Several guidelines exist for the identification and treatment of osteoporosis. Patients diagnosed with the condition should be prescribed bisphosphonates, if suitable, in the first instance

### Osteoporosis treatment and risk assessment

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The recent publication of guidance from the National Osteoporosis Guideline Group (NOGG) and two technology appraisals from the National Institute for Health and Clinical Excellence has led to a rethink in the way osteoporosis should be managed. Once patients have been identified as being at raised risk of an osteoporotic fracture, preventive measures are needed. The main preventive treatments are bisphosphonates and strontium ranelate. Less frequently used are raloxifene, hormone replacement therapy and teriparatide. This article outlines the available drug therapies and discusses clinical guidance.

#### Calcium and vitamin D

Calcium and vitamin D are recognised as having important roles in bone development. Populations deficient in these nutrients show signs of bone abnormalities. Calcium is important in bone remodelling; absorption from the gastrointestinal tract is improved when taken with vitamin D.

As a preventive measure alone the evidence base is poor, with the only evidence for sole use being in housebound elderly patients. However, it is generally accepted that patients who are taking bone protection treatments should be taking calcium and vitamin D unless sufficient dietary intake is assured.

#### Bisphosphonates

Bisphosphonates are now regarded as first-line treatment for primary and secondary prevention of osteoporotic fractures. They act to reduce resorption of bone and increase bone mineral density (BMD) by having an inhibitory action on osteoclast function and activity. Bisphosphonates have a low oral bioavailability (approximately 5%), hence specific administration directions need to be followed to ensure that the necessary amount of drug is absorbed from the gastrointestinal tract (see Box 1, p218).

Alendronate and risedronate (dosed either daily or weekly) account for most bisphosphonate prescriptions issued in the UK. Other oral bisphosphonates available are disodium etidronate (the original bisphosphonate but rarely used today) and ibandronic acid (available as a monthly dose). Ibandronic acid and zoledronic acid are available as IV infusions, which are given at three-monthly and annual intervals, respectively.

Although there is a strong evidence base supporting the use of bisphosphonates to prevent osteoporotic fractures, adverse events are common. Their use is frequently associated with gastrointestinal side effects. All oral bisphosphonates have caused cases of serious upper-GI damage (eg, oesophageal ulceration). Recently atrial fibrillation has been linked with the IV bisphosphonate zoledronic acid and there has been some suggestion that this could be a group effect.

Osteonecrosis of the jaw has also been associated with bisphosphonate use. This may be precipitated in patients...
who have undergone a dental procedure. There is insufficient evidence to warrant any change in practice but prescribers should warn patients to report any adverse effects following dental procedures. Pharmacists should also be aware that all bisphosphonates can cause severe musculoskeletal and bone pain.16 This usually resolves when therapy is stopped.

Recently the Medicines and Healthcare products Regulatory Agency has warned prescribers to be mindful of insufficiency fractures (atypical stress fractures) with bisphosphonates (especially alendronate).17 Prescribers are advised to discontinue alendronate and review the patient. Considering that alendronate currently costs the NHS around £20 per annum per patient compared with £250 for risedronate, and both have similar efficacy, the first-line choice should be alendronate.1–3

Strontium ranelate
Strontium ranelate has a dual mechanism of action — reducing bone resorption and increasing bone formation.

It is licensed for reducing the risk of vertebral and hip fractures in postmenopausal women and is not currently licensed for men. Strontium comes as a powder for reconstitution as an oral mixture and is taken once daily at night. It is recommended that patients also take a calcium and vitamin D product.

There is sufficient evidence for the effectiveness of strontium. In one large study including over 5,000 postmenopausal women aged over 70 years, with osteoporosis (T-score ≤–2.5) and an additional risk factor, a reduction in non-vertebral fractures was seen for strontium compared with placebo (P=0.04) over 36 months. Subgroup analysis showed that, over 36 months, patients who took strontium suffered fewer hip fractures than those who took placebo (P=0.046).18

In another study of over 1,500 postmenopausal women with at least one vertebral fracture and T-score ≤–2.5, the incidence of new vertebral fractures was lower in the strontium group than in the placebo group (P<0.001).19

The most common side effects are nausea and diarrhoea. In clinical trials strontium has been shown to confer a slightly higher risk of venous thromboembolism than placebo.20 The manufacturers recommend using it with caution for patients at risk of VTE; it may be sensible to prescribe strontium only once patients are successfully remobilised following hip fracture surgery.

At a cost of £332 per annum per patient strontium remains a second-line option after alendronate.

Hormonal treatments
Hormone replacement therapy is no longer recommended for prevention of osteoporosis. It may still be considered for women for whom other options have failed and this should be done under specialist supervision.

DESPITE THE STRONG EVIDENCE BASE SUPPORTING THE USE OF BISPHOSPHONATES TO PREVENT OSTEOPOOROTIC FRACTURES, ADVERSE EVENTS ARE COMMON
Raloxifene  Raloxifene is an oestrogen-receptor modulator that acts by selectively binding to oestrogen receptors, having an oestrogen agonist effect on bone. Raloxifene 60mg daily has been shown to reduce vertebral fractures in women who have osteoporosis, or who have had a previous fragility fracture, compared with placebo (relative risk reduction 0.65, 95% confidence interval 0.50–0.80).21 Research has not demonstrated raloxifene’s efficacy in preventing non-vertebral or hip fractures.

Teriparatide  Teriparatide, a fragment of recombinant human parathyroid hormone, acts by stimulating bone formation. It has been shown to reduce non-vertebral and vertebral fractures and is currently only licensed for postmenopausal women with established osteoporosis. The main evidence for teriparatide comes from a randomised controlled trial investigating women with established osteoporosis.22 Compared with those taking placebo, patients taking teriparatide experienced a reduced risk of vertebral fractures (risk ratio 0.35, CI 0.22–0.55) and grouped non-vertebral fractures (0.65, CI 0.43–0.98). However, when individual fracture types were considered teriparatide was shown not to be effective at preventing hip and wrist fractures. There are also concerns that bisphosphonates (in particular, alendronate) might reduce the effect of teriparatide.22

National guidelines  Recently three national guidelines for osteoporosis have been published: two technology appraisals from NICE and a guideline from NOGG. As outlined in this section, these guidelines differ in that NOGG considers both genders but not second-line drug treatment, whereas NICE focuses its appraisals on postmenopausal women and includes set criteria for using second-line treatments. Both organisations advocate opportunistic identification of patients with risk factors and not population screening. It should be noted that the Scottish Intercollegiate Guidelines Network published osteoporosis guidelines in 2003.7

Primary prevention  The NICE technology appraisal 160 relates to the primary prevention of fragility fractures (ie, no previous fracture) in postmenopausal women who have osteoporosis as defined by a T-score of less than −2.5 from dual-energy X-ray absorptiometry (DXA) scanning. NICE’s advice is drug-specific: it recommends the
bisphosphonate alendronate first line for women aged 70–74 years who have an independent risk factor (IRF) for osteoporosis or an indicator of low BMD (see Box 2, p223), and who are confirmed to have osteoporosis by DXA scan (T-score \(-2.5\)).

Alendronate is also recommended first line for:

- Women aged 75 years and over who have two or more IRFs or indicators of low BMD (BMD measurement not necessary)
- Younger women (aged 65–69 years) who have an IRF and who are confirmed to have osteoporosis by DXA scan
- Postmenopausal women younger than 65 years who have an IRF for fracture and at least one additional indicator of low BMD and who are confirmed to have osteoporosis by DXA scan

NICE makes specific recommendations for second- and third-line treatment. Risedronate, etidronate and strontium are only to be considered in cases of intolerance to alendronate and if the patients meet criteria based on a combination of T-score, age and number of IRFs. Raloxifene is not recommended for the primary prevention of osteoporotic fragility fractures in postmenopausal women.

In contrast to NICE’s recommendations, the NOGG guidance covers a broader range of primary and secondary risk factors for osteoporosis and suggests that a patient’s risk of fracture should be calculated using risk tables or the World Health Organization Fracture Risk Assessment Tool (available at www.sheffield.ac.uk/FRAX) — management is based on that risk.

As with NICE’s advice, the NOGG guideline recommends alendronate 70mg weekly as first-line treatment because of the medicine’s strong evidence base and low price. However, it makes no specific recommendations for second-line therapy, simply stating that other bisphosphonates, strontium ranelate or raloxifene may be appropriate treatment options. NOGG also suggests that teriparatide should be restricted to very-high-risk patients, especially for vertebral fractures.

Secondary prevention The NICE technology appraisal 161 refers to the secondary prevention of fragility fractures in postmenopausal women who have osteoporosis and have a previous fragility fracture. It states that alendronate should be used first line for postmenopausal women who have had one or more fragility fracture and osteoporosis confirmed by a T-score below \(-2.5\). Women aged 75 years and over who have had a previous fracture can start treatment with alendronate without DXA scanning if the managing clinician considers DXA scanning inappropriate. This is in contrast to the NOGG guidance, which recommends that all women with previous fragility fractures should receive treatment without any further assessment of BMD measurement.

NICE gives specific recommendations for teriparatide: as an alternative to bisphosphonates and strontium ranelate for a particular subset of patients. In both of its technology appraisals NICE assumes that women have adequate calcium intake and are not vitamin replete and recommends calcium and vitamin D supplementation if this is not the case.

Which guideline?
The NOGG guideline covers multiple risk factors and offers an easy-to-use interface to calculate risk of fracture and base treatment on that risk. Conversely, NICE only considers three clinical risk factors and five indicators of low BMD in the primary prevention technology appraisal and only previous fractures in the secondary prevention appraisal. Arguably, the NICE guidance is also more complicated for practitioners to apply, with tables based on T-scores, IRFs and body mass index used to decide which second- and third-line treatments should be used.

NOGG covers men and women over 50 years, whereas NICE restricts its advice to postmenopausal women. None of the existing guidance documents cover falls and, as discussed, these are a significant risk factor for fractures.

The NOGG guideline offers an approach to managing patients that is similar to that for primary and secondary prevention of cardiovascular disease. Patients’ risk can be easily assessed and the management guidelines are clear. By following NOGG guidelines clinicians can meet the first-line treatment recommendations in NICE TA160 and TA161. NICE’s second- and third-line treatment recommendations were contested by the pharmaceutical industry and patient groups but, following a ruling in February 2009, these currently remain as published.

Deciding which set of guidance to follow will have implications for resources. Clearly the NOGG guideline is going to identify a larger number of patients at risk compared with the technology appraisals from NICE. Nonetheless, it can be argued that NICE stratifies those at higher risk and most in need of management. Furthermore, following NICE is a requirement for NHS organisations in England and Wales.

NICE is planning to produce a clinical guideline on osteoporosis.
Pharmacist involvement

Frail elderly patients are especially vulnerable to falls, which often lead to fractures. Polypharmacy can increase the likelihood of drug-induced side effects (which can contribute to falls) and patient non-compliance (making osteoporosis treatment ineffective). Medication reviews can highlight such issues for individual patients. [The contributions of a pharmacist to falls prevention in an outpatient clinic are described in an article on page 235.]

Clinical pharmacists in hospitals will have contact with patients with osteoporosis across many specialisms. All pharmacists should be aware of risk factors for osteoporosis and falls and be willing to manage or advise on treatment. For example, respiratory pharmacists will often see patients who are at a high risk of osteoporosis secondary to regular use of oral corticosteroids. Similarly, pharmacists working in primary care can identify and manage patients at risk.

Community pharmacists could help to identify patients with risk factors either through medicines use reviews or health promotion campaigns (similar to those for diabetes, blood pressure and cholesterol testing offered by some pharmacies). Patient group directions or independent prescribing could allow pharmacists in the community to initiate treatment alongside detailed counselling.

Pharmacists can provide information about appliances and aids designed to reduce falls risk, for example walking aids (sticks, Zimmer frames, etc) or hip protectors (external padding incorporated into specially designed underwear). Hip protectors can help reduce the impact of a fall and also improve the confidence of a patient hesitant to walk after falling.

Pharmacists should be aware of any local help available to reduce hazard risks in the home. For example, in Northumberland the “Fit, involved, safe and healthy, through investment in sustainable community networks” (FISHNETS) project aims to support independent living of older people in the community and promote healthy and active ageing. As well as providing falls prevention education and training, the initiative provides home improvements through access to home help and physical activity programmes.

References