

# Osteoporosis and its treatment

In this second article of two on osteoporosis, **Nuttan Tanna** looks at the treatments available for the condition

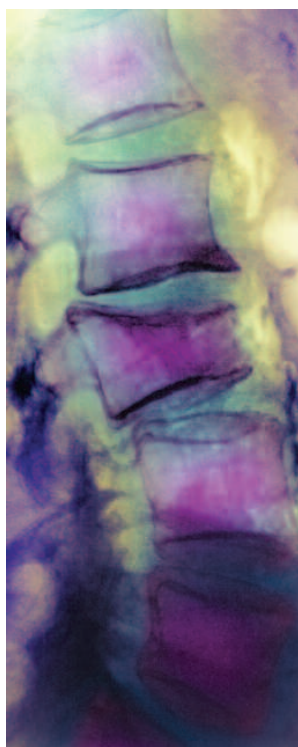
Often, the first sign of low bone mineral density (BMD) is a non-traumatic fracture. Vertebral fractures can occur after an ordinary activity, such as lifting a bag, and even at rest. Early on in the disease, intermittent periods (lasting for days or weeks) of acute back pain (mild or severe) are interspersed with pain-free periods. After multiple compression fractures have occurred, however, a continuous dull, aching pain can develop in association with spinal deformity. After the first non-traumatic fracture, the incidence of vertebral fractures is about one per year. Multiple fractures, usually of the vertebrae, hip and distal radius can also occur.

Patients with osteoporotic pain are usually prescribed paracetamol or a non-steroidal anti-inflammatory drug, or both. Calcitonin may also be useful after a vertebral fracture if other analgesics are ineffective (see below).

## Treatment

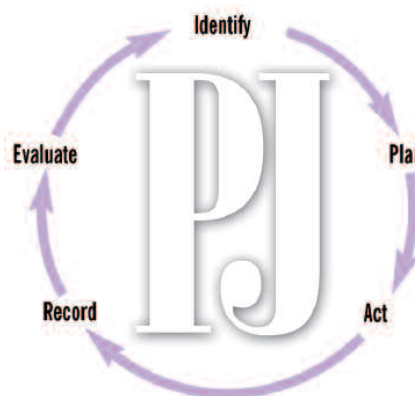
Most therapeutic agents currently used to treat osteoporosis inhibit bone resorption. Two exceptions include teriparatide, which promotes bone formation, and strontium ranelate, which has a dual mode of action. The aim of anti-resorptive treatment is to improve bone repair and increase bone strength — by inhibiting resorption, there are smaller cavities for the osteoblasts to fill.

When considering treatment options, it is important to assess the evidence not only on the basis of prevention or reduction of bone loss but also on anti-fracture efficacy. Guidelines from the Royal College of Physicians make recommendations after considering the evidence for efficacy of different interventions in these two categories for postmenopausal women (see Table, p583). Selection should also take into account the long-term effects of agents and the differing



Vertebral fractures are typical in osteoporosis

Dr P Marazzi/SPL



## Identify knowledge gaps

1. What evidence-based measures can be used to treat osteoporosis?
2. How do osteoporosis treatments work?
3. What factors affect choice of therapy?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: [www.rpsgb.org/education](http://www.rpsgb.org/education)). This article relates to "common disease states"

modes of action, although further research is needed in these areas. Finally, treatment selection should be based on individual circumstances (see Panel 1). Patient views will impact on compliance and should inform prescribing.

Osteoporosis treatments can be categorised according to their licensed indications. Some agents are only licensed for postmenopausal osteoporosis and some have a fracture prevention indication.

**Bisphosphonates** Three bisphosphonates are licensed for use in postmenopausal osteoporosis and glucocorticoid-induced osteoporosis in the UK: cyclical disodium etidronate with calcium carbonate (Didronel PMO), alendronate (Fosamax) and risedronate sodium (Actonel). In addition, etidronate and alendronate are licensed for osteoporosis in men. Bisphosphonates decrease osteoclast activity and induce osteoclast apoptosis. This allows more time for secondary mineralisation so increases the mechanical resistance of bone.

The optimum duration of treatment has not been established. Alendronate has been used safely for up to 10 years. For risedronate, data indicate safety with up to seven years of use. Studies have reported significant reductions in both vertebral and non-vertebral fracture rate in postmenopausal women with established osteoporosis following a year's treatment. Cummings *et al*<sup>1</sup> reported that the greatest fracture reduction is achieved in women with lower BMD.

## Panel 1: Influences on treatment choice

Factors affecting the osteoporosis treatment chosen include age, sex, disease severity, other co-morbidities and, for women, the presence of menopausal symptoms. For example:

- For premature menopause, hormone replacement therapy is the first-line choice for women up to 50 years old.
- For symptomatic menopausal women aged (usually between 45 and 55 years), benefits of HRT generally outweigh the risks for use up to five years; but patients can choose alternatives for symptom control and use another anti-resorptive treatment for osteoporosis.
- Raloxifene is best prescribed for asymptomatic postmenopausal women, generally over 55 years, with a risk of vertebral fractures. Raloxifene may be preferred by older women with osteoporosis who cannot tolerate bisphosphonates.
- For severe osteoporosis, the suitability of raloxifene, bisphosphonates, teriparatide or strontium ranelate should be considered.
- Etidronate and alendronate are licensed for use in male osteoporosis but risedronate has been prescribed off-licence for men who experience side effects with alendronate.
- Bisphosphonates can worsen the symptoms of oesophageal ulcers and this will drive the prescribing decision.

## Panel 2: Bone mineral density scanning



John Greim/SPL

The definition of osteoporosis highlights low bone mass as an important component of fracture risk. Other skeletal abnormalities and non-skeletal factors, such as falls, should also be considered. Currently, however, only bone mineral density (BMD) can be measured with precision and accuracy and this forms the basis for diagnosis. Current consensus is that the measurement of BMD of the hip using a dual energy X-ray absorptiometry (DEXA) scanner is the gold standard. With daily quality control and appropriately trained technologists the DEXA equipment should deliver a precision of about 1 per cent at the spine and 2 per cent at the hip. To monitor changes of BMD with time and treatment, spinal values are more useful but these can be artificially raised in patients with osteoarthritis or other degenerative changes. BMD is presented as  $\text{g}/\text{cm}^2$ . A DEXA report will typically provide BMD values as T scores and Z scores for the spine, femoral neck and total hip. BMD T scores can vary according to the site and method of measurement so reference standards have been published for the different measurement sites. The prediction of fracture risk is usually based on BMD measurements at the femoral neck. In general the fracture risk doubles for each standard deviation fall in BMD.

**T and Z scores** A T score is the number of standard deviations that separate the patient from the mean value for 25-year-old women. The T score value, therefore, classifies severity of osteoporosis. The World Health Organization defines T scores as follows:

- $-1$  or higher is normal
- Between  $-1$  to  $-2.5$  indicates osteopenia (a decrease in bone density but no increase in fracture risk)
- Lower than  $-2.5$  indicates osteoporosis
- Lower than  $-2.5$  plus a fragility fracture indicates severe osteoporosis

The T and Z scores are based on data obtained from caucasian women, but consensus is that these cut off SD scores can be generally applied to male populations as well. The Z score is the number of standard deviations which separate the patient from an age- and sex-matched healthy caucasian population.

BMD measurements are recommended in the following situations and where assessment will influence initiation of treatment and management:

- Radiographic evidence of osteoporosis or vertebral deformity or both
- Loss of height, thoracic kyphosis (after radiographic confirmation of vertebral deformity)
- Previous fragility fracture
- Prolonged corticosteroid therapy (eg, oral prednisolone daily for three months or more)
- Premature menopause (ie, below 45 years of age)
- Prolonged secondary amenorrhoea ( $>1$  year)
- Primary hypogonadism
- Chronic disorders associated with osteoporosis (eg, hyperparathyroidism)
- Family history of hip fracture
- Low body mass index ( $<19\text{kg}/\text{m}^2$ )

**Other screening methods** Other measures of BMD include peripheral DEXA scanning and quantitative ultrasound. The National Osteoporosis Society has published position statements for guidance on the various scanning methods and these can be accessed at: [www.nos.org.uk/healthprof\\_info.asp#pub](http://www.nos.org.uk/healthprof_info.asp#pub). Bone biochemistry tests include checking levels of calcium, corrected calcium, albumin and alkaline phosphate (osteoblasts are alkaline phosphatase rich). Vitamin D and PTH measurements are ordered when further investigation is warranted.

Bisphosphonates do not work optimally when there is underlying vitamin D deficiency. This is especially relevant for patients who may not get enough sun exposure, such as the elderly and strict vegetarians who do not eat eggs and who may have underlying osteomalacia (bone softening due to poor mineralisation). Fosavance, a treatment recently licensed in the UK, offers patients alendronate combined with vitamin D supplementation in one formulation.

Another recently launched product is Bonviva (ibandronic acid). This bisphosphonate is licensed for the treatment of postmenopausal osteoporosis and patients need only take one tablet (150mg) every month. The main adverse effects of ibandronate in clinical trials were similar to other bisphosphonates and included dyspepsia, diarrhoea, myalgia, arthralgia and non-specific rash.

**Postmenopausal osteoporosis** The link between oestrogen levels and bone density was discussed previously (*PJ*, 22 October, pp521–4). Treatments licensed for postmenopausal osteoporosis include calcitriol, calcitonin, raloxifene, strontium ranelate and teriparatide. Their evidence base for fracture prevention is presented in the Table.

**Calcitriol** Calcitriol (1,25-dihydroxycholecalciferol) is available in capsules (Rocaltrol). The recommended dose for postmenopausal osteoporosis is 0.25ng twice daily. Generally, treatment is initiated on specialist recommendation. Plasma calcium concentrations and creatinine levels need to be monitored. Calcitriol has been shown to decrease bone loss in women with osteoporosis, but study results differ. A decrease in vertebral fracture frequency has been demonstrated but no protective effect has been shown for hip fracture.

**Calcitonin** Calcitonin is a hormone that transiently inhibits osteoclast activity without decreasing osteoblast collagen synthesis. Usually initiated in a consultant clinic, it is available as a nasal spray and in a formulation for subcutaneous or intramuscular injection. With the recommended dose of 100 units daily, patients are also prescribed 600mg calcium and 400IU of vitamin D. Calcitonin (Miacalic) prevents bone loss in a dose dependent manner. Calcitonin has analgesic properties, offering pain relief when used for up to three months in patients with acute pain following crush fracture (collapsed vertebrae).

**Raloxifene** Raloxifene (Evista) is a novel selective oestrogen receptor modulator (SERM) with agonist effects in bone, but antagonist effects in the breasts and uterus. Although the term “SERM” was introduced following increased understanding of the tissue-specific action of raloxifene, tamoxifen was the first SERM to be discovered. During pre-clinical development it was noted that raloxifene lacked some of the agonist properties demonstrated by tamoxifen and this led to the idea that different agonist-antagonist properties

could be developed for use especially, in this case, in breast and endometrial tissues.

Raloxifene has been shown to slow the rate of bone loss. It increases bone density by 0.5 to 1.0 per cent — less than that achieved with oestrogen. The recommended dose is one tablet (60mg) daily. Use is associated with a small increase in the frequency of hot flushes, leg cramps, peripheral oedema and thrombosis risk.

Raloxifene has some favourable effects on biochemical markers of cardiovascular risk. Both raloxifene and HRT appear to reduce low density lipoprotein cholesterol. Raloxifene has little effect on high density lipoprotein (HDL) cholesterol but with HRT (combined oestrogen and progestogen), a 10 per cent increase in HDL cholesterol has been reported. Raloxifene does not appear to affect triglyceride levels, but oral HRT increases the triglyceride level by 15 to 20 per cent.

The rate of breast cancer in those treated with raloxifene in the Multiple Outcomes of Raloxifene Evaluation trial was significantly lower than in those treated with placebo. There was a greater reduction in the risk of oestrogen receptor-positive cancer with no significant reduction in the risk of oestrogen receptor negative breast cancers. CORE (continued outcomes for raloxifene evaluation) trials suggest that raloxifene could be used safely for up to eight years. Further clinical trial data are needed to determine long-term breast cancer safety with raloxifene.

Raloxifene has been shown to increase the risk of venous thromboembolism to the same degree as oestrogen. One advantage of raloxifene is its antagonistic action in the endometrium. When taken over two years, raloxifene did not affect endometrial depth.

**Strontium ranelate** With a dual action (reducing bone resorption and increasing bone formation), strontium ranelate (Protelos) is the first of a new class of osteoporosis treatments.

A randomised controlled trial of strontium ranelate in 1,649 postmenopausal women with osteoporosis, and at least one vertebral fracture, reported increases in BMD of 12.7 per cent in the lumbar spine and 8.6 per cent in the hip, with a 41 per cent reduction in the incidence of new vertebral fractures after three years' treatment.<sup>2</sup> In another study, strontium ranelate reduced the incidence of non-vertebral fractures by 16 per cent in 5,091 women with osteoporosis. Sub-group analysis of 1,977 women aged over 74 years with a T score below -3.0 (see Panel 2), showed that the risk of hip fracture was reduced by 36 per cent.<sup>3</sup> It is important to note that nearly 50 per cent of the increase in BMD relates to skeletal incorporation of strontium and this can be misleading in terms of bone density scan reports, results of which are calculated using calcium.

Strontium ranelate is available as a daily dose of 2g. A sachet of granules is mixed in water and taken at bed-time, at least two hours after eating, to ensure optimal absorption from the bowel. Avoidance of calcium-

**Table: Assessment of evidence for efficacy of different interventions\***

Intervention	Effect on the prevention or reduction of postmenopausal bone loss	Anti-fracture efficacy in postmenopausal osteoporotic women		
		Spine	Non-vertebral	Hip
Alendronate	A	A	A	A
Calcitonin	A	A	B	B
Calcitriol	A	A	A	—
Calcium	A	A	B	B
Calcium and vitamin D	A	—	A	A
Cyclic etidronate	A	A	B	B
Hip protectors	—	—	—	A
Hormone replacement therapy	A	A	A	A
Physical exercise	A	—	B	B
Raloxifene	A	A	—	—
Reduced alcohol consumption	C	—	—	—
Risedronate	A	A	A	A
Smoking cessation	B	—	—	—
Tibolone	A	—	—	—
Vitamin D	—	—	B	B

\* Grade A: meta-analysis of randomised controlled trials or from at least one RCT or evidence from at least one well-designed controlled study without randomisation. Grade B: evidence from at least one other type of well-designed quasi-experimental study or from well-designed non-experimental descriptive studies (eg, comparative studies, correlation studies, case-control studies). Grade C: evidence from expert committee reports or clinical experience of authorities

containing foods and tablets within two hours of taking the strontium ranelate is important to avoid drug interactions and loss of efficacy. In clinical trials there was no evidence of an increased incidence of upper gastrointestinal side effects and the main side effect of diarrhoea is reported to be short-lived. An increased risk for thrombosis has been noted with strontium ranelate and this is being investigated by the manufacturers.

**Teriparatide** Teriparatide (Forsteo), a recombinant human parathyroid hormone, promotes bone growth. It is the first licensed anabolic drug used to reduce the risk of vertebral fractures in established osteoporosis. This injectable treatment (similar to an insulin pen) is prescribed and supervised by consultants and is supported by "home care" that includes training and telephone support. The treatment dose of 20µg daily is currently limited to 18 months' use, costing around £5,200. Teriparatide is contraindicated in those with a baseline risk of osteosarcoma, such as those with Paget's disease. Use of an anti-resorptive drug either before or with teriparatide may reduce its anabolic skeletal effects.

Treatment with teriparatide over 21 months in 1,637 postmenopausal women with osteoporosis and a mean age of 69 years reported increased BMD by 9 to 13 per cent more than placebo. New vertebral fractures were reduced by 65 per cent and non-vertebral fractures by 53 per cent.<sup>4</sup> Recent guidance on secondary prevention of osteoporosis fragility fractures from the National Institute for Health and Clinical Excellence identifies the groups of patients for whom this treatment is suitable, for example, patients over 75 years old who have had four vertebral fractures and no improvement in BMD after bisphosphonate treatment. However it would not be suitable for patients who do not like having daily injections.

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## Prophylaxis

The present evidence base for the bisphosphonates supports their use to prevent postmenopausal and corticosteroid-induced osteoporosis. Raloxifene is licensed to prevent postmenopausal osteoporosis.

**Hormone replacement therapy** The menopause is a strong marker for increased risk of osteoporosis. The decline in ovarian function and associated oestrogen deficiency results in a number of detrimental effects on bone, including suppression of osteocyte survival and impairment of osteoblast response to mechanical stimuli and repair of ageing bone.

Many women suffering from menopausal symptoms use HRT and, while on treatment, will benefit with prevention of further bone loss. Oestrogens suppress bone remodelling to the premenopausal level, maintaining the function of osteoblasts and osteocytes. However, with ageing, the risks of HRT can outweigh the benefits. In addition, HRT would not normally be used to relieve menopausal symptoms for more than four or five years but the duration of therapy to prevent osteoporotic fractures needs to be long. Oral estradiol doses of 1mg and above are licensed for osteoporosis protection. For the conjugated equine oestrogens the minimum dose for bone protection is 0.3mg daily (Premique Low Dose). Transdermal patch systems with estradiol at doses of 50µg or higher are licensed for osteoporosis prophylaxis.

There is ongoing debate about the role of HRT in elderly postmenopausal women, especially in those with multiple comorbidities. More research to identify maximum duration of therapy is needed.

**Calcium** Calcium supplements have been shown to slow bone loss in postmenopausal women in at least two studies. In one study this effect was maintained when calcium supplements were taken for four years. However in another study with a cohort of women who had undergone menopause five or fewer years previously, supplementation did not affect spinal bone loss. Calcium is less effective than other interventions and there is little convincing evidence that it reduces fractures. It may be of some benefit, however, if dietary intake is inadequate. Supplements should provide 1g or more of elemental calcium daily, in line with doses used in clinical trials.

## Fractures

Bone loss is the main underlying cause of age-related fractures. In the absence of severe trauma, fractures do not occur unless bone density falls below a threshold of about 1.0g/cm<sup>2</sup> for both vertebrae and femurs. With further bone loss the incidence of both types of fractures increases, and although not so well studied, other age-related fractures probably exhibit a similar relationship.

Non age-related fracture pathogenesis is more complex and low bone density is not the sole determinant. This is emphasised by

the large overlap in bone density values of the vertebrae and hip in age and sex matched individuals with and without vertebral and hip fractures. Intrinsic abnormalities in bone structure can also contribute because of accumulation of microdamage, architectural abnormalities and impaired mineral properties. The co-existence of nutritional osteomalacia in some elderly individuals can further increase susceptibility to fractures, particularly hip fractures. The propensity of the elderly to fall is an independent risk factor for fractures, particularly fractures of the hip and wrist.

**Fracture prevention** Fractures of the hip and wrist, the most common fractures in elderly patients with osteoporosis, almost always result from trauma, usually a fall. In severe osteoporosis, even a minor fall can break a femur or wrist. Prevention of injury is, therefore, crucial.

Tendency to fall is a consequence of ageing. Risk increases with decline in vision, hearing, muscle mass and balance preserving reflexes, as well as diseases that affect the elderly, drugs that they are treated with and environmental hazards (eg, poor lighting) and other hazards (eg, alcohol abuse).

Strategies for preventing falls and consequent fractures should therefore include:

- Optimal management of balance-disturbing disorders, including visual loss
- Limitation of patient's use of balance-disturbing drugs, including alcohol
- Regular medication reviews as advocated within the National Service Framework for Older People
- Appropriate education for patients and their carers on the dangers of falling, including information about periods of greatest risk (for example, patients should be warned about rising too quickly after eating or resting and should use a support aid if they tend to experience dizziness)
- Awareness and reduction of home hazards — increasing home safety includes optimal lighting, elimination of slippery or otherwise hazardous floor surfaces, and ensuring adequate hand supports

## References

1. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the fracture intervention trial. *JAMA* 1998;280:2077–82.
2. Meunier PJ, Roux C, Seeman E, Ortolani S, Slosman DO, Delmas PD, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *New England Journal of Medicine* 2004;350:459–68.
3. Reginster JY, Seeman E, De Vernejoul MC, Adams 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. *Journal of Clinical Endocrinology and Metabolism* 2005;90:2816–22.
4. Eriksen EF, Robins DA. Teriparatide: a bone formation treatment for osteoporosis. *Drugs Today* 2004; 40:935–48.

## Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Osteoporosis is being considered for inclusion within the new general medical services contract, within the quality and outcome framework designed to improve patient care. Audits can be undertaken with practices to identify patients on long-term steroids and women with premature menopause or with a family history of hip fracture, who might benefit from an osteoporosis risk assessment
2. Medicines use reviews can be used to check for good compliance with osteoporosis treatments and to assess for drugs being taken that can cause falls.
3. Work with local practices and PCT committees on developing osteoporosis guidelines and link these within area-wide patient pathways developed by local falls services.

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?