



# New drugs for osteoporosis

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## Summary

**Despite numerous treatments, the majority of Australians with osteoporosis remain untreated. The newer parenteral treatments, intravenous zoledronic acid and subcutaneous denosumab injections, are administered less frequently (annually or six monthly, respectively) than the oral bisphosphonates, potentially overcoming compliance issues. Two other daily treatments – strontium ranelate and teriparatide – do not have major inhibitory effects on bone resorption (anti-catabolic), and teriparatide stimulates new bone formation (anabolic). With the exception of teriparatide, which is reserved for women and men with the most severe osteoporosis, all of these newer drugs are first-line therapy for osteoporosis in postmenopausal women. However, only bisphosphonates are also currently approved for this indication in men and in patients with corticosteroid-induced osteoporosis.**

Key words: bone diseases, denosumab, strontium ranelate, teriparatide, zoledronic acid.

*(Aust Prescr 2011;34:176–81)*

## Introduction

Osteoporosis results from reduced bone strength and predisposes patients to an increased risk of fracture. Bone strength is determined by both bone density and bone quality. All fractures due to osteoporosis reduce the quality of life and increase mortality. The most common sites of minimal trauma fractures are the hip and pelvis (40.5%) and wrist and forearm (17.1%). Hip fracture is the most catastrophic of osteoporotic fractures resulting in chronic pain, disability and increased mortality in up to 35% of patients within 12 months.<sup>1,2</sup> Conservative estimates indicate that 692 300 Australians had diagnosed osteoporosis in 2007–08. The annual cost of osteoporosis remains very high at \$1.9 billion for direct costs alone.

Despite the public health burden, only 20–30% of Australians with fragility fractures due to osteoporosis are being treated. The causes for this are multifactorial, but include a

low awareness of the importance and common nature of osteoporosis among both family doctors and patients.

The most commonly prescribed medications for osteoporosis are the oral bisphosphonates, risedronate (daily, weekly or monthly dose) or alendronate (weekly dose). Weekly risedronate is available with calcium and colecalciferol supplements. Alendronate is available either alone or in combination with 5600 IU colecalciferol (vitamin D<sub>3</sub>). Other medicines are raloxifene (a selective oestrogen receptor modulator), etidronate and calcitriol, although the latter two medications have largely been superseded.

For osteoporosis treatments to act optimally on bone, adequate calcium and vitamin D are required. The average diet contains only small amounts of vitamin D, and safe sunlight exposure (ultraviolet index <3) is required to generate adequate serum levels (>50 nmol/L in winter/early spring) of 25-hydroxyvitamin D (25(OH)D). When this is not possible, vitamin D supplements (colecalciferol) may be used, with a dose of 800–2000 IU per day being effective in most people. Regular weight-bearing exercise is also recommended.

There are several new Pharmaceutical Benefits Scheme (PBS)-listed drugs for osteoporosis (Table 1). A summary of their safety and efficacy is shown in Table 2.

## Zoledronic acid

Bisphosphonates are synthetic analogues of pyrophosphate and bind to bone mineral with high affinity. They are taken up by osteoclasts during bone resorption and either inhibit the adenosine triphosphate (etidronate or clodronate) or farnesyl pyrophosphate synthase (aminobisphosphonates) pathways.<sup>3</sup> This inhibits bone resorption through reduced recruitment of osteoclasts and decreased osteoclast activity, with formation of giant dysfunctional osteoclasts.<sup>4</sup>

Zoledronic acid is the most potent bisphosphonate and has the longest skeletal half-life. It is administered as an intravenous infusion (5 mg in 100 mL) over at least 15 minutes once per year, for a maximum of three years. Patients must be appropriately hydrated before the infusion, especially the elderly and those with renal impairment or receiving diuretic therapy. Treatment is contraindicated when creatinine clearance is less than 35 mL/minute. Hypocalcaemia and vitamin D deficiency (25(OH)D <50 nmol/L) should be corrected before the infusion. Adequate calcium and vitamin D supplementation should also be recommended after starting therapy.

Table 1

**Pharmaceutical Benefits Scheme-listed indications for osteoporosis drugs**

Drug	Indication
Zoledronic acid, risedronate, alendronate	Established osteoporosis in women and men with fractures due to minimal trauma, and for the treatment of osteoporosis in women and men aged 70 years or older with a bone mineral density T-score of $\leq -3.0$ at the femoral neck or lumbar spine  People on long-term high-dose corticosteroid therapy (at least 3 months at $\geq 7.5$ mg daily prednisolone or equivalent) and with a bone mineral density T-score of $-1.5$ or less
Denosumab, strontium ranelate*	Women aged 70 years of age or older with a bone mineral density T-score of $-3.0$ or less, or established postmenopausal osteoporosis with a fracture due to minimal trauma
Teriparatide	Severe osteoporosis in patients with a bone mineral density T-score of $-3.0$ or less, and at least two minimal trauma fractures, one of which occurred after 12 months of first-line therapy, or for severe osteoporosis when first-line therapy cannot be tolerated

\* Strontium ranelate is not approved for osteoporosis in men, but can be obtained through the Repatriation Pharmaceutical Benefits Scheme

Table 2

**New drugs for the treatment of osteoporosis**

	Denosumab	Strontium ranelate	Zoledronic acid	Teriparatide
<b>Administration</b>	60 mg SC every six months	2 g daily as oral powder	5 mg IV yearly	20 microgram SC daily
<b>Limitations</b>	Lacks long-term data	Increased DVTs, rash Compliance	Must be given IV Lacks long-term data	Restricted use Lacks long-term data
<b>Advantages</b>	Compliance	Long-term data are available	Compliance	Anabolic effects
<b>Fracture risk reduction in postmenopausal women</b>	Vertebral, non-vertebral, hip	Vertebral, non-vertebral, hip (age $\geq 74$ , T-score $-3$ or less)	Vertebral, non-vertebral, hip	Vertebral, non-vertebral
<b>Fracture risk reduction in men</b>	No data	No data	Clinical vertebral, non-vertebral fractures, clinical fractures	Vertebral
<b>Mortality reduction</b>	No	No	Yes (post-hip fracture)	No

SC subcutaneous IV intravenous DVT deep vein thrombosis

**Efficacy**

In a large placebo-controlled clinical trial, zoledronic acid treatment reduced vertebral fractures by 70% (10.9% vs 3.3%,  $p < 0.001$ ), non-vertebral fractures by 25% (10.7% vs 8.0%,  $p < 0.001$ ) and hip fractures by 41% (2.5% vs 1.4%,  $p = 0.002$ ) over three years in postmenopausal women with osteoporosis.<sup>5</sup> All-cause mortality decreased by 28% (13.3% vs 9.6%,  $p = 0.01$ ) and all clinical fractures by 35% (13.9% vs 8.6%,  $p = 0.001$ ) in older men and women who received zoledronic acid 5 mg versus placebo within three months of sustaining a hip fracture.<sup>6</sup> The mechanisms responsible for mortality reduction in patients treated with zoledronic acid remain unclear, but

may be related to an effect on reducing cardiovascular events and pneumonia.<sup>7</sup> If treatment was deferred for two weeks after the fracture, the improvements in bone mineral density and reductions in mortality and re-fracture rate were greater.<sup>8</sup>

**Adverse effects**

Infusion-related acute-phase reactions are common, occurring in about a third of patients after the first infusion, and only 7% and 3% of patients after the second and third infusion, respectively.<sup>5</sup> Symptoms including fever, myalgia, influenza-like symptoms, headache, nausea and arthralgia occur for 1–3 days. Giving paracetamol shortly after the infusion reduces these

symptoms. Zoledronic acid may also increase serum creatinine concentrations, particularly in patients with pre-existing renal impairment.

In postmenopausal women with osteoporosis, the incidence of serious atrial fibrillation was increased versus placebo (1.3% vs 0.5%,  $p < 0.001$ ).<sup>5</sup> However, as this was not found in the other zoledronic acid trials, the association remains uncertain and a report from the Food and Drug Administration found no association between bisphosphonates and atrial fibrillation. Rare events reported with both oral and intravenous bisphosphonates include severe ocular inflammation, and severe and incapacitating musculoskeletal pain. In this trial, atypical femoral fractures did not occur.<sup>5</sup>

In osteoporosis trials of zoledronic acid, there was only one case of osteonecrosis of the jaw reported in each of the treatment and placebo groups. The risk is estimated to be very low (about 1:10 000) and is most strongly associated with high cumulative intravenous bisphosphonate doses in patients with malignancy, rather than in patients with osteoporosis.

## Denosumab

Denosumab is a fully human monoclonal antibody to RANKL (receptor activator of nuclear factor- $\kappa$ B ligand) that prevents its interaction with osteoclasts. It reversibly inhibits bone resorption by reducing both osteoclast formation and differentiation and increasing osteoclast apoptosis (New drugs, Aust Prescr 2010;33:193-8).

The potential benefits of denosumab include the absence of gastrointestinal adverse effects that may limit oral bisphosphonate use, and the ease of administration by family doctors, which may lead to improved adherence. Also dose adjustment is not necessary in patients with renal impairment.

Vitamin D deficiency should be corrected before initiating denosumab therapy. Adequate calcium and vitamin D supplementation should also be recommended after starting therapy. As hypocalcaemia may be exacerbated by denosumab, patients with conditions that predispose them to hypocalcaemia (such as hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, severe renal impairment – creatinine clearance  $< 30$  mL/min, or renal dialysis) should be aware of the symptoms of hypocalcaemia and be monitored regularly.

## Efficacy

When given as a 60 mg subcutaneous injection every six months, compared with placebo, denosumab increases the bone mineral density at the lumbar spine and hip, with associated relative risk reductions of 68% (7.2% vs 2.3%,  $p < 0.001$ ) for vertebral fractures, 20% (8.0% vs 6.5%,  $p = 0.01$ ) for non-vertebral fractures and 40% (1.2% vs 0.7%,  $p = 0.04$ ) for hip fractures.<sup>9,10</sup> Additionally, comparison trials with alendronate,

either in treatment-naïve patients or in patients pre-treated with alendronate, have shown non-inferiority in bone mineral density increases at all sites compared with denosumab.<sup>10-12</sup> No head-to-head studies with primary fracture outcomes have been performed.

## Adverse effects

Denosumab is well tolerated with adverse effect rates generally similar to placebo.<sup>9,11-16</sup> The most common adverse reactions include musculoskeletal pain, hypercholesterolaemia and eczema, and discontinuation should be considered if the latter is severe.<sup>13</sup> Hypocalcaemia may rarely occur, especially in patients with stage 5 chronic kidney disease. Pancreatitis has also been reported. Denosumab has the potential to increase the risk of infection and neoplasia. Increased rates of serious skin infections, predominantly cellulitis, have been observed in trials and patients should seek prompt medical attention if they develop signs and symptoms of infection. No significant increases in malignancy rates have been noted to date. Atypical fractures and delayed fracture healing have not been observed in trials.

Osteonecrosis of the jaw has rarely been reported (two cases) and a routine oral examination is recommended before starting treatment.<sup>17</sup> In patients with bone metastases from breast or prostate cancer, osteonecrosis of the jaw may be associated with denosumab treatment, suggesting decreased bone turnover may be an important contributing factor.

## Strontium ranelate

Although the mechanism of action of strontium is unclear, this orally administered daily treatment decreases bone resorption, increases bone formation markers and maintains bone microarchitecture. It should be administered two hours after the evening meal for optimal absorption and should not be taken at the same time as calcium supplements.

## Efficacy

Strontium increased spinal and hip bone density and reduced vertebral fractures by 41% (32.8% vs 20.9%,  $p < 0.001$ ) and nonvertebral fractures by 16% (12.9% vs 11.2%,  $p = 0.04$ ) in postmenopausal women with osteoporosis over three years in the SOTI trial,<sup>18</sup> and for up to five years in the TROPOS trial.<sup>19</sup> A *post hoc* analysis showed it also reduces hip fractures in women aged 74 years and over with a T-score of  $-3.0$  or less.<sup>19</sup> Strontium also reduces vertebral and non-vertebral fractures and improves quality of life in women aged over 80 years<sup>20,21</sup> and reduces vertebral fractures in postmenopausal women with or without prevalent fractures and osteopenia.<sup>22</sup> Although the increases of spinal and hip bone mineral density appear to be greater than for other osteoporosis treatments, just under 50% of the increase in spinal bone mineral density is artefactual and is related to the substitution of strontium, a heavier element, for calcium in hydroxyapatite crystals in bone. Nevertheless,

increases in bone mineral density after strontium treatment are related to fracture risk reduction.

### **Adverse effects**

The annual incidence of venous thromboembolism over five years was 0.9% with strontium ranelate versus 0.6% with placebo (relative risk of 1.4).<sup>23</sup> Strontium has also been associated with rare and potentially fatal cases of hypersensitivity reactions with eosinophilia and systemic symptoms. The incidence of this adverse reaction is extremely low, estimated at 1:54 000 patient-years of treatment. Patients should be warned of the possibility of a rash and it may be prudent to stop strontium if this occurs within the first 6–8 weeks of treatment. Diarrhoea and nausea also occur. Initiating treatment every second day for one month may reduce these adverse effects.

### **Teriparatide**

Anti-catabolic therapies like zoledronic acid and denosumab prevent bone loss but do not add new bone, nor do they restore disrupted bone microarchitecture. In severe osteoporosis, preventing further bone loss may not be enough to stop further fractures. In these cases, treatments that stimulate bone formation and reverse skeletal deterioration may be a valuable option. Teriparatide or human parathyroid hormone (1–34) is the only anabolic drug currently approved for treatment of osteoporosis in Australia.

Continuous high circulating parathyroid hormone has catabolic effects on bone as seen in people with primary hyperparathyroidism. However, low-dose intermittent parathyroid hormone (20 microgram per day subcutaneously) has an anabolic effect.<sup>24</sup> Based on bone marker studies, teriparatide increases both bone formation and resorption. However, during the first three months of treatment parathyroid hormone stimulates bone formation to a greater extent than bone resorption, suggesting that teriparatide could initially induce bone apposition without previous bone resorption through modelling-based formation.<sup>25,26</sup> After 3–6 months of teriparatide treatment, the bone remodelling rate is globally increased, with bone formation favoured over bone resorption resulting in a net gain of bone deposited in each basic multicellular unit.

Treatment needs to be initiated by a specialist and treatment duration is limited to 18 months.

### **Efficacy**

Teriparatide therapy increases spine and hip bone mineral density and reduces vertebral and non-vertebral fractures in postmenopausal women.<sup>27</sup> It has similar effects in men but there are no data on non-vertebral fractures.<sup>28,29</sup> The effect of teriparatide on hip fracture reduction has not been reported for men or women. Decreases in vertebral fractures of 65% (14% vs 5%,  $p < 0.001$ ) and non-vertebral fractures by 53%

(6% vs 3%,  $p = 0.02$ ) compared with placebo in postmenopausal women are similar to those seen with zoledronic acid and denosumab. A meta-analysis has shown that severe back pain was reduced by 61% with teriparatide compared to the comparators (placebo, alendronate or hormonal therapy).<sup>30</sup> The risk reduction for back pain was evident after only six months of teriparatide.

### **Adverse effects**

Adverse reactions reported during phase III trials with teriparatide generally have been mild. The most frequent events were dizziness, headache and leg cramps in fewer than 10% of patients. Injection site hypersensitivity occurred in a small number of patients. Allergic reactions, including dyspnoea, urticaria and chest pain, occurred in less than one in 1000 patients.<sup>31</sup> About 5% of recipients experienced mild transient hypercalcaemia which resolved within 24 hours. If hypercalcaemia occurs, it is generally recommended to reduce calcium intake to 1000 mg daily or less or to decrease the frequency of injections. Monitoring of serum calcium is not routinely needed, however it may be worth measuring serum calcium at baseline and after a month of therapy. A recent study evaluating the effect of teriparatide on urinary calcium at one, six and 12 months<sup>27,28</sup> showed small increases in urinary calcium excretion, with less than 1% of the participants requiring a dose change in calcium or teriparatide due to hypercalcaemia.

Osteosarcoma was reported in a rat oncogenicity model. However, only two cases have been reported in patients during postmarketing studies of approximately one million patients to date. This frequency is less than anticipated for people aged over 60 years. Each patient commencing teriparatide must sign a consent form acknowledging they are aware of this risk and treatment should be avoided in patients at increased baseline risk for osteosarcoma, such as children, and those with Paget's disease, unexplained elevations in alkaline phosphatase, or prior radiation therapy involving the skeleton.

### **Conclusion**

New treatments for osteoporosis may offer advantages over existing oral bisphosphonates, particularly regarding compliance. Although there are no direct head-to-head studies, relative risk reductions in vertebral fractures may be greater for zoledronic acid, denosumab and teriparatide than for oral bisphosphonates. However, reductions in non-vertebral fractures appear similar for zoledronic acid, denosumab, strontium ranelate and oral bisphosphonates. A comparison of absolute risk reductions (and the number needed to treat) is confounded by baseline differences in the severity of osteoporosis. Each class of drug has potential adverse effects.

## References

1. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA* 2009;301:513-21.
2. Ebeling PR. Clinical practice. Osteoporosis in men. *N Engl J Med* 2008;358:1474-82.
3. van Beek E, Peiterman E, Cohen L, Lowick C, Papapoulos S. Nitrogen-containing bisphosphonates inhibit isopentenyl pyrophosphate isomerase/farnesyl pyrophosphate synthase activity with relative potencies corresponding to their antiresorptive potencies in vitro and in vivo. *Biochem Biophys Res Commun* 1999;255:491-4.
4. Kavanagh KL, Guo K, Dunford JE, Wu X, Knapp S, Ebetino FH, et al. The molecular mechanism of nitrogen-containing bisphosphonates as antiosteoporosis drugs. *Proc Natl Acad Sci USA* 2006;103:7829-34.
5. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809-22.
6. Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid in reducing clinical fracture and mortality after hip fracture. *N Engl J Med* 2007;357:nihpa40967.
7. Colón-Emeric CS, Mesenbrink P, Lyles KW, Pieper CF, Boonen S, Delmas P, et al. Potential mediators of the mortality reduction with zoledronic acid after hip fracture. *J Bone Miner Res* 2010;25:91-7.
8. Eriksen EF, Lyles KW, Colón-Emeric CS, Pieper CF, Magaziner JS, Adachi JD, et al. Antifracture efficacy and reduction of mortality in relation to timing of the first dose of zoledronic acid after hip fracture. *J Bone Miner Res* 2009;24:1308-13.
9. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361:756-65.
10. Ebeling PR. Metabolic bone diseases: translational research-preventing fractures with denosumab. *Nat Rev Rheumatol* 2009;5:660-1.
11. Kendler DL, Roux C, Benhamou CL, Brown JP, Lillestol M, Siddhanti S, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. *J Bone Miner Res* 2010;25:72-81.
12. Brown JP, Prince RL, Deal C, Recker RR, Kiel DP, de Gregorio LH, et al. Comparison of the effect of denosumab and alendronate on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. *J Bone Miner Res* 2009;24:1-34.
13. Australian Public Assessment Report for Denosumab. [www.tga.gov.au/pdf/auspar/auspar-prolia.pdf](http://www.tga.gov.au/pdf/auspar/auspar-prolia.pdf) [cited 2011 Nov 8]
14. Bekker PJ, Holloway DL, Rasmussen AS, Murphy R, Martin SW, Leese PT, et al. A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. *J Bone Miner Res* 2004;19:1059-66.
15. Miller PD, Bolognese MA, Lewiecki EM, McClung MR, Ding B, Austin M, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone* 2008;43:222-9.
16. Bone HG, Bolognese MA, Yuen CK, Kendler DL, Wang H, Liu Y, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. *J Clin Endocrinol Metab* 2008;93:2149-57.
17. Aghaloo TL, Felsenfeld AL, Tetradis S. Osteonecrosis of the jaw in a patient on denosumab. *J Oral Maxillofac Surg* 2010;68:959-63.
18. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004;350:459-68.
19. Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. *J Clin Endocrinol Metab* 2005;90:2816-22.
20. Inderjeeth CA, Foo AC, Lai MM, Glendenning P. Efficacy and safety of pharmacological agents in managing osteoporosis in the old old: review of the evidence. *Bone* 2009;44:744-51.
21. Seeman E, Boonen S, Borgstrom F, Vellas B, Aquino JP, Semler J, et al. Five years treatment with strontium ranelate reduces vertebral and nonvertebral fractures and increases the number and quality of remaining life-years in women over 80 years of age. *Bone* 2010;46:1038-42.
22. Seeman E, Devogelaer JP, Lorenc R, Spector T, Brixen K, Balogh A, et al. Strontium ranelate reduces the risk of vertebral fractures in patients with osteopenia. *J Bone Miner Res* 2008;23:433-8.
23. Protos Product Information. [www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-02840-3](http://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-02840-3) [cited 2011 Nov 8]
24. Tam CS, Heersche JN, Murray TM, Parsons JA. Parathyroid hormone stimulates the bone apposition rate independently of its resorptive action: differential effects of intermittent and continuous administration. *Endocrinology* 1982;110:506-12.
25. Dempster DW, Zhou H, Cosman F, Nieves J, Adachi JD, Fraher LJ, et al. PTH treatment directly stimulates bone formation in cancellous and cortical bone in humans. *J Bone Miner Res* 2001;16(S1):S179.
26. Bilezikian JP. Combination anabolic and antiresorptive therapy for osteoporosis: opening the anabolic window. *Curr Osteoporos Rep* 2008;6:24-30.
27. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344:1434-41.
28. Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, et al. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res* 2003;18:9-17.

29. Kaufman JM, Orwoll E, Goemaere S, San Martin J, Hossain A, Dalsky GP, et al. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. *Osteoporos Int* 2005;16:510-6.
30. Nevitt MC, Chen P, Kiel DP, Reginster JY, Dore RK, Zanchetta JR, et al. Reduction in the risk of developing back pain persists at least 30 months after discontinuation of teriparatide treatment: a meta-analysis. *Osteoporos Int* 2006;17:1630-7.
31. Gagnon C, Li V, Ebeling PR. Osteoporosis in men: its pathophysiology and the role of teriparatide in its treatment. *Clin Interv Aging* 2008;3:635-45.

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### Self-test questions

*The following statements are either true or false (answers on page 195)*

5. Zoledronic acid reduces mortality after hip fracture.
6. Denosumab can exacerbate hypocalcaemia in patients with hypoparathyroidism.

## Dental notes

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### New drugs for osteoporosis

The newer drugs for the management of osteoporosis widen the range of treatment options, but are not without risk. The main dental concern is bisphosphonate-related osteonecrosis of the jaw. It took several years before the true relation and incidence of bisphosphonate-related osteonecrosis was established and accepted. Multiple independent studies have shown a relation between osteonecrosis after dental extraction and bisphosphonate use. The incidence is approximately 1/500 to 1/1500. For patients taking intravenous bisphosphonates for cancer who have dental extractions the incidence is much higher at 1/10–15.<sup>1</sup>

At present, the incidence of osteonecrosis of the jaw for patients on intravenous zoledronic acid and subcutaneous denosumab for osteoporosis is unknown, but is probably low. These are potent drugs and it is even more important that

patients have their oral health checked before treatment, as immediately post-infusion their bone turnover is markedly suppressed. Post-infusion extractions are probably best avoided for at least several months if possible.

Strontium ranelate and teriparatide have different mechanisms of action and osteonecrosis of the jaw is not a risk. Indeed initial reports have shown that teriparatide may be a good potential treatment for established bisphosphonate-related osteonecrosis of the jaw.<sup>2,3</sup>

### References

1. Lo JC, Gordon NP, Yang J, Hui RL, Martin D, Hutchinson M, et al. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. *J Oral Maxillofac Surg* 2010;68:243-53.
2. Grey A. Teriparatide for bone loss in the jaw. *N Engl J Med* 2010;363:2458-9.
3. Subramanian G, Cohen HV, Quek SY. A model for the pathogenesis of bisphosphonate-associated osteonecrosis of the jaw and teriparatide's potential role in its resolution. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2011 Aug 6. Epub ahead of print.

## National Medicines Symposium 2012

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