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# Bisphosphonates for the prevention and treatment of osteoporosis

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Osteoporosis is a skeletal disorder characterized by loss of bone mass, reduced bone mineral density, and deterioration of bone microarchitecture, which lead to bone fragility.

Two million fractures are attributed to osteoporosis annually in the US, resulting in more than 432 000 admissions to hospital, almost 2.5 million medical office visits, and about 180 000 admissions to nursing homes.<sup>2</sup>

Bisphosphonates that are currently approved by the Food and Drug Administration for the prevention or treatment (or both) of osteoporosis include alendronate, ibandronate, risedronate, and zoledronic acid. This review will discuss the rationale for treatment with bisphosphonates in patients with osteoporosis and osteopenia, focusing on the associated benefits and risks. It will also review approaches to management, such as treatment monitoring and duration of therapy.

## Pharmacology and mechanism of action

Bisphosphonates are used orally or intravenously. Bisphosphonates bind at the bone mineral surface, where they potently inhibit osteoclast mediated bone resorption (fig 1), and subsequently embed in the bone, being released only during subsequent resorption.<sup>9</sup>

In contrast to other antiresorptive agents, bisphosphonates with the greatest binding affinity to bone (zoledronic acid > alendronate > ibandronate > risedronate) may persist in bone, and patients continue to be exposed to the pharmacologic effects of these drugs several years after discontinuation.<sup>8 10 11</sup>

All bisphosphonates rapidly reduce bone resorption, which leads to decreased bone formation because resorption and formation are coupled. Within three to six months equilibrium is reached at a lower rate of bone turnover. The end result is preservation or improvement in bone mass and microarchitecture, which leads to a reduced risk of fracture as early as six months after administration.<sup>15 16</sup>

## Comparative effectiveness

No head to head studies have compared the effects of bisphosphonates on reducing the risk of fractures, so it is not possible to conclude that one is superior to another.<sup>17</sup>

A meta-analysis published in 2014 reported high quality evidence that bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid) reduce fractures compared with placebo in postmenopausal women, with relative risks in the range of 0.4 to 0.6 for vertebral fractures and 0.6 to 0.8 for non-vertebral fractures.<sup>18</sup> The effect of ibandronate on the risk of hip fracture is unclear because hip fracture was not a separately reported outcome in trials of this agent.<sup>18</sup>

Similarly, a network meta-analysis,<sup>19</sup> which included studies with low to moderate risk of bias, found moderate to high quality evidence to support the efficacy of bisphosphonates. A network meta-analysis of eight randomized controlled trials (RCTs) that assessed the relative effectiveness of alendronate, ibandronate, risedronate, and zoledronic acid on many fracture outcomes concluded that zoledronic acid has the highest probability of achieving the greatest reduction in any fracture. However, this analysis was sponsored by and included authors employed by the manufacturer of zoledronic acid.<sup>20</sup>

## Adverse effects

Figure 2 details the adverse effects associated with bisphosphonates.

### Gastrointestinal

Gastrointestinal side effects, including esophageal irritation, dysphagia, and heartburn, are well known for all oral bisphosphonates and represent a potential barrier to tolerance and adherence. RCTs often report similar rates of upper gastrointestinal events in control and active arms (about half of patients),<sup>21</sup> but this could be related to patient selection bias.

A meta-analysis of adverse events including numerous RCTs showed an increased risk of mild upper gastrointestinal side effects with the use of alendronate (odds ratio 1.07, 95% confidence interval 1.01 to 1.14).<sup>18</sup> A network meta-analysis found no significant differences between alendronate, risedronate, and zoledronic acid in the discontinuation of treatment because of adverse events.<sup>22</sup>

The risk of gastrointestinal events can be decreased by ensuring proper drug administration (appropriate quantity of water and post-dosing postural positioning), so patient education is crucial.<sup>23</sup> Patients who cannot remain upright or who have pre-existing gastrointestinal disorders, such as esophageal strictures, severe gastroesophageal reflux, or achalasia, should preferably not be treated with oral bisphosphonates.

The FDA has not concluded that patients receiving bisphosphonates have an increased risk of esophageal cancer.

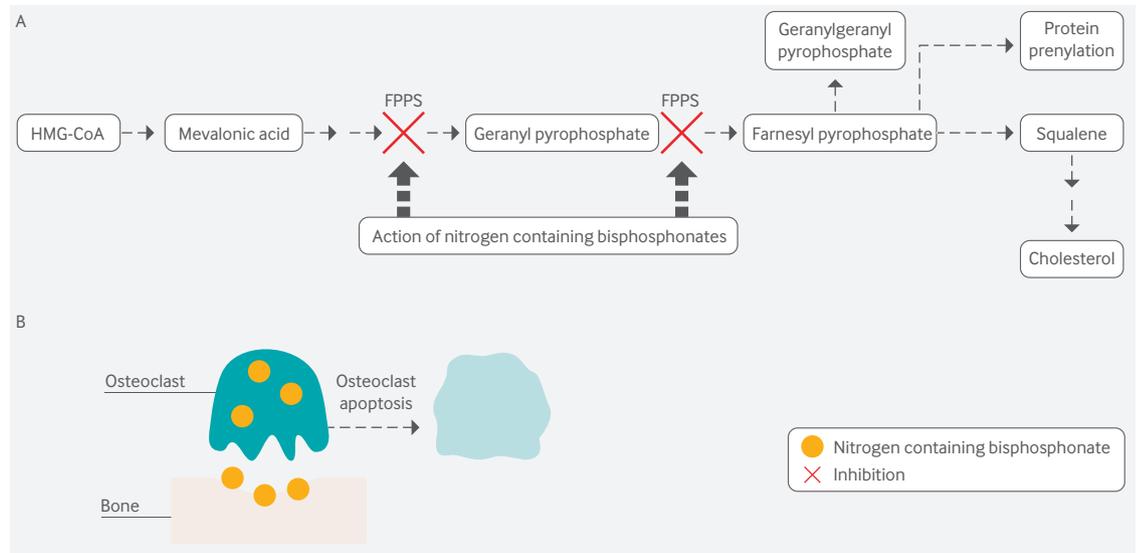
### Acute phase response

Intravenous administration of bisphosphonates has been

## HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Two patients accepted an invitation to review the manuscript and registered as patient reviewers for *The BMJ*. They were asked to indicate which sections or information were of greatest importance and relevance to them as patients and which sections were the least useful. Alternatively, or in addition, they could write general comments about what they felt was missing or underemphasized. As a result of these patients' input, the authors expanded the discussion of bisphosphonate therapy in the setting of osteopenia. The authors also put more emphasis on the importance of effective communication between patients and providers, shared decision making, and care coordination for the use of bisphosphonates in the management of osteoporosis.

**Fig 1 | Mechanism of action of nitrogen containing bisphosphonates. (A) Nitrogen containing bisphosphonates selectively inhibit farnesyl pyrophosphate synthase (FPPS) within osteoclasts, which disrupts the HMG CoA-reductase pathway. (B) Osteoclast endocytosis of bisphosphonate from the bone surface leads to inhibition of FPPS and osteoclast apoptosis. HMG-CoA=3-hydroxy-3-methylglutaryl coenzyme A**



associated with transient mild to moderate inflammatory symptoms, such as fever, myalgia, arthralgias, and headache, collectively known as an acute phase response.

**Hypocalcemia**

Bisphosphonates reduce calcium efflux from bone by inhibiting osteoclastic bone resorption. This can cause a small, clinically unimportant, decrease in serum calcium as long as baseline serum calcium is normal.<sup>28</sup>

**Nephrotoxicity**

Risedronate and ibandronate are contraindicated in patients with a creatinine clearance of 30 mL/min/1.73m<sup>2</sup> or less, whereas the threshold is less than 35 mL/min/1.73m<sup>2</sup> for alendronate and zoledronic acid.<sup>30</sup> With the use of these thresholds, oral bisphosphonates for osteoporosis have not been associated with adverse renal effects. Several cases of severe nephrotoxicity with intravenous zoledronic acid have been reported, and this has resulted in an FDA warning for healthcare professionals.<sup>31</sup> Given that renal toxicity after intravenous bisphosphonates is related to the maximum drug level achieved, rather than the area under the curve for drug exposure,<sup>32</sup> it is not surprising that severe nephrotoxicity has been reported in patients with cancer who receive high intravenous doses.

**Osteonecrosis of the jaw**

Osteonecrosis of the jaw (ONJ) has emerged as a rare complication of bisphosphonate. Most cases have been reported in patients with cancer who receive high doses of intravenous bisphosphonates for the prevention of skeletal complications of cancer.<sup>33</sup>

A recent systematic review reported an incidence of ONJ among bisphosphonate users ranging from 0.028% to 4.3% and refrained from further analysis due to multiple identified limitations.<sup>34</sup>

The risk of ONJ seems to increase when treatment is for longer than three years.<sup>42</sup> Oral bone manipulating surgery and dental extractions are considered the most important risk factors. Moreover, the International Task Force on ONJ suggests withholding bisphosphonates before and after invasive dental procedures until soft tissue has healed, particularly for patients with other risk factors for ONJ.<sup>44</sup>

**Atypical femur fractures**

Atypical femur fractures constitute only 4-10% of all femur fractures.<sup>6</sup>

A pooled analysis of several phase III clinical trials of bisphosphonates found no increased incidence of these fractures but was limited by study population size, study duration, and access to radiographs.<sup>46</sup> The predominant

BISPHOSPHONATE	DOSING/ADMINISTRATION	GENERIC	PRIMARY ADVERSE EFFECTS (RANGE)
 ALENDRONATE	<b>Prevention:</b> Oral 5 mg daily; 35 mg weekly <b>Treatment:</b> Oral 10 mg daily; 70 mg weekly; 70 mg weekly with 2800 or 5600 IU vitamin D <sub>3</sub> ; 70 mg effervescent tablet	✓	<ul style="list-style-type: none"> <li>• Hypocalcemia (&lt;1%)</li> <li>• Nephrotoxicity (0-0.6%)</li> <li>• Osteonecrosis of the jaw (0.001-0.067%)</li> <li>• Atypical femoral fractures (rare, true incidence unknown)</li> </ul>
 RISEDRONATE	<b>Prevention/treatment:</b> Oral 5 mg daily; 35 mg weekly; 35 mg weekly delay release; 35 mg weekly with 6 tablets of 500 mg calcium carbonate; 75 mg on 2 consecutive days monthly; 150 mg monthly	✓	
 IBANDRONATE	<b>Treatment*:</b> Oral 150 mg monthly <b>Treatment*:</b> Intravenous 3 mg every 3 months	XX	
 ZOLEDRONIC ACID	<b>Prevention:</b> Intravenous 5 mg every 2 years <b>Treatment:</b> Intravenous 5 mg once yearly	✓	

\*Not Food and Drug Administration approved for use in men with osteoporosis.

Oral IV

**Fig 2 | Dosing, administration, and primary adverse effects of bisphosphonates for the treatment and prevention of osteoporosis**

evidence for this association comes from observational studies with various definitions of atypical femur fracture, so results need to be interpreted with caution.

Atypical femur fractures are rare but may be associated with the long term use of bisphosphonates.

#### *Suppression of bone formation and resorption*

It has been suggested that prolonged suppression of bone formation and resorption as a result of the use of bisphosphonates may have negative skeletal effects, with daily bone microdamage accumulating and bones becoming too brittle.<sup>52</sup>

#### *Orbital inflammatory syndromes*

Although this is not well known, bisphosphonates have been associated with uveitis, conjunctivitis, episcleritis, and scleritis.<sup>60</sup> A prospective study reported a 1.1% incidence of uveitis after intravenous zoledronic acid, which is thought to be part of the acute phase reaction.<sup>61</sup>

#### **Pretreatment evaluation**

Before starting treatment it is important to assess the patient with a complete history and physical examination (box). Unrecognized metabolic bone diseases other than osteoporosis, such as hyperparathyroidism, osteomalacia, or chronic kidney disease-metabolic bone disease, may also be associated with low BMD. In such cases it can be ineffective or harmful to diagnose osteoporosis solely on the basis of BMD and to start treatment with bisphosphonates.

Baseline vertebral imaging could be performed according to National Osteoporosis Foundation (NOF) guidelines to assess for asymptomatic vertebral deformities in selected patients.<sup>64</sup> Moreover, relevant tests should be obtained when the patient's history, physical examination, or BMD (for example, low Z score) raises the suspicion of secondary causes of osteoporosis,<sup>65</sup> especially when treatment of such could obviate the need for bisphosphonates (table 1, see [thebmj.com](http://thebmj.com)).

#### **Whether to start**

Randomized trials have shown that bisphosphonates prevent osteoporotic fractures in selected patients.<sup>66</sup> Data from the pivotal trials showed benefit in preventing clinical fractures only in patients with previous vertebral or hip fracture or a hip BMD T score of  $-2.5$  or less.<sup>29 36 67-74</sup>

In the absence of fragility fractures, screening BMD may be performed to detect osteoporosis in postmenopausal women.<sup>64 75</sup> However, validation trials of screening and starting bisphosphonates that have outcomes on fractures are lacking.<sup>76</sup>

One of several available tools,<sup>78</sup> FRAX, is commonly used in clinical practice to calculate patients' 10 year probability of hip and major osteoporotic fractures. However, FRAX has limitations,<sup>79 80</sup> including underestimation of the risk of fracture in patients with recent fractures, as well as those with multiple osteoporosis related fractures, low BMD at the lumbar spine with a relatively normal femoral neck BMD, and increased fall risk. Moreover, FRAX is not intended for use in patients under 50 years and has not been validated in patients who had been previously treated for osteoporosis.

Patients with osteopenia (T score between  $-1.0$  and  $-2.5$ ) at the femoral neck or lumbar spine and a 10 year probability of a major hip fracture or osteoporosis related fracture of  $\geq 3\%$  or  $\geq 20\%$ , respectively, based on the US adapted World Health Organization algorithm, could be considered appropriate for bisphosphonates therapy.<sup>64</sup> However, results from retrospective analyses of clinical trials regarding the correlation between FRAX based fracture probability and the anti-fracture efficacy of bisphosphonates treatment are inconsistent.<sup>81 82</sup>

Bisphosphonates are approved by the FDA for preventing osteoporosis in menopausal women,<sup>64</sup> but it is not known whether their use decreases the risk of fractures. Patients with osteopenia who require drugs that could induce bone loss<sup>83</sup>—such as glucocorticoids,<sup>84</sup> aromatase inhibitors,<sup>85 86</sup> and androgen deprivation therapy<sup>86</sup>—could potentially benefit from bisphosphonates.

#### **How to start**

##### **Oral bisphosphonates**

Alendronate is FDA approved for the prevention and treatment of postmenopausal osteoporosis, treatment of osteoporosis in men, and treatment of glucocorticoid induced osteoporosis in men and women.<sup>93</sup> Alendronate was shown to reduce the annualized incidence of clinical vertebral fracture (0.82/100 person years of alendronate, 1.77/100 person years of placebo; relative risk 0.46, 0.28 to 0.75) and hip fractures (0.37/100 person years of alendronate, 0.77/100 person years of placebo; 0.49, 0.23 to 0.99) versus placebo over three years in women with a previous vertebral fracture and hip fractures (0.23/100 person years of alendronate, 0.53/100 person years of placebo; 0.44, 0.18 to 0.97) in those with a femoral neck T score of  $-2.5$  or less.<sup>72</sup> It also reduced the incidence of clinical vertebral fractures (13.1% alendronate, 19.6% placebo; 0.64, 0.50 to 0.82) over about four years in women with a femoral neck T score of  $-2.5$  or less, but there was no benefit for those whose score was greater than  $-2.5$ .<sup>74</sup>

Oral ibandronate is FDA approved for the prevention and treatment of postmenopausal osteoporosis. Ibandronate daily (2.5 mg) or intermittently (12 doses of 20 mg every other day every three months) reduced the incidence of clinical vertebral fractures using life table analysis by about 50% (estimated incidence rate 5.3% (3.7% to 6.9%) in the placebo group, 2.8% (1.6% to 3.9%; relative risk 0.51;  $P=0.0117$ ) in the daily group, 2.8% (1.6% to 3.9%; 0.52;  $P=0.0143$ ) in the intermittent group) compared with placebo over three years in patients with a previous vertebral fracture and lumbar spine T score of less than  $-2.0$ . No reduction in the risk of non-vertebral fractures was documented however.<sup>69</sup>

Risedronate is approved for the prevention and treatment of postmenopausal osteoporosis, osteoporosis treatment in men, and for the prevention and treatment of glucocorticoid induced osteoporosis in men and women.<sup>94</sup> In one of the larger trials, risedronate reduced the incidence of radiographic vertebral fractures (absolute risk 18.1% risedronate v 29% placebo; relative risk 0.51, 0.36 to 0.73;  $P=0.001$ ) and non-vertebral fractures (absolute risk 5.2% risedronate v 8.4% placebo;

relative risk 0.61, 0.39 to 0.94; P=0.02) over three years in patients with a previous vertebral fracture.<sup>68 70</sup> In elderly women with a femoral neck T score less than -4.0 and those with a femoral neck T score less than -3.0 and a non-skeletal risk factor for hip fracture, two years of daily risedronate reduced the risk of hip fracture by 40% (absolute risk 1.9% risedronate v 3.2% placebo; relative risk, 0.6; 95% CI, 0.4 to 0.9; P=0.009).<sup>73</sup>

Once weekly regimens with alendronate and risedronate are pharmacologically equivalent to daily regimens and may improve long term adherence to treatment.

### Intravenous bisphosphonates

Intravenous bisphosphonates provide an alternative for patients who cannot tolerate oral bisphosphonates

or who have difficulty with the administration requirements. Evidence from RCTs shows that the intravenous formulation of ibandronate improves BMD to a similar degree seen with daily oral ibandronate.<sup>96 97</sup> Intravenous ibandronate is approved for treatment (but not prevention) of postmenopausal osteoporosis.

Zoledronic acid is approved for the prevention and treatment of osteoporosis in postmenopausal women and the treatment of osteoporosis in men. It is also approved for the prevention and treatment of osteoporosis in men and women expected to be on glucocorticoid therapy for at least 12 months.<sup>37 98</sup>

### Adherence

A systematic review found that about half of patients prescribed oral bisphosphonates discontinue treatment within one year.<sup>99</sup> It has been suggested that weekly dosing could increase adherence compared with daily dosing. The systematic review supported this suggestion—compliance at one year was higher in patients receiving weekly versus daily alendronate. However, overall patient adherence and persistence (duration of time from initiation to discontinuation) with treatment remained below that needed for optimal fracture prevention.<sup>99 100</sup>

A systematic review found that periodic follow-up appointments with health professionals improve adherence and persistence with osteoporosis drugs,<sup>104</sup> but few intervention strategies had a large effect size.

A recent systematic review of 20 studies found that simplification of dosing regimens, decision aids, electronic prescriptions, and patient education may help to improve adherence to or persistence with osteoporosis drugs.<sup>105</sup>

### Monitoring

#### BMD

NOF guidelines recommend that patients on bisphosphonates should have clinical and BMD re-evaluation after two years, or more often if medically appropriate. Vertebral imaging should be performed in patients with height loss, new back pain, or postural changes during treatment.<sup>64</sup> Bisphosphonates increase BMD in most patients, but trials of bisphosphonates have found that even when serial BMD measurements have not increased or have modestly decreased, the risk of fracture has still significantly decreased.<sup>106-109</sup>

#### Incident fractures

In the face of limited evidence, experts recently proposed criteria for treatment failure to include when two or more incident fractures have occurred during treatment, when serial measurements of bone remodeling markers are not suppressed by anti-resorptive therapy, and when BMD continues to decrease.<sup>118</sup> If a BMD decrease truly reflects a treatment failure, clinicians could consider transition to a different drug (for example, from an oral to intravenous bisphosphonates or other osteoporosis agents).

#### When to stop or not to stop

After starting bisphosphonates, changes can occur that affect the benefits versus risks of continuing treatment.

### Principal considerations for bisphosphonate therapy in osteoporosis

#### Considerations before starting treatment

- Take a complete history and perform a pertinent physical evaluation
- Assess patient factors that could increase fracture risk or affect dosing and administration of bisphosphonates
- Assess fall risk and treat modifiable risk factors
- Obtain bone mineral density (BMD) measurements and assess fracture risk:
  - Check calcium, vitamin D, and renal function
  - Consider excluding metabolic bone diseases other than osteoporosis
  - Exclude secondary causes of osteoporosis
- Counsel on the risk of osteoporosis related fractures and decide about starting bisphosphonates using clinical judgment and taking into account patient preferences
- Assure optimal oral health
- Advise on calcium and vitamin D intake
- Advise on stopping smoking and avoiding excessive alcohol intake where appropriate

#### Considerations during treatment

- Assess for adverse effects and patient adherence
- Perform a clinical assessment for new fractures or new risk factors for bone loss
- Consider vertebral imaging in patients with height loss, new back pain, or postural changes
- Consider re-evaluating BMD after two years or more often when medically appropriate
- Consider checking bone turnover markers:
  - Not recommended for routine use
  - Could be useful for assessing treatment efficacy or patient adherence if baseline data are available
- Consider transition to a different osteoporosis agent in case of treatment failure:
  - Two or more incident fractures have occurred during treatment
  - Bone remodeling markers are not suppressed by bisphosphonates on serial measurements
  - BMD continues to decrease
- Consider a drug holiday after comprehensive risk reassessment, including femur neck BMD, as follows:
  - In patients at modest fracture risk bisphosphonates could be discontinued after 3-5 years
  - In patients with higher fracture risk, continue bisphosphonates
  - Transition to another type of osteoporosis treatment can be considered

#### Considerations after discontinuing bisphosphonates

- Clinical assessment for new fractures or new risk factors for bone loss
- Consider ending drug holiday. The decision to resume bisphosphonates incorporates several factors, such as:
  - Potency of the initial bisphosphonate
  - Duration of the drug holiday
  - Baseline femur neck BMD
  - Presence of other clinical risk factors for fractures
  - Short term changes in BMD and increases in bone turnover markers (of limited value)

**Table 2 | Food and Drug Administration approved bisphosphonates for osteoporosis\***

Agent	Prevention		Treatment			Fracture Endpoint Registry Trial			
	GIO	PMO	In men	GIO	PMO	Recurrent	Hip	Vertebral	Non-vertebral
Alendronate	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Risedronate	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Ibandronate	No	Yes†	No	No	Yes	No	No	Yes	No
Zoledronic acid	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

\*Abbreviations: PMO=postmenopausal; GIO=glucocorticoid induced.  
†Only the oral preparation.

These include:

- Changes in patients’ characteristics as they get older (such as the development of sarcopenia and changes in adherence or social, environmental, or behavioral factors)
- The biology of the underlying disease (for example, the appearance or resolution of relevant risk factors, such as a low body weight or glucocorticoid use)
- The degree to which continued treatment modifies the risk of fracture
- The cumulative risk of the adverse effects of therapy.

The fact that rare adverse effects, such as ONJ and atypical femur fractures, seem to be more common with long term use of bisphosphonates adds to the uncertainty regarding the optimal duration of treatment.<sup>44 45</sup> Residual antiresorptive activity of retained bisphosphonates in bone is expected to maintain some degree of anti-fracture efficacy after discontinuation.<sup>11 121</sup>

**Evidence on the effects of discontinuing bisphosphonates**

In the Fracture Intervention Trial Long-term Extension (FLEX) study, after a 10 year follow-up, no significant difference in the risk of non-vertebral fractures was seen between patients who continued (19%) or discontinued alendronate (18.9%).<sup>124</sup> However, patients who continued taking alendronate had a significantly lower risk of a clinical vertebral fracture (2.4% for alendronate v 5.3% for placebo; relative risk 0.45, 0.24 to 0.85). A retrospective analysis of the FLEX data showed that in women without vertebral fractures at baseline, continuing alendronate reduced non-vertebral fractures only in those with femoral neck T scores –2.5 or less (0.50, 0.26 to 0.96) at the start of the drug holiday.<sup>125</sup> However, the FDA analysis of the FLEX trial showed that the rates of clinical fractures were similar whether patients continued on alendronate or switched to placebo during the extension even for the subgroup of patients with femoral neck T scores –2.5 or less.<sup>126</sup>

Further analysis of these data found that older age and lower hip BMD at discontinuation of alendronate after four to five years of treatment predict clinical fractures during the next five years.<sup>127</sup>

In the HORIZON-PFT, women who had received zoledronic acid for three years were randomly assigned to continue for another three years or to switch to placebo. The women who continued on zoledronic acid had a lower incidence of radiographic vertebral fractures (3.0% v 6.2%; odds ratio 0.51, 0.26 to 0.95), but there were no significant differences in clinical fractures.<sup>128</sup> Overall, these findings suggest that after three years of treatment with zoledronic acid, many patients could discontinue treatment for up to three years.

The extension of the Vertebral Efficacy with Risedronate Therapy MultiNational trial showed that one year after discontinuation of risedronate in patients who had received up to seven years of treatment the risk of new radiographic vertebral fractures was reduced in the former risedronate users compared with the former placebo users (6.5% v 11.6%; relative risk 0.54, 0.34 to 0.86).<sup>129</sup> However, the interpretation of these data is limited by the small sample size and the lack of information on clinical vertebral fractures.

The data on long term use of bisphosphonates suggest that the use of alendronate for five years and zoledronic acid for three years may allow residual anti-fracture benefits even after these drugs are discontinued, but this may not be applicable to risedronate.

No data are available on anti-fracture effects after discontinuing ibandronate.<sup>130</sup> In addition, it should be noted that the statistical limitations of all these retrospective analyses preclude the identification with confidence of a subgroup of patients who are more likely to benefit from treatment for longer than three to five years.

**Clinical practice**

Given that there is limited evidence of efficacy to guide treatment decisions beyond three to five years, the decision about drug holidays needs to be based on the individual.<sup>11 123</sup> Patients at high risk (as defined by the extension trials) with femoral neck T scores –2.5 or less might continue on treatment for an additional three to five years,<sup>131</sup> switch from an oral to an intravenous bisphosphonate (typically zoledronic acid), or switch to an alternative drug such as denosumab or teriparatide. Those with femoral neck T scores greater than –2.5 should be clinically reassessed for factors that might preclude discontinuation of osteoporosis drugs, such as intercurrent fractures, new chronic diseases, or the use of drugs that could increase bone loss (for example, corticosteroids, aromatase inhibitors, androgen deprivation therapy). Otherwise, for patients who are not at high risk or those whose femoral neck T score is greater than –2.5, it is reasonable to discontinue bisphosphonates after three to five years.<sup>131</sup>

**Guidelines**

Updated guidelines for the prevention and treatment of osteoporosis applicable to postmenopausal women and men age 50 years or more were recently released by NOF in the US.<sup>64</sup> European guidelines for assessing and treating postmenopausal women with osteoporosis at risk of fractures were published in 2013.<sup>132</sup> Revised in 2010, the Canadian guidelines concentrate on the assessment and management of women and men over 50 years who are at high risk of fragility fractures.<sup>133</sup> Bisphosphonates are universally recommended as first line therapy for patients with osteoporosis and those with an increased risk of fractures (who do not have a contraindication). Responding to an increasing focus on rare adverse effects, the Endocrine Society published a position statement in 2012 emphasizing that the risk of serious complications associated with bisphosphonates is very low, particularly when the established benefits of fracture risk reduction in patients with osteoporosis or those with high risk for fractures are taken into account.<sup>66</sup>