Osteoporosis is defined by the World Health Organization (WHO) as bone density measured by dual energy X-ray absorptiometry (DXA) scanning more than 2.5 standard deviations below the mean bone density of a healthy young adult (the T score). However, it has become increasingly clear over the last 10 or so years that bone density is only one risk factor for fracture. As a consequence we have moved away from treating the T score identified by DXA scans, and instead aim to reduce an individual’s risk of future fracture. This change in emphasis has been enabled by the development of fracture risk assessment tools.

Assessment of fracture risk
Assessment of fracture risk involves combining an individual’s clinical risk factors (including body mass index (BMI), family history of hip fracture, alcohol intake, smoking, use of oral corticosteroids and secondary causes such as rheumatoid arthritis) with their bone density measured by DXA. The most widely available tool for assessing fracture risk is FRAX (see www.shef.ac.uk/FRAX) but others are available such as QFracture (www.qfracture.org); both of these tools have been validated in UK populations. FRAX requires less information from the patient and is therefore easier and quicker to complete, but QFracture may be more appropriate for older people as it has a stronger focus on falls and co-morbidities. Both tools provide a probability for fracture risk in the future (FRAX is fixed at 10 years but for QFracture the time period can be varied) in terms of percentage risk of fracture. FRAX has the added advantage that it is linked to advice provided by the National Osteoporosis Guidelines Group (NOGG) on treatment thresholds, but these thresholds are controversial.

There are no nationally agreed treatment thresholds for the UK, but there is broad agreement on what is sensible. There is
good evidence that secondary fracture prevention, i.e., in those who have already had a low-trauma fracture, is cost-effective from the UK NHS perspective, and this is the basis for development of fracture liaison services. Primary prevention in those who have not fractured is controversial, except perhaps when considering prevention of medication-induced bone fragility, particularly that associated with glucocorticoids.

The three most commonly used treatment thresholds when considering secondary fracture prevention are: low bone density, thresholds devised by NOGG that vary with age, and fixed treatment thresholds. In terms of low bone density, if an individual has had a low trauma fracture, is aged >50 years and a DXA scan shows they have osteoporosis, then most clinicians agree that this person should be treated. The thresholds that vary with age such as those produced by NOGG are controversial: although they are easy to understand and can be accessed directly through the FRAX website, they tend to deny treatment to high-risk elderly people while recommending treatment to lower risk young people.

In response to this, there is a move towards using fixed treatment thresholds. In the USA, a 10-year probability of 20 per cent for any osteoporotic fracture and 3 per cent for hip fracture is classed as high risk and treatment is recommended for anyone with a fracture risk above this. In the UK there is a move towards adopting 20 per cent risk for any osteoporotic fracture and 5 per cent for hip fracture. Fixed treatment thresholds for people in the UK are attractive as they are easy to use and allow clear division into low risk (less than 10 per cent for any fracture and 3 per cent for hip fracture), intermediate risk (10-19 per cent for any fracture and 3-5 per cent for hip fracture) and high risk (>20 per cent for any and >5 per cent for hip fracture). In the absence of national guidance, the decision as to which treatment threshold to use needs to be agreed locally.

NICE has produced a useful clinical guideline on how to assess fracture risk, and the current recommendations are first to identify an individual’s risk of fracture based on clinical risk factors alone using FRAX or QFracture without measurement of bone density. If a patient is identified as having a low fracture risk, they should be reassured and given appropriate lifestyle advice on maintaining healthy bones. If they are at a high fracture risk, they require treatment, and a DXA scan at baseline may be useful to monitor response to treatment in the future. If they have an intermediate fracture risk, they should have a DXA scan, the results of which will either push them into the “low risk” group and the person can then be reassured, or the “high risk” group and they should be given active treatment. NICE does not provide a definition of low, intermediate or high risk.

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**Figure 1.** Summary of an ideal treatment pathway for patients started on medications to reduce fracture risk. Recommended duration of drug holidays are based on the pharmacokinetics of individual agents.
Management of high fracture risk
Management of high fracture risk involves reducing the risk of falls and improving bone health.

Reducing the risk of falls
NICE recommends that all individuals aged 65 years and over should be asked if they have fallen in the past year. If so, they should be asked how often, when and how they fell. Patients who have fallen or who are at risk of falling due to problems with their balance and gait should be offered a multifactorial assessment of their falls risk, ideally within the setting of a falls service. This assessment should include: a review of the individual’s falls history and injuries sustained; co-morbidities that may increase their falls risk; medication, cognition, continence, footwear and vision; and as well as their postural stability, mobility and balance. The individual’s fear of falling should also be explored. Investigations and interventions should then be tailored to each individual’s needs. Common interventions to reduce risk of falls include strength and balance training, an assessment of home hazards, and advice regarding appropriate walking aids and footwear. Psychotropic medication should be carefully reviewed and stopped where possible.

Improving bone health
To improve bone health in people identified as having a high fracture risk, there are two main strands of prevention: lifestyle advice for healthy bones and medications.

Lifestyle advice
Patients who smoke should be advised to stop and those who drink alcohol to excess (more than 14 units a week for women and more than 21 units a week for men) should be advised to reduce their intake to below these levels, although it is not known whether stopping drinking or smoking leads to an increase in bone mass or even whether it slows the rate of bone loss. Weight-bearing exercise should be recommended and tailored to the ability of individual patients. Ensuring adequate calcium intake is also important: the recommended daily intake for women and men aged 50 years and over is 1200mg calcium daily. Encouraging patients to spend 15 minutes per day outside without sunscreen can be helpful in maintaining vitamin D levels.

Supplementation with calcium/vitamin D preparations should also be considered.

Medications
All bone protective agents for osteoporosis should be given while ensuring that patients are vitamin D and calcium replete. Current medications available to reduce fracture risk are antiresorptive medications (mainly bisphosphonates, denosumab and selective oestrogen-receptor modulators) and anabolic agents (teriparatide). Bisphosphonates act by inhibiting osteoclastic bone resorption, and have been shown to reduce risk of future fracture by 41-70 per cent. The oral bisphosphonate alendronate is the first-line treatment recommended by NICE for the secondary prevention of fragility fractures in women with osteoporosis. Risedronate and etidronate are alternative oral bisphosphonates. All oral bisphosphonates need to be used in caution in the presence of renal impairment, but can theoretically be given to people with any eGFR.

Raloxifene and strontium ranelate are other second-line agents for the secondary prevention of fragility fractures, but are less frequently used. Raloxifene is an oestrogen-receptor activator of the nuclear factor kappa B ligand (RANKL), which reduces osteoclast action thus reducing bone resorption, is given six-monthly as a subcutaneous injection. Denosumab, a fully human monoclonal antibody to the receptor activator of the nuclear factor kappa B ligand (RANKL), which reduces osteoclast action thus reducing bone resorption, is given six-monthly as a subcutaneous injection. Denosumab has an amber status, requiring the first dose to be given in secondary care and the remaining doses to be given in primary care under a shared care agreement. Denosumab can also be associated with hypocalcaemia, particularly in the presence of renal impairment, but can theoretically be given to people with any eGFR.

Figure 2. Osteonecrosis of the jaw: a rare side-effect of bisphosphonates and denosumab. Image provided with kind permission from Mr Christopher Bell, senior clinical lecturer in oral and dental sciences, University of Bristol.
A modulator that inhibits bone resorption. It is contraindicated in patients with a history of venous thromboembolism or previous stroke and severe renal or hepatic impairment. The mode of action of strontium ranelate is not fully understood but it impairs bone resorption and improves bone formation. It should be used with caution in patients with a history of venous thromboembolism and is associated with an increased risk of myocardial infarction so should only be used in those with severe osteoporosis at high risk of fracture. Strontium ranelate also causes artifactual elevations in DXA readings and its use is therefore difficult if fracture risk needs to be reassessed.

Challenges of bone protective therapy

There are four important areas to consider with medications to reduce fracture risk: adherence, length of time on treatment, treatment failure and rare but important adverse effects. Adherence to oral medications to reduce fracture risk is generally poor, with approximately one-third to a half of people prescribed bisphosphonates having low or nonadherence. This poor adherence is associated with an increased risk of fracture and compliance should be reviewed at each encounter, with efforts made to find more acceptable agents where necessary, such as parenteral agents.

A fairly recent concept change is that bone protective agents are not viewed as a treatment for life. Instead, the need for these medications should be reviewed every five years (possibly three for zoledronic acid), or if there is a suggestion that they are not working, such as a further fragility fracture. If at five years the person still has a high fracture risk, treatment should continue for a further five years. If the person has a low fracture risk, treatment should be stopped. If their fracture risk is borderline, it is worth considering a break from therapy (a so-called drug holiday) before restarting for a further five years (see Figure 1). By ensuring only those...
KEY POINTS

- Patients should have their fracture risk assessed using FRAX or Q Fracture without DXA scanning.
- Intermediate or high-risk patients should have a DXA scan.
- High-risk patients should be offered management to improve bone health and reduce falls risk.
- Management to improve bone health includes lifestyle modification and medications.
- First-line medication is oral alendronate.
- Parenteral therapies are useful alternatives for people experiencing adverse effects or who have difficulty with compliance.
- The need for ongoing treatment should be reviewed after five years.

Final risk levels after 10 years

At the highest fracture risk remain on long-term medications, it is hoped that rare side-effects like atypical femoral fractures are limited.

Two rare but important side-effects of treatment with bisphosphonates and denosumab are osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF). ONJ is defined as exposed and necrotic bone in the maxillofacial region that does not heal within eight weeks (see Figure 2). It is a rare adverse event (less than 1 in 100018) that has been reported with bisphosphonates (particularly intravenous) and denosumab, but the risk of ONJ is far outweighed by the potential benefit of fracture risk reduction. It is thought that the risk of ONJ can be reduced by patients undergoing any necessary dental treatment before starting these medications.19 AFFs are atraumatic or low-trauma fractures in the subtrochanteric and diaphyseal regions of the femur that have been reported in people on long-term bisphosphonates and denosumab20 (see Figure 3). They arise in the lateral cortex, have an unusual transverse/short oblique configuration and can be bilateral. Patients on these medications should be advised to report any hip, groin or thigh pain, which may indicate such a fracture. However, a causal association between osteoporosis medications and AFF has not been proven,19,20 and the number of fragility fractures prevented by bisphosphonate therapy far outweighs the number of AFFs that occur.

Summary

There has been a considerable change in emphasis in osteoporosis management over the last few years, with a clear move towards assessment and reduction in fracture risk, rather than treatment. A range of medications are available, with oral alendronate being the first-line therapy for the majority of patients. The main challenge in pharmacotherapy to reduce fracture risk is overcoming poor adherence to oral medications.

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Declaration of interests

None to declare.

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