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# Osteoporosis

## Pharmacological prevention and management in older people

### Background

Osteoporosis remains undertreated in Australian primary care, with as few as 30% of postmenopausal women with a fracture and 10% of men with osteoporosis receiving pharmacological treatment.

### Objective

This article presents an overview of the pharmacological management of osteoporosis in older people in the general practice setting.

### Discussion

Lifestyle factors and ensuring adequate calcium and vitamin D intake are important in preventing and treating osteoporosis. Pharmacological treatments are recommended for patients with a minimal trauma fracture, for those aged 70 years or over with a T-score of  $-3.0$  or lower, or for those who are currently taking prolonged high dose corticosteroids and who have a T-score of  $-1.5$  or lower. Bisphosphonates are recommended as first line therapy for established postmenopausal osteoporosis. Medicine selection is guided by patient gender, menopausal status, medical and fracture history, patient preference and eligibility for government subsidy.

### Keywords

osteoporosis; osteoporosis, postmenopausal; fractures, bone/prevention and control



Osteoporosis (OP) is common in Australian primary care, yet it remains undertreated. Among people aged 80 years and over who participated in the Geelong Osteoporosis Study, 51% of women and 19% of men had OP (defined as a T-score less than  $-2.5$ ).<sup>1</sup> A population based study in Sydney (New South Wales) reported that 25% of men aged 70 years or over met the Pharmaceutical Benefits Scheme (PBS) criteria for OP treatment, of whom 90% were actually unaware that they had OP.<sup>2</sup>

The lifetime risk of osteoporotic fracture in people aged over 60 years is approximately 56% for women and 29% for men.<sup>3</sup> Following a low trauma fracture the risk of subsequent fractures is increased for up to 10 years.<sup>4</sup> Mortality increases in the first year after all major fractures (including vertebral fractures), but vertebral fractures go largely undetected. All low trauma fractures were associated with increased mortality for 5–10 years in the Dubbo Osteoporosis Epidemiology Study.<sup>5</sup>

While there is no known cure for OP, fracture rates attributable to OP can be reduced through identifying risk factors and by appropriate management.<sup>6</sup> However, OP remains undertreated in Australian primary care. Fewer than 30% of Australian women with a fracture after menopause,<sup>7</sup> and only 10% of Australian men with OP receive pharmacological treatments.<sup>2</sup>

### Ensuring adequate calcium and vitamin D intake

Evidence supports the use of calcium and vitamin D for the prevention of OP in people aged 50 years and over.<sup>8</sup> Recent advice from the Institute of Medicine in the United States of America suggests that women aged over 50 years and men aged over 70 years should maintain a daily calcium intake of 1200 mg<sup>9</sup> (Australian guidelines recommend 1200–1300 mg/day).<sup>3,10</sup> To optimise efficacy, it is recommended that calcium supplements be taken together with at least 800 IU of vitamin D3 (cholecalciferol) per day.<sup>3,8</sup> Recent meta-analyses suggesting an increased risk of cardiovascular events with the use of calcium supplements continue to be the subject of international debate,<sup>11–13</sup>



and the findings are not universally accepted. The role of vitamin D in OP prevention and management is addressed in the article by Winzenberg et al in this issue of *Australian Family Physician*.

## When to prescribe pharmacological treatments

It is recommended that clinicians consider adjunct pharmacological treatment in the following patients:<sup>3</sup>

- those with a minimal trauma fracture
- those aged 70 years or over with a T-score of  $-3.0$  or lower
- those currently on prolonged (at least 3 months) high dose corticosteroid treatment (at least 7.5 mg/day prednisolone or equivalent) and with a T-score of  $-1.5$  or lower.

Clinicians are also advised to screen for secondary causes of OP. Z-scores (number of standard deviations away from the age and sex-matched mean bone mineral density [BMD]) are often used to assess additional reasons for bone loss.<sup>14,15</sup> A Z-score of less than  $-2.0$  should prompt investigation of possible underlying causes of low BMD, although a Z-score greater than  $-2.0$  does not necessarily exclude secondary causes of OP.<sup>15</sup>

## Pharmacological treatments

Choice of pharmacological treatment is influenced by patient gender, menopausal status, medical history, whether it is for primary or secondary fracture prevention, patient preference and eligibility for government subsidy. Calcium and vitamin D are usually provided to all participants in randomised controlled trials (RCTs) evaluating the efficacy of pharmacological treatments for OP. The combined use of calcium and vitamin D is recommended with all anti-osteoporosis treatments if intake is inadequate. Epidemiological and small scale clinical studies suggest vitamin K plays an important role in bone health.<sup>16,17</sup> However, on the basis of the current evidence, vitamin K is not routinely recommended for OP treatment or prevention. While hormone therapy (HT) may have a role in the management of postmenopausal OP in women under the age of 60 years, it is not routinely recommended as an OP treatment for older women, or for those whose last spontaneous menstrual period occurred more than 5 years ago, due to the possible adverse effects.<sup>3,10</sup>

## Bisphosphonates

Bisphosphonates slow bone loss, improve BMD and reduce fracture rates.<sup>19–21</sup> Alendronate, risedronate and zoledronic acid are PBS listed and recommended as first line therapy in men and women for primary and secondary prevention of vertebral, nonvertebral and hip fractures (*Table 1*).<sup>3</sup> Etidronate is PBS listed for the secondary prevention of osteoporosis. Zoledronic acid is an intravenous infusion that is administered once per year for osteoporosis treatment and prevention.

Gastrointestinal adverse effects are the most common and upper gastrointestinal disorders or oesophageal abnormalities are considered a contraindication to oral bisphosphonate use.<sup>3,10</sup> Atypical femoral stress fractures with long term bisphosphonate use have been reported, but the increased risk is approximately five fractures per 10 000 patient years.<sup>22</sup>

Osteonecrosis of the jaw (ONJ) has also been reported with bisphosphonate treatment, although the risk is low (approximately one per 10 000 to one per 250 000 patients receiving oral bisphosphonates) and more than 95% of cases occur in people receiving treatment for cancer rather than for OP.<sup>23,24</sup> Good dental hygiene and care is recommended, especially for people receiving long term bisphosphonate treatment, to reduce the risk of ONJ.<sup>3</sup>

Combination approaches involving co-administration of bisphosphonates with other antiresorptive medicines (eg. strontium) or anabolic medicines (eg. teriparatide) are not recommended. Combination treatment with antiresorptive medicines and teriparatide does not appear to provide any advantages over monotherapy.<sup>25</sup>

Evidence in relation to the optimum duration of bisphosphonate treatment is lacking.<sup>26,27</sup> One RCT reported that women who discontinued alendronate after 5 years did not have higher fracture rates (except clinically recognised vertebral fractures) than those who took alendronate for 10 years.<sup>28</sup> Australian guidelines recommend re-evaluating the need for bisphosphonate therapy after 5–10 years in postmenopausal women and older men who respond well to treatment, as determined by BMD testing and fracture risk assessment (ie. T-score above  $-2.5$  and no recent fractures).<sup>3</sup> A recent US Food and Drug Administration report suggested that due to the lack of evidence for further increases in fracture benefit after 3–5 years of treatment, bisphosphonates could be safely discontinued for a period of time.<sup>26</sup> The decision to discontinue bisphosphonate treatment should be based on individual patient risk. If treatment has been discontinued, BMD should be measured 1 year later and the risk of falling should be reassessed. Bisphosphonates may be restarted if BMD has decreased significantly (lumbar spine decrease of 5% or more) or with any additional fracture. Bone turnover markers (eg. CrossLaps<sup>®</sup>) measure current rate of bone loss and are a useful adjunct to BMD in monitoring the effect of treatment for osteoporosis.

## Denosumab

Denosumab is a monoclonal antibody that inhibits receptor activator of nuclear factor kappa B ligand (RANKL), resulting in decreased bone resorption and increased bone density (*Table 2*).<sup>29</sup> In a RCT of women with OP aged 60–90 years, denosumab administered subcutaneously every 6 months for 36 months was associated with a reduced risk of vertebral, nonvertebral and hip fractures compared to placebo.<sup>30</sup> Denosumab is only listed on the PBS for postmenopausal women who meet the criteria for primary or secondary prevention. As with bisphosphonates, treatment with denosumab results in significant suppression of bone remodelling.<sup>31</sup> The PBS listing does not place any restriction on the duration of therapy. At present, published evidence is available to support the use of denosumab for 3 years.<sup>30</sup>

## Raloxifene

Raloxifene is a selective oestrogen receptor modulator (SERM) that has been shown to prevent postmenopausal bone loss (*Table 2*). It has beneficial oestrogen-like effects on bone, but also has anti-oestrogen effects on the breast and endometrium. A RCT has demonstrated that



raloxifene increases BMD in the spine and femoral neck and reduces vertebral fractures.<sup>32</sup> However, there is minimal evidence to suggest raloxifene may prevent nonvertebral fractures. There are concerns that raloxifene may increase the risk of venous thromboembolism (VTE).<sup>10</sup> Raloxifene is PBS listed for postmenopausal women with a minimal trauma fracture (secondary prevention). Raloxifene may be used as a second line treatment for postmenopausal OP in women considered at risk of breast cancer.<sup>10</sup>

**Strontium ranelate**

Strontium ranelate is an antiresorptive medicine that increases BMD (Table 2).<sup>33</sup> A Cochrane systematic review of three RCTs reported a 37% reduction

in vertebral fractures and a 14% reduction in nonvertebral fractures over 3 years with 2 g/day of strontium ranelate when used for OP treatment.<sup>34</sup> Use of strontium ranelate increased BMD at all sites after 5 years when used for both treatment and prevention.<sup>35</sup> It is PBS listed for primary and secondary prevention of vertebral fractures in postmenopausal women. It is usually taken at bedtime at least 2 hours after eating. The granules should be mixed in a glass of water and drunk immediately. Strontium ranelate has rarely been associated with VTE and severe hypersensitivity reactions, including Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms (DRESS). Patients should be advised to seek immediate medical advice if they develop a rash. Strontium ranelate binds to bone, increases X-ray absorption and therefore may result in inflated BMD measurements.

**Table 1. Bisphosphonates for the treatment and prevention of osteoporosis<sup>3,10,27</sup>**

Medicine	Examples of brands	Dose*^	Considerations for bisphosphonates^
Alendronate	Fosamax® Various generic brands	70 mg tablet weekly (10 mg daily tablet also available, but this is not PBS listed)	Contraindications: <ul style="list-style-type: none"> <li>• hypocalcaemia</li> <li>• uveitis</li> <li>• for tablets (other than Actonel® EC), inability to sit or stand upright for 30 minutes, or any disorders which delay oesophageal emptying</li> </ul> Not recommended in moderate to severe renal impairment (creatinine clearance <35 mL/min) Tablets taken in morning on empty stomach with a full glass of water; patient should remain upright for 30 minutes and not eat or drink anything else in that time. (Note: Actonel® EC can be taken with or without food) Calcium supplements should be taken 2 hours apart from oral bisphosphonates Vitamin D should be corrected to a level above 50 nmol/L before commencing therapy ONJ reported rarely. Good dental hygiene and care is essential. Consider dental assessment and complete any dental procedures before starting treatment to minimise risk of ONJ. Cease treatment if arises Zoledronic acid is an IV infusion over 15 minutes. Headache, myalgia and fever, may be experienced soon after IV infusion
Alendronate plus vitamin D3	Fosamax Plus™ Dronalen™ Plus	70 mg/70 µg or 140 µg tablet weekly	
Alendronate plus vitamin D3 with calcium carbonate	Fosamax Plus D-Cal™ Dronalen Plus D-Cal™	70 mg/140 µg tablet weekly; 1.25 g calcium tablets daily	
Risedronate	Actonel® Various generic brands (35 mg tablets only)	5 mg tablets daily, 35 mg tablets weekly or 150 mg tablet monthly	Calcium supplements should be taken 2 hours apart from oral bisphosphonates Vitamin D should be corrected to a level above 50 nmol/L before commencing therapy ONJ reported rarely. Good dental hygiene and care is essential. Consider dental assessment and complete any dental procedures before starting treatment to minimise risk of ONJ. Cease treatment if arises Zoledronic acid is an IV infusion over 15 minutes. Headache, myalgia and fever, may be experienced soon after IV infusion
	Actonel® EC (enteric coated)**	35 mg tablets weekly	
Risedronate with calcium carbonate	Actonel® Combi Actonel® EC Combi (enteric coated)**	35 mg tablet weekly; 1.25 g calcium tablets daily on other 6 days of the week	ONJ reported rarely. Good dental hygiene and care is essential. Consider dental assessment and complete any dental procedures before starting treatment to minimise risk of ONJ. Cease treatment if arises Zoledronic acid is an IV infusion over 15 minutes. Headache, myalgia and fever, may be experienced soon after IV infusion
Risedronate with calcium carbonate/ vitamin D	Actonel® Combi D Actonel® EC Combi D (enteric coated)**	35 mg tablet weekly; 2.5 g calcium/22 µg vitamin D effervescent granules daily on other 6 days of the week	
Zoledronic acid	Aclasta®	5 mg in 100 mL IV solution yearly	
Etidronate with calcium carbonate	Didrocal®	2 x 200 mg tablets nightly for 14 days then 1.25 g calcium tablets daily for 76 days	

Note: 1 µg vitamin D = 40 international units (IU); ONJ = osteonecrosis of the jaw  
 \* Doses are for brands listed in the table; ^ Refer to full product information for details; \*\* Replacing conventional Actonel® 35 mg tablets in January 2012  
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## Teriparatide

Teriparatide is a synthetic form of human parathyroid hormone which acts by inhibiting bone resorption and increasing bone formation (Table 2).<sup>36,37</sup> In the Fracture Prevention Trial, parathyroid hormone was associated with a decreased risk of vertebral and nonvertebral fractures and increased vertebral, femoral and total body BMD.<sup>38</sup> Pharmaceutical Benefits Scheme listing parameters restrict subsidised access to patients with a very high risk of fracture and when other drugs have failed (ie. fracture has occurred during antiresorptive treatment) or are not tolerated. Its use is restricted to a total of 18 months.<sup>10</sup> Teriparatide is also indicated for use in

men with a high risk of fractures and where other treatments are unsuitable. Following a course of teriparatide it is recommended that patients use an antiresorptive medicine (eg. a bisphosphonate) to further increase BMD and maintain the antifracture effect.<sup>14</sup>

## Special considerations

### Renal impairment

Due to age related physiologic changes the renal and hepatic clearance of many medicines is decreased in older people. A patient's renal function is an important consideration when

**Table 2. Other medicines for the treatment and prevention of osteoporosis<sup>3,10,27,29,33,37</sup>**

Medicine	Examples of brands	Dose* ^	Practice points^	Safety considerations^
Denosumab	Prolia®	60 mg in 1 mL subcutaneous injection, 6 monthly	Consider dental assessment and complete any dental procedures before starting treatment to minimise risk of ONJ	No dose adjustment is necessary in renal impairment Contraindicated in hypocalcaemia. Correct hypocalcaemia before initiating Long term safety and efficacy data are lacking; there are particular concerns regarding effects: <ul style="list-style-type: none"> <li>• on the immune system (eg. increased risk of infection)</li> <li>• on bone, including after treatment has stopped</li> <li>• of taking denosumab after bisphosphonate use</li> </ul>
Raloxifene	Evista®	60 mg tablet daily	Fasting is not required	Contraindicated in patients with a history of VTE VTE rarely reported. Cease in patients who require immobilisation for long periods (eg. hospitalisation)
Strontium ranelate	Protos®	2 g sachet nightly	Taken at bedtime, mixed with >30 mL of water at least 2 hours after food, calcium containing products or antacids	Contraindicated in severe renal impairment VTE reported rarely – use with caution in patients with or at risk of thromboembolic disorders Severe hypersensitivity reactions (eg. Stevens-Johnson syndrome, DRESS) reported rarely. DRESS is a life threatening allergic reaction; strontium should be ceased
Teriparatide	Forteo®	20 µg subcutaneous injection daily in the thigh or abdomen (multi-dose prefilled pen)	Initiated by a specialist	Restricted to 18 month lifetime exposure (caused osteosarcoma in animal studies); informed consent required

Note: 1 µg vitamin D = 40 international units; VTE = venous thromboembolism; DRESS = drug rash with eosinophilia and systemic symptoms

\* Doses are for brands listed in the table; ^ Refer to full product information for details

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selecting an appropriate medicine. Plasma calcium concentration should be monitored in patients with renal impairment who receive calcium supplements.<sup>10</sup> Calcium supplements may need to be used at a lower dose or be ceased. Bisphosphonates are excreted mainly unchanged via the kidneys. Australian guidelines suggest that bisphosphonates should not be used in patients with an estimated glomerular filtration rate of less than 35 mL/min (*Table 1*). Strontium ranelate and teriparatide are not recommended in patients with an estimated glomerular filtration rate less than 30 mL/min.<sup>10</sup> Raloxifene mainly undergoes hepatic metabolism and is excreted in faeces.<sup>36</sup> No dosage reduction of denosumab is required in renal impairment.

### Corticosteroid induced osteoporosis

Corticosteroids are the most common secondary cause of OP, with up to 30–50% of people receiving long term corticosteroid treatment sustaining a fracture.<sup>39</sup> The risk of fracture is increased by up to 75% during the first 3 months of treatment. It is recommended that clinicians assess BMD before initiating corticosteroid treatment which is likely to last longer than 3 months. While all patients should receive adequate calcium and vitamin D, these alone are not considered sufficient to counteract the adverse effects of long term corticosteroids on BMD.

### Adherence to treatment

Approximately half of postmenopausal women discontinue taking OP treatment within the first 6 months, and two-thirds discontinue within the first year.<sup>40</sup> Discontinuation of treatment has been linked to gastrointestinal adverse effects to bisphosphonates.<sup>41</sup> Rates of treatment discontinuation may be lower among women prescribed formulations of bisphosphonates that require less frequent administration, although rates of treatment discontinuation are still high.

**Table 3. Risk factors that indicate the need for bone mineral density testing\***

- Pre-existing minimal trauma fracture(s)
- Women and men aged 70 years or over
- Female hypogonadism lasting more than 6 months before the age of 45 years
- Certain medicines (eg. prolonged corticosteroid treatment)
- Secondary causes (eg. rheumatoid arthritis, hyperparathyroidism, chronic kidney or liver disease, male hypogonadism, proven malabsorption conditions, or conditions associated with excess corticosteroid secretion or thyroxine excess)

\* Medicare reimburses DXA scanning for these risk factors

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### When to review

#### BMD retesting

To monitor treatment efficacy and disease progression consider bone densitometry testing by dual energy X-ray absorptiometry (DXA) every 2 years after therapy begins, or every 12 months if there is significant change in therapy (eg. change in medicine class rather than dosage regimen change) or if the patient is receiving long term corticosteroid treatment (defined as >4 months).<sup>3</sup> Bone mineral density testing is also recommended for patients not receiving pharmacological treatment who are considered to be at high risk of OP. Risk factors for OP that indicate the need for BMD testing are outlined in *Table 3*. In these patients, DXA may be repeated every 2 years to re-assess the fracture risk and possible need for anti-osteoporosis treatment.

#### Review use of medicines that may increase the risk of falls

Falls prevention strategies are universally recommended, as falls are responsible for 90% of hip fractures and 50% of vertebral fractures in older patients.<sup>42</sup> Multiple factors can contribute to falls, including poor balance and muscle strength, unsafe footwear, poor eyesight and some medicines (*Table 4*).<sup>43</sup> A Home Medicines Review may help to educate patients about their OP medicines and assist to identify any medicines that may increase the risk of falling.

#### Key points

- Consider pharmacological treatment in patients:
  - with a minimal trauma fracture
  - aged 70 years or over with a T-score of –3.0 or lower (primary prevention)
  - currently on prolonged high dose corticosteroid treatment with a T-score of –1.5 or lower.
- Calcium and vitamin D is recommended with all anti-osteoporosis treatment if intake is inadequate.
- Review the use of medicines that may increase the risk of falls (eg. antidepressants, antipsychotics, sedatives, hypnotics, antihypertensives).
- To monitor treatment efficacy, consider BMD testing by DXA every 2 years after therapy begins, or every 12 months if there is significant change in therapy or if the patient is receiving long term corticosteroid treatment.

**Table 4. Medicines that can increase the risk of falls<sup>40,27,43</sup>**

- |                     |                   |
|---------------------|-------------------|
| • Antidepressants   | • Diuretics       |
| • Antipsychotics    | • Hypnotics       |
| • Antihypertensives | • Sedatives       |
| • Antiparkinsonians | • Anticonvulsants |

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## References

1. Henry MJ, Pasco JA, Nicholson GC, et al. Prevalence of osteoporosis in Australian men and women: Geelong Osteoporosis Study. *Med J Aust* 2011;195:321–2.
2. Bleicher K, Naganathan V, Cumming RG, et al. Prevalence and treatment of

- osteoporosis in older Australian men: findings from the CHAMP study. *Med J Aust* 2010;193:387–91.
3. The Royal Australian College of General Practitioners. Clinical guideline for the prevention and treatment of osteoporosis in post-menopausal women and older men. 2010. Available at [www.racgp.org.au/guidelines/musculoskeletal/diseases/osteoporosis](http://www.racgp.org.au/guidelines/musculoskeletal/diseases/osteoporosis) [Accessed 23 August 2011].
4. Center JR, Bliuc D, Nguyen TV, et al. Risk of subsequent fracture after low-trauma fracture in men and women. *JAMA* 2007;297:387–94.
5. Bliuc D, Nguyen ND, Milch VE, et al. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA* 2009;301:513–21.
6. Center JR, Bliuc D, Nguyen ND, et al. Osteoporosis medication and reduced mortality risk in elderly women and men. *J Clin Endocrinol Metab* 2011;96:1006–14.
7. Eisman J, Clapham S, Kehoe L, et al. Osteoporosis prevalence and levels of treatment in primary care: the Australian BoneCare Study. *J Bone Miner Res* 2004;19:1969–75.
8. Tang BM, Eslick GD, Nowson C, et al. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet* 2007;96:657–66.
9. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab* 2011;96:53–8.
10. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd, 2007.
11. Bolland MJ, Grey A, Avenell A, et al. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ* 2011;342:d2040.
12. Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010;341:c3691.
13. Wang L, Manson JE, Song Y, et al. Systematic review: vitamin D and calcium supplementation in prevention of cardiovascular events. *Ann Intern Med* 2010;152:315–23.
14. Endocrinology Expert Group. Therapeutic Guidelines: Endocrinology, Version 4. Melbourne: Therapeutic Guidelines Ltd, 2009.
15. Winzenberg T, Jones G. Dual energy X-ray absorptiometry. *Aust Fam Physician* 2011;40:43–4.
16. Adams J, Pepping J. Vitamin K in the treatment and prevention of osteoporosis and arterial calcification. *Am J Health Syst Pharm* 2005;62:1574–81.
17. Stevenson M, Lloyd-Jones M, Papaioannou D. Vitamin K to prevent fractures in older women: systematic review and economic evaluation. *Health Technol Assess* 2009;13:1–134.
18. Bowring CE, Francis RM. National Osteoporosis Society's Position statement on hormone replacement therapy in the prevention and treatment of osteoporosis. *Menopause Int* 2011;17:63–5.
19. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet* 1996;348:1535–41.
20. Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* 2004;350:1189–99.
21. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA* 1999;282:1344–52.
22. Schilcher J, Michaëlsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. *N Engl J Med* 2011;364:1728–37.
23. Woo SB, Hellstein JW, Kalmar JR. Narrative review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006;144:753–61.
24. Watts NB, Marciani RD. Osteonecrosis of the jaw. *South Med J* 2008;101:160–5.
25. Cusano NE, Bilezikian JP. Combination antiresorptive and osteoanabolic therapy for osteoporosis: we are not there yet. *Curr Med Res Opin* 2011;27:1705–7.
26. Food and Drug Administration. Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and



- Risk Management Advisory Committee. 2011. Available at [www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM270958.pdf](http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM270958.pdf) [Accessed 15 October 2011].
27. Australian Medicines Handbook. Drug Choice Companion: Aged care. 3rd edn. Adelaide, 2010.
  28. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA* 2006;296:2927–38.
  29. NPS better choices better health. Denosumab (Prolia) for postmenopausal osteoporosis. NPS RADAR. 2010. Available at [www.nps.org.au/health\\_professionals/publications/nps\\_radar/2010/december\\_2010/denosumab](http://www.nps.org.au/health_professionals/publications/nps_radar/2010/december_2010/denosumab) [Accessed 28 September 2011].
  30. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361:756–65.
  31. Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. *J Bone Miner Res* 2009;24:153–61.
  32. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 1999;282:637–45.
  33. NPS better choices better health. Strontium (Protos) for postmenopausal osteoporosis. NPS RADAR. 2010. Available at [www.nps.org.au/\\_\\_data/assets/pdf\\_file/0017/24119/Strontium.pdf](http://www.nps.org.au/__data/assets/pdf_file/0017/24119/Strontium.pdf).
  34. O'Donnell S, Cranney A, Wells GA, et al. Strontium ranelate for preventing and treating postmenopausal osteoporosis. *Cochrane Database Syst Rev* 2008: DOI: 10.1002/14651858.CD005326.pub3.
  35. Reginster JY, Felsenberg D, Boonen S, et al. Effects of long-term strontium ranelate treatment on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis: results of a five-year, randomized, placebo-controlled trial. *Arthritis Rheum* 2008;58:1687–95.
  36. Gates BJ, Sonnett TE, DuVall CAK, et al. Review of osteoporosis pharmacotherapy for geriatric patients. *Am J Geriatr Pharmacother* 2009;7:293–323.
  37. NPS better choices better health. Teriparatide (Forteo) for postmenopausal osteoporosis. NPS RADAR. 2009. Available at [www.nps.org.au/\\_\\_data/assets/pdf\\_file/0003/70869/OKA7115\\_NPS\\_RADAR\\_Teriparatide\\_Article\\_V2.pdf](http://www.nps.org.au/__data/assets/pdf_file/0003/70869/OKA7115_NPS_RADAR_Teriparatide_Article_V2.pdf) [Accessed 28 September 2011].
  38. Neer RM, Arnaud CD, Zanchetta JR, 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.
  39. Weinstein RS. Clinical practice. Glucocorticoid-induced bone disease. *N Engl J Med* 2011;365:62–70.
  40. Li L, Roddam A, Gitlin M, et al. Persistence with osteoporosis medications among postmenopausal women in the UK General Practice Research Database. *Menopause* 2011; Sep 15 [Epub ahead of print] DOI 10.1097/gme.0b013e318221bacd.
  41. Penning-van Beest FJ, Goettsch WG, Erkens JA, et al. Determinants of persistence with bisphosphonates: a study in women with postmenopausal osteoporosis. *Clin Ther* 2006;28:236–42.
  42. Osteoporosis Australia. Stop the next fracture. Consumer guide - managing osteoporosis. 2010. Available at [http://osteoporosis.org.au/images/stories/documents/internal/Stopfracture\\_consumer.pdf](http://osteoporosis.org.au/images/stories/documents/internal/Stopfracture_consumer.pdf) [Accessed 28 September 2011].
  43. Deandrea S, Lucenteforte E, Bravi F, et al. Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. *Epidemiology* 2010;21:658–68.