriksen EF, Miller PD 2008 Renal safety of annual zoledronic acid infusions in osteoporotic postmenopausal women. *Kidney Int* 74:641–648
 58. Miller PD 2009 Diagnosis and treatment of osteoporosis in chronic renal disease. *Semin Nephrol* 29:144–155
 59. Miller PD 2009 The role of bone biopsy in patients with chronic renal failure. *J Am Soc Nephrol* 3(Suppl 3):S144–S155
 60. Miller PD 2007 Is there a role for bisphosphonates in chronic kidney disease? *Semin Nephrol* 27:186–190
 61. Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB 2000 Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. *J Bone Miner Res* 15:613–620
 62. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CYC 2005 Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab* 90:1294–1301
 63. Visekruna M, Wilson D, McKiernan FE 2008 Severely suppressed bone turnover and atypical skeletal fragility. *J Clin Endocrinol Metab* 93:2948–2952
 64. Armamento-Villareal R, Napoli N, Diemer K, Watkins M, Civitelli R, Teitelbaum S, Novack D 2009 Bone turnover in bone biopsies of patients with low-energy cortical fractures receiving bisphosphonates: a case series. *Calcif Tiss Int* 85:37–44
 65. Schneider JP 2006 Should bisphosphonates be continued indefinitely? An unusual fracture in a healthy woman on long-term alendronate. *Geriatrics* 61:31–33
 66. Lee P, van der Wall H, Seibel MJ 2007 Looking beyond low bone mineral density: multiple insufficiency fractures in a woman with post-menopausal osteoporosis on alendronate therapy. *J Endocrinol Invest* 30:590–597
 67. Imai K, Yamamoto S, Anamizu Y, Horiuchi T 2007 Pelvic insufficiency fracture associated with severe suppression of bone turnover by alendronate therapy. *J Bone Miner Metab* 25:333–336
 68. Odvina CV, Levy S, Rao S, Zerwekh JE, Rao SD Unusual mid-shaft fractures during long term bisphosphonate therapy. *Clin Endocrinol (Oxf)*
 69. Lenart BA, Lorch DG, Lane JM 2008 Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *N Engl J Med* 358:1304–1306
 70. Kwek EB, Goh SK, Koh JS, Png MA, Howe TS 2008 An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? *Injury* 39:224–231
 71. Lee P, Seibel MJ 2008 More on atypical fractures of the femoral diaphysis. *N Engl J Med* 359:317
 72. Armamento-Villareal R, Napoli N, Panwar V, Novack D 2006 Suppressed bone turnover during alendronate therapy for high-turnover osteoporosis. *N Engl J Med* 355:2048–2050

73. **Capeci CM, Tejwani NC** 2009 Bilateral low-energy simultaneous or sequential femoral fractures in patients on long-term alendronate therapy. *J Bone Joint Surg Am* 91:2556–2561
74. **Goh SK, Yang KY, Koh JS, Wong MK, Chua SY, Chua DT, Howe TS** 2007 Subtrochanteric insufficiency fractures in patients on alendronate therapy: a caution. *J Bone Joint Surg Br* 89:349–353
75. **Neviaser AS, Lane JM, Lenart BA, Edobor-Osula F, Lorich DG** 2008 Low-energy femoral shaft fractures associated with alendronate use. *J Orthop Trauma* 22:346–350
76. **Lenart BA, Neviaser AS, Lyman S, Chang CC, Edobor-Osula F, Steele B, van der Meulen MC, Dorich DG, Lane JM** 2009 Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. *Osteoporos Int* 20:1353–1362
77. **Abrahamsen B, Eiken P, Eastell R** 2009 Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. *J Bone Miner Res* 24:1095–1102
78. **Kuehn BM** 2009 Long-term risks of bisphosphonates probed. *JAMA* 301:710–711
79. **Solomon DH, Rekedal L, Cadarette SM** 2009 Osteoporosis treatments and adverse events. *Curr Opin Rheumatol* 21:363–368
80. **Kennel KA, Drake MT** 2009 Adverse effects of bisphosphonates: implications for osteoporosis management. *Mayo Clin Proc* 84:632–637; quiz 638
81. **Watts NB, Chines A, Olszynski WP, McKeever CD, McClung MR, Zhou X, Grauer A** 2008 Fracture risk remains reduced one year after discontinuation of risedronate. *Osteoporos Int* 19:365–372
82. **Mellström DD, Sörensen OH, Goemaere S, Roux C, Johnson TD, Chines AA** 2004 Seven years of treatment with risedronate in women with postmenopausal osteoporosis. *Calcif Tissue Int* 75:462–468
83. **Papapoulos SE, Cremers SC** 2007 Prolonged bisphosphonate release after treatment in children. *N Engl J Med* 356:1075–1076
84. **Rodan G, Reszka A, Golub E, Rizzoli R** 2004 Bone safety of long-term bisphosphonate treatment. *Curr Med Res Opin* 20:1291–1300
85. **Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE** 1996 Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 348:1535–1541
86. **Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ, Fracture Intervention Trial Research Group** 1998 Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the fracture intervention trial. *JAMA* 280:2077–2082
87. **Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, Lund B, Ethgen D, Pack S, Roumagnac I, Eastell R, on behalf of the Vertebral Efficacy with Risedronate Therapy (VERT) Study Group** 2000 Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int* 11:83–91
88. **McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, Adami S, Fogelman I, Diamond T, Eastell R, Meunier PJ, Reginster JY, for the Hip Intervention Program (HIP) Study Group** 2001 Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med* 344:333–340
89. **Schwartz AV, Bauer DC, Cauley JA, Ensrud KE, Palermo L, Wallace RB, Hochberg MC, Feldstein AC, Lombardi A, Cummings SR, Black DM** 2007 Efficacy of continued alendronate for fractures in women without prevalent vertebral fracture: the FLEX trial. *J Bone Miner Res* 22(Suppl 1):S16–S17 (Abstract)
90. **Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, Nevitt MC, Suryawanshi S, Cummings SR, Fit RG** 2000 Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. *J Clin Endocrinol Metab* 85:4118–4124
91. **Pols HA, Felsenberg D, Hanley DA, Stepán J, Muñoz-Torres M, Wilkin TJ, Qin-sheng G, Galich AM, Vandormael K, Yates AJ, Stych B, for the Fosamax International Trial Study Group** 1999 Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. *Osteoporos Int* 9:461–468
92. **Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, Chesnut 3rd CH, Brown J, Eriksen EF, Hoeseyni MS, Axelrod DW, Miller PD, for the VERT Study Group** 1999 Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 282:1344–1352
93. **Chesnut III CH, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, Felsenberg D, Huss H, Gilbride J, Schimmer RC, Delmas PD, Oral IO, V** 2004 Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 19:1241–1249