Osteoporosis: managing the non-generic patient

Osteoporosis is a chronic disease affecting the whole skeleton, causing bones to become more fragile, and increasing the risk of fracture. Having one fracture increases the risk of future fractures, so patients who have had a fracture need assessment and many need therapy. Both the National Institute for Health and Clinical Excellence (NICE) and the National Osteoporosis Guideline Group (NOGG) recommend generic alendronic acid (AA) as first-line therapy due to cost effectiveness. However many patients will be unsuitable for or not tolerate AA. This article offers guidance on other therapies and highlights how they can be used within current guidelines.

Dr Pam Brown GP and Speciality Doctor in Osteoporosis, Swansea
email pambrown@easynet.co.uk

Osteoporosis is a chronic disease affecting the whole skeleton, causing bones to become more fragile and increasing fracture risk. Fractures can be thought of as the acute exacerbations of the underlying chronic disease of osteoporosis. It is, therefore, logical when someone fractures to ensure the underlying disease is managed with therapy to prevent further fractures, rather than simply treating the fracture. Although we do this automatically in other chronic disease areas, (eg, when someone suffers a myocardial infarct, the underlying cardiovascular disease is assessed and treated as well as the MI to reduce the risk of a second MI), the treatment of the underlying osteoporosis has been neglected until recently.

Osteoporosis is defined by dual energy X-ray absorptiometry (DXA), with T-score values ≤-2·5 representing osteoporosis and T-scores between -1·0 and –2·5 representing osteopenia. Osteoporosis is a common condition, with one in three women over the age of 50 suffering an osteoporotic fracture. There are around 230,000 osteoporotic fractures in the UK each year, and more than 70,000 of these are hip fractures. These contribute to significant mortality (20% at four months and 30% within 12 months) and morbidity (50% of women are not able to return to independent living after their hip fracture). The biggest challenges of this disease are its silent nature until the first fracture occurs, underdiagnosis with less than half of sufferers achieving a diagnosis, and the low adherence/persistence with therapy with >50% discontinuation after one year of treatment.

NICE guidance

The National Institute for Health and Clinical Excellence (NICE) has issued Technology Appraisal (TA) 160 for primary prevention of osteoporotic fractures in postmenopausal women,[1] and TA 161 for secondary prevention[2] (summarised in box 1).

The guidelines are controversial. The cost-effectiveness threshold was set at only £20,000 rather than £30,000 per quality adjusted life year (QALY) for the primary prevention TA,[1] and both appraisals set differential thresholds for the use of different therapies, meaning that a woman might qualify for alendronic acid but if she is intolerant of it or has contraindications to it, she will only be able to receive an alternative if her T-score worsens and/or if she has additional risk factors.

Following a judicial review initiated by Servier Laboratories, NICE reviewed its guidance for strontium ranelate but did not any make changes to its recommendations.[1]

Box 1: Summary of NICE osteoporosis guidelines for postmenopausal women

Primary prevention

Generic alendronate first line is recommended for women with a T-score of ≤ –2·5 *AND*: age ≥ 70 and an independent risk factor for fracture *OR* an indicator of low bone-mineral density (BMD); age 65–69 and an independent risk factor for fracture; age <65 with an independent risk factor for fracture *AND* at least one additional indicator of low BMD*. Women age ≥ 75 who have two or more independent risk factors or indicators of low BMD may not need DXA.

Risedronate (or etidronate) is recommended for women who are unable to comply with dosing instructions or who are intolerant or have a contraindication to alendronic acid *AND* who exhibit a specific combination of T-score, clinical risk factors and age outlined by NICE. For example, a woman aged 65–69 can only receive treatment with risedronate or etidronate if she has at least one independent clinical risk factor for fracture and a T-score of -3·5 (or -3·0 if she has two risk factors). A patient aged ≥75 with two or more independent risk factors or indicators of low BMD may not need DXA.

Strontium ranelate is recommended for women when they cannot take alendronate, etidronate, and risedronate *AND* have a NICE-specified combination of T-score, age and risk factors. For example, a 70-year-old needs to have a T-score of -4·0 and one independent risk factor·

Neither *raloxifene* nor *teriparatide* is recommended for primary prevention.

Secondary prevention

Generic alendronate is recommended first-line for women with a T-score ≤-2·5 (DXA may not be needed for women age ≥75).

Risedronate (or etidronate) is recommended for those who are unable to comply with the dosing instructions for alendronate (or who have contraindications or are intolerant), *AND* who exhibit a NICE-specified combination of T-score, risk factors and age. For example, a woman aged 67 can only receive treatment if she has a T-score of -3·0 (or -2·5 if she has at least one clinical risk factor). DXA may not be needed for woman age ≥75.

Strontium ranelate or raloxifene is recommended for women who cannot take risedronate or etidronate (or alendronate) *AND* who have a NICE-specified combination of T-score, age and risk factors. For example, to receive either of these drugs, a 69-year-old woman must have a T-score of 4·0 (or -3·0 if she has two clinical risk factors). DXA may not be needed for a woman age ≥75 who has one or more clinical risk factors.

Teriparatide is recommended for women who are unable to take alendronate and either risedronate or etidronate, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate, or who have a contraindication to, or are intolerant of strontium ranelate, or who have had an unsatisfactory response to treatment with alendronate, risedronate or etidronate *AND:* aged ≥65 with T-score ≤ -4·0 *OR* T-score ≤ -3·5 and has had more than two fractures; aged 55–64, T-score ≤ -4·0 and has had more than two fractures .

For the full combinations of T-score, age and risk factors, see the NICE primary and secondary prevention guidelines.[1,2]

** Independent clinical risk factors for fracture — parental hip fracture, ≥4 units alcohol/day, rheumatoid arthritis Indicators of low BMD: BMI <22, untreated premature menopause, prolonged immobility, ankylosing spondylitis, Crohn's disease. Unsatisfactory response — a further fragility fracture despite adhering fully to treatment for one year, and decline in BMD below pre-treatment levels. (This will be impossible to identify in women age >75 who qualified for treatment without BMD).*

Figure 1: The FRAX calculation tool

FRAX and NOGG

The World Health Organization Fracture Risk Assessment Tool (FRAX) allows calculation of absolute fracture risks for all those over 50, including men and those without a previous fragility fracture. This is available at http://www.shef.ac.uk/FRAX/.

Calculation of the 10-year risk of a major osteoporotic fracture or hip fracture using clinical risk factors alone, or with femoral neck BMD from DXA if this is available, brings fracture risk calculation in line with our ability to calculate 10-year cardiovascular risk, facilitating treatment decisions (figure 1). The FRAX website links to guidance from the National Osteoporosis Guideline Group (NOGG)[3] on whether the patient meets recommended treatment thresholds.

NICE guidance is used to inform treatment decisions in the following cases — clinicians should decide whether to follow these or FRAX and NOGG, and discuss therapy choices and thresholds with their local prescribing teams. Metabolic bone services will have local criteria for referral.

Case studies

Alendronic acid

Case study 1

A 65-year-old lady, menopause aged 52, asked about her osteoporosis risk as her mother had sustained a hip fracture in her early 70s. DXA scan showed a T score of –2·8 at her lumbar spine and –1·9 at her hip. She was given detailed lifestyle advice (stop smoking, moderate alcohol intake, and continue vigorous weight-bearing exercise). She was started on alendronic acid 70 mg weekly to be taken exactly as directed, and calcium and vitamin D supplements twice daily. A three-month review was arranged with the practice nurse.

Under NICE TA 160, this lady's maternal hip fracture is an independent clinical risk factor so she qualifies for a DXA scan, which confirms osteoporosis, so treatment is recommended. Following NICE guidance, DXA scans in women without fractures are only appropriate if they meet the age-related criteria for independent clinical risk factors and/or indicators of low BMD. FRAX calculates the 10-year risk score for the patient; after calculating a patient's risk, clicking through to NOGG's treatment graphs will demonstrate whether treatment, reassurance or DXA scan is recommended. Regardless of whether they follow the recommendations of NICE or NOGG, clinicians must also use their own clinical experience to make a treatment decision in an individual patient.

Alendronic acid (AA) is a cheap (£17.03 per year) and effective therapy for prevention of vertebral, non-vertebral and hip fractures and is recommended first-line therapy for primary and secondary prevention of osteoporotic fractures by NICE and NOGG, and for prevention and treatment of steroid-induced bone loss in men and women.

Key points:

- Bisphosphonates must be taken exactly as directed: once weekly, on an empty stomach, with a full glass of tap water, and no food, drink or other medication for at least 30 minutes (AA or risedronate) or 60 minutes for ibandronate. Patients must remain upright after ingestion to aid transit down

the oesophagus
- Upper GI side effects are common and oesophageal damage can occur. Side effects may be more common with an incorrect dosing method.

Case study 2

A 74-year-old, previously fit lady developed sudden onset severe thoracolumbar back pain while shopping. Analgesics failed to improve the pain and an X-ray demonstrated a T12 crush vertebral fracture. Investigations (FBC, ESR/CRP, myeloma screen, bone profile, thyroid profile, transglutaminase antibodies) were normal and she was initiated on weekly AA and calcium and vitamin D while awaiting a DXA scan, and she was reviewed three months later to check adherence/persistence with therapy.

One third of vertebral fractures are asymptomatic, one third are treated as mechanical back pain, and only one third are correctly diagnosed in the UK. It is important to have a high index of suspicion when postmenopausal women or others at risk of osteoporosis develop acute onset back pain, particularly if this is thoracic. By diagnosing the fracture, we can exclude causes other than osteoporosis for the fracture and ensure patients receive treatment to reduce future fracture risk. Symptomatic vertebral fractures can cause severe pain — short-term treatment with nasal calcitonin 200IU daily[4] may have analgesic effects if started early. Multiple vertebral fractures cause long-term pain and disability, including respiratory and abdominal symptoms.

Key points:
- Remember vertebral fracture as a cause of acute back pain in those at risk of osteoporosis. All patients with vertebral fractures need investigation to exclude underlying causes (eg, myeloma)
- 20% of patients suffering a vertebral fracture will have a further fracture within one year, so rapid treatment is needed. Identifying and treating the underlying osteoporosis helps reduce further fractures.

Calcium and vitamin D

Case study 3

A frail 86-year-old lives in a care home and falls regularly but has no history of fragility fracture (fracture over the age of 50 caused by a fall from standing height or less). She is a smoker (15/day) and drinks 2–3 units of alcohol daily. She was given advice to stop smoking and reduce alcohol intake. Initiation of calcium and vitamin D, together with posture and balance training, reduced her fall rate[5] over the following year.

In elderly institutionalised patients with no previous history of fragility fracture, calcium (1200 mg) and vitamin D (700–800IU daily) can reduce the risk of hip fracture by around 30% and decrease vertebral fracture risk.[6] Vitamin D reduces falls.[5]

Key points
- Both NICE and NOGG recommend the use of calcium and vitamin D supplements as adjuvant therapy for everyone receiving any bone-sparing therapies to ensure optimal efficacy
- Calcium supplements without vitamin D should no longer be used except for renal patients due to a possible increased risk of cardiovascular disease[7]
- Allowing patients to choose their calcium and vitamin D product may increase adherence; once daily therapy may be used when there is an interacting medication, eg, thyroxine.

Risedronate

Case study 4

A 65-year-old lady sustained a hip fracture. Despite a previous wrist fracture, she was on no bone-sparing therapy. Her mother also sustained a hip fracture in her 80s. She has a long history of mild upper GI symptoms controlled by omeprazole with no evidence of oesophageal damage. Her T-scores were –2·8 and –2·0 at the lumbar spine and hip respectively. She immediately developed upper GI side effects when commenced on once weekly alendronic acid and twice daily calcium/vitamin D preparation. Her symptoms were allowed to settle and she was changed to once weekly risedronate, which she tolerated.

Under NICE TA 161 guidance, this woman would qualify for risedronate. Although NOGG recommend using AA first line, they accept that other treatments (apart from PTH) can be used at the same treatment threshold in those genuinely intolerant of AA, so even without an independent clinical risk factor or if younger, she could

still have changed treatments. Once we have persuaded a patient that they need treatment, it is clearly inappropriate to leave them without therapy if intolerant of AA.

Key points:

- Only a small percentage of those with previous osteoporotic fractures receive treatment
- Risedronate may cause less upper GI side effects than AA[8]
- Starting calcium and vitamin D prior to bisphosphonate will help clarify which treatment is causing side effects.

Ibandronate

Case study 5

A 65-year-old lady with mild dementia lives alone with family support. Her eight daily medications are administered by dosette box with carer prompts. She suffered a vertebral fracture after a simple trip inside her flat, leaving her with persistent back pain. It proved impossible to co-ordinate carers to administer weekly alendronate appropriately and she was therefore changed to once monthly oral ibandronate which her daughter administers, followed 60 minutes later by her other morning medication. Weekly therapy would impose a much larger burden and risk incorrect dosing.

Ibandronate prevents vertebral fractures, and a "bridging study"[9] using a different dosing regimen supports hip fracture reduction. Monthly administration is preferred to weekly by some patients, and persistence with therapy was slightly higher in those also receiving a patient support programme[10] compared with those on weekly alendronate.

Zoledronate

Case study 6

An 82-year-old lady suffered a hip fracture following a simple trip in her home. She had been on oral bone-sparing therapy sporadically since a wrist fracture four years earlier but declared she was intolerant and therefore only took each drug for a few doses then lapsed. Following hip replacement, her rehabilitation was slow and she was discharged to a care home due to poor mobility. She was started on oral calcium and vitamin D supplements immediately post-op and received an IV infusion of zoledronate 5 mg prior to discharge.

Zoledronate is given by annual intravenous infusion, and decreases hip, vertebral and non-vertebral fractures.[11] A small but significant increased risk of atrial fibrillation was identified in those receiving the drug. Daily calcium and vitamin D supplements must be continued between infusions to reduce hypocalcaemia and to optimise benefits. Risk of osteonecrosis of jaw is low with oral or IV bisphosphonates in doses used to treat osteoporosis, but is much more common in those with breast cancer receiving high dose IV bisphosphonates.

Denosumab

Case study 7

A 74-year-old lady has multiple osteoporotic vertebral fractures and confirmed osteoporosis on DXA scan. She is referred to the osteoporosis clinic, as she is intolerant of oral bisphosphonates. She is initiated on 60 mg subcutaneous denosumab, encouraged to take calcium and vitamin D supplements, and to return to clinic for a repeat injection six months later and a DXA scan after 18 months of therapy.

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor-kappa B (RANK) ligand, which inhibits the activation of osteoclasts, reducing bone resorption and increasing bone density. It reduces the risk of vertebral, non-vertebral and hip fractures in women with osteoporosis.[12]

NICE[13] recommends the use of denosumab for secondary prevention of osteoporotic fractures in women at increased risk of fracture who are unable to tolerate AA and either risedronate or etidronate, or are intolerant or have a contraindication to these drugs. For primary prevention they must additionally have a combination of T-scores and independent clinical risk factors as indicated in the guideline, while no additional risk factors are required for use in secondary prevention.

Key points

- Although this drug is currently initiated mainly in secondary care, shared care protocols will be developed to ensure appropriate use in primary care by doctors with an interest in osteoporosis.

Raloxifene

Case study 8

A 65-year-old lady with severe osteoporosis (T-3·5 at lumbar spine and –2·8 at hip) and two previous wrist fractures, has a strong family

history of breast cancer and maternal hip fracture. She has been intolerant of AA and risedronate due to upper GI problems. She has no history of thromboembolic disease. After discussion with her GP about remaining therapies, she chose to commence raloxifene therapy since it is easy to take on a daily basis along with her other medication.

Raloxifene reduces risk of vertebral fractures but does not reduce hip fracture risk, and significantly reduces risk of oestrogen positive breast cancer. Therefore, the logical place for this drug would be for early postmenopausal women at risk of vertebral but not yet hip fractures. However, NICE has contraindicated its use in primary prevention, and has currently positioned it for secondary prevention as third-line therapy in those with severe osteoporosis. Other selective oestrogen receptor modulators are close to market.

Strontium ranelate

Case study 9

An 84-year-old lady sustained a hip fracture two years after being started on AA for previous wrist and vertebral fractures. She is mentally alert, mobile and lives alone and her eGFR is 60. As she had re-fractured more than one year after treatment initiation, a decision was made to change her treatment to strontium ranelate, a 2 g sachet dissolved in water and taken at bedtime at least two hours after eating, and once daily calcium and vitamin D.

Strontium ranelate reduces bone resorption and increases bone formation. It is licensed for treatment of postmenopausal osteoporosis to reduce risk of vertebral and hip fracture.[13,14] Rarely, hypersensitivity skin reactions may occur and patients should be warned to stop therapy immediately and seek medical advice should skin rashes occur.

Key points

- Since patients often experience loose stools during the first three months of strontium ranelate therapy, laxatives should be reduced and titrated against need
- Once daily calcium in the morning avoids interaction with the evening dose of strontium ranelate
- Following a review, NICE recommendations remain the same.

Parathyroid hormone/ teriparatide

Case study 10

A 68-year-old lady with severe vertebral osteoporosis (T-3·8 at lumbar spine, T-3·0 at hip) and multiple fractures had continued to fracture on oral and IV bisphosphonate therapy despite no underlying malabsorption or other major health problem. In view of her young age, osteoporosis severity, failure to respond to therapies and meeting the NICE criteria, she was offered an 18-month course of daily injections of teriparatide.

Teriparatide is an anabolic drug that is administered by daily injection over 18 months; therefore, NICE recommends it is for those with severe osteoporosis. There is no hip fracture data at present and thus many patients are now treated with IV zoledronate or denosumab in preference.

Conclusion

Osteoporosis is underdiagnosed and undertreated. A range of treatments are available to reduce fracture risk. For some patients, NICE and NOGG offer differing guidance on treatment thresholds, so clinicians must decide which to follow, and should consult their metabolic bone unit and prescribing team for local guidance on treatment and referral.

Conflict of interest: Dr Brown has received honoraria for advisory board work and for speaking at educational meetings from several pharmaceutical companies

References

1. National Institute for Health and Clinical Excellence. Alendronate, etidronate, risedronate and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. http://guidance.nice.org.uk/TA160 (accessed 28 January 2011)
2. National Institute for Health and Clinical Excellence. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. http://guidance.nice.org.uk/TA161/Guidance/pdf/English (accessed 28 January 2011)
3. Compston J, Cooper A, Cooper C, et al. Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 in the UK. http://

www.shef.ac.uk/NOGG/ (accessed 28 January 2011)
4. Knopp J, Diner B, Blitz M, et al. Calcitonin for treating acute pain of vertebral compression fractures: a systematic review of randomised controlled trials. *Osteoporos Int* 2005; **16**: 1281–90
5. Bischoff-Ferrari H, Dawson-Hughes B, Willett W, et al. Effect of vitamin D on falls. *JAMA* 2004; **291**: 1999–06
6. Chapuy M, Arlot M, Delmas P, et al. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *BMJ* 1994; **308**: 1081–82.
7. Bolland M, Avenell A, Baron J, et al. Effect of calcium supplements on risk for myocardial infarction and cardiovascular events: meta-analysis: *BMJ* 2010; doi: 10.1136/bmj.c3691
8. Lanza F, Hunt R, Thomson A, et al. Endoscopic comparison of esophageal and gastroduodenal effects of risedronate and alendronate in postmenopausal women. *Gastroenerology* 2000; **119**: 631–38
9. Miller, P, McClung, M, et al.. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. *Journal Bone and Mineral Research* 2005; **20**: 1315–22
10. Cooper A, Drake J, Brankin E. Treatment persistence with once-monthly ibandronate and patient support vs once-weekly alendronate: results from the PERSIST study. *Int J Clin Pract* 2006; **60**: 896–05
11. Black D, Delmas P, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *NEJM* 2007; **356**: 1809–22
12. Cummings S, Martin J, McClung M, et al. Denosumab for the prevention of fracture in postmenopausal women with osteoporosis. *NEJM* 2009; **361**: 756–65
13. NICE. Osteoporotic fractures - denosumab. http://guidance.nice.org.uk/TA204 (accessed 28 January 2011)
14. Reginster J, Bruyere O, Swawicki A, et al. Long-term treatment of postmenopausal osteoporosis with strontium ranelate: Results at 8 years. *Bone* 2009; **45**: 1059–64
15. Reginster J, Seeman E, De Vernejoul M, 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