Management of osteoporosis in a post-menopausal woman

SUMMARY

This Bulletin describes the management of a postmenopausal woman with risk factors for osteoporosis in a case-study format. It illustrates use of the two NICE technology appraisals on drug treatments for primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women, and outlines some issues for healthcare professionals to consider. The management of osteoporosis in other situations (e.g. corticosteroid-induced osteoporosis, women with osteopenia and osteoporosis in men) is outside the scope of this Bulletin. Further information on the management of osteoporosis is available in a suite of materials on the osteoporosis floor of NPCi and via the related resources section of this Bulletin (see Panel 2 page 5).

Case study

Sandra is an active 62-year-old woman who presents to 'discuss her concerns about osteoporosis'. Six years ago her mother (now aged 83 years) sustained a fractured neck of femur and was diagnosed with osteoporosis. Sandra is worried that she may also be at risk of an osteoporotic fracture. Sandra smokes 20 cigarettes and drinks one small glass of wine a day on average. She is 170cm tall, weighs 60kg and has no other relevant medical conditions. Her menopause was not premature.

What factors increase Sandra’s risk of osteoporotic fracture?

It is important to distinguish between Sandra’s risk of osteoporosis and her risk of osteoporotic fracture. As well as increasing age and low bone mineral density (BMD), many other factors can determine the risk of fracture. NICE has divided them into two groups (see Panel 1): firstly, those that independently raise fracture risk; and secondly, indicators of low BMD. Other issues may impact on the risk of falls or fractures, for example, calcium and vitamin D deficiency, physical activity level, muscle strength, maintenance of balance while upright, visual impairment and use of sedating medications.

Estimating the risk of fracture using an individual’s risk characteristics is inaccurate. Therefore, as with cardiovascular disease, a risk calculator (FRAX®) has been developed. NICE has not assessed the use of FRAX® and their recommendations are not based on this risk calculator for a number of reasons. Firstly, not all the risk factors it includes may be appropriate, e.g. smoking. Secondly, absolute risk of fracture is not an accurate predictor of the cost effectiveness of fracture prevention drugs because different fracture sites have different impacts on quality of life, cost and mortality. Thirdly, the evidence base does not currently show that modifying all of the risk factors included in the calculator results in clinical benefit.

Panel 1: Risk factors for fracture in postmenopausal osteoporosis

Independent clinical risk factors for fracture:
- Parental history of hip fracture
- Alcohol intake of 4 or more units a day
- Prior fracture*
- Rheumatoid arthritis (RA).

Indicators of low BMD:
- Low body mass index (BMI) (<22kg/m²)
- Medical conditions e.g. ankylosing spondylitis, Crohn’s disease, RA
- Conditions that result in prolonged immobility
- Untreated premature menopause.

* Not covered by NICE TA 160

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Management of osteoporosis in a post-menopausal woman

NICE used detailed modelling of the cost-effectiveness of each therapy at various stages before making treatment recommendations for a number of groups. They concluded that it is appropriate to recommend treatment on the basis of a combination of T-score, age and the number of independent clinical risk factors for fracture. T-score relates to the measurement of BMD using hip and/or spine dual-energy X-ray absorptiometry (DXA) scanning and is calculated by comparing the observed BMD with that of an average healthy young premenopausal woman. It is expressed as the number of standard deviations (SD) from peak BMD. Confirmed osteoporosis is defined as a T-score of less than or equal to –2.5 SDs at the hip or spine on DXA scanning.\(^1\,^2\)

Sandra has several risk factors for fracture. Firstly, she is postmenopausal. The prevalence of osteoporosis in women increases after the menopause from approximately 2% at 50 years to more than 25% at 80 years.\(^1\,^2\) In addition, her mother has had an osteoporotic hip fracture. Sandra’s body mass index (BMI) is 20.8kg/m\(^2\), which is below the NICE threshold for low body weight of 22kg/m\(^2\) and is likely to contribute to her fracture risk. Smoking is also a weak risk factor for fracture.\(^3\) NICE guidance identifies consumption of four or more units of alcohol a day as a risk factor for fracture.\(^1\,^2\) Sandra’s alcohol consumption is lower than this.

Would you refer Sandra for a DXA scan?

Low BMD should be thought of as a risk factor for fracture, in much the same way that high blood pressure and high cholesterol are risk factors for a stroke or myocardial infarction. BMD measurement is a relatively poor predictor of fracture and there is a large overlap between the BMDs of those people who sustain a fracture and those who do not. The test does not accurately identify those who will go on to have a fracture. Therefore, widespread population BMD measurement is not appropriate.\(^3\) NICE specifically states that its guidance on primary prevention of osteoporotic fractures in postmenopausal women does not imply that a dedicated screening programme should be created. Instead it refers to opportunistic identification of women who may be appropriate for referral for scanning or for treatment.\(^1\)

Interpreting BMD results is not without problems. DXA scanning is the most commonly used method, and the site used is important because the size of the bone affects apparent density. For comparative readings in an individual person, the same bone site and the same scanner should be used throughout treatment, wherever possible, to minimise errors that can result from differences in bone size and instrumentation. However, errors can still arise for various reasons, such as inadequate operating procedures.\(^3\)

Sandra has not had a fracture and any intervention would be for primary prevention. Whether or not DXA scanning is appropriate for Sandra depends very much on what, if any, drug treatment may be required. The NICE technology appraisal on primary prevention recommends the following women as suitable for treatment consideration (with the bisphosphonate, alendronate, first-line):\(^1\)

- Age ≥70 years, with one independent clinical risk factor for fracture or indicator of low BMD (see panel 1, page 1), and confirmed osteoporosis (a T-score of –2.5 SDs or below)
- If aged ≥75 years with two or more independent clinical risk factors for fracture or indicators of low BMD, a DXA scan may not be required if the clinician considers it to be clinically inappropriate or unfeasible
- Age 65–69 years, with one independent clinical risk factor for fracture and confirmed osteoporosis (a T-score of –2.5 SDs or below)
- Age <65 years, with one independent clinical risk factor for fracture and at least one additional indicator of low BMD and confirmed osteoporosis (a T-score of –2.5 SDs or below)

The cost-effectiveness of interventions depends on the absolute level of fracture risk, the costs related to each fracture as well as the efficacy of the various treatments and their costs. Although the recommendations of NICE may appear complex, they present a step-wise approach to management, which places interventions with the most robust evidence of clinical effectiveness and highest levels of cost-effectiveness as first-line choices. For individual patients who cannot take, use or tolerate particular treatments, alternatives are available. However, these alternatives are sometimes subject to additional criteria because their increased cost means that the fracture risk needs to be higher in order to maintain cost-effectiveness.\(^1\,^2\)

Sandra is 62 years old and has one clinical risk factor for fracture (parental history of hip fracture) and one additional indicator of low BMD (BMI <22kg/m\(^2\)). Therefore, her BMD should be determined before treatment is considered, as to qualify for treatment she must have a T-score of –2.5 SDs or below. If she didn’t have a clinical risk factor and an indicator of low BMD there, would be no point referring her for DXA scanning because she wouldn’t qualify for treatment even if she did have an osteoporotic BMD.

Sandra is referred for a DXA scan and her T-score, measured at the hip, is –1.5 SD. A T-score of between –1.0 and –2.5 SD is classed as osteopenia and a T-score of –1.0 SD or above is considered normal. Therefore, Sandra does not have osteoporosis and drug treatment

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Management of osteoporosis in a post-menopausal woman

is not appropriate according to current NICE guidance based on cost-effectiveness and the balance of risks and benefits.

**What advice would you offer Sandra?**

Sandra should be offered advice about adequate dietary intake of calcium and vitamin D. The Food Standards Agency website outlines which foods good sources of calcium and vitamin D.

**Supplements** may be considered for women who do not have an adequate calcium intake and who may not be vitamin D replete, i.e. those with inadequate dietary intake and insufficient exposure to sunlight. However, most of the evidence for fracture prevention using calcium and vitamin D supplements has involved studies of people living in care homes and/or the frail elderly and it is unclear whether the results are generalisable to women living in the wider community. There are a number of licensed preparations that will supply the evidence-based doses of around 1g per day for calcium (measured as elemental calcium) and 700–800 units per day for vitamin D.

About 90% of hip fractures in both sexes result from a simple fall from standing height or lower. The risk of falling is greater in older women, increasing from about one fifth of women aged 45–49 years falling each year to nearly half of women aged ≥85 years.

A recent Cochrane review (111 RCTs, n=55,303) showed that multiple-component group exercise (targeting at least two of strength, balance, flexibility or endurance), Tai Chi group exercise, and individually prescribed exercise reduced the rate of falls and risk of falling in people aged 60 years and over living in the community. Multifactorial interventions integrating assessment with individualised intervention, usually involving a multi-professional team, were effective in reducing the rate of falls but not risk of falling. Overall, home safety interventions alone did not appear to reduce rate of falls or risk of falling, except in people at high risk (e.g. those with severe visual impairment). Limited evidence supported the effectiveness of interventions targeting medications likely to cause falls (e.g. withdrawal of psychotropics).

The NICE clinical guideline on the assessment and prevention of falls in older people (≥65 years) provides advice on case identification and multifactorial falls risk assessment. It recommends that all older people with recurrent falls, or assessed as being at increased risk of falling, should be considered for an individualised multifactorial intervention, including strength and balance training, home hazard assessment and intervention, vision assessment and referral, and medication review with modification or withdrawal.

Although Sandra is still relatively young and has no underlying medical conditions predisposing her to falls, it is still worth considering fall prevention measures, including medication review and exercise programmes. Sandra should be encouraged to stop smoking, moderate her alcohol intake and remain physically active.

Twelve years later, now 74-years old, Sandra returns, having suffered a wrist fracture by tripping over at home onto a carpeted floor. Her weight and height remain unchanged from when she came to see you ten years ago.

**Would you prescribe drug treatment now?**

The fracture Sandra suffered suggests she may have osteoporosis. It would meet the definition of a clinically apparent osteoporotic fragility fracture: ‘a fracture sustained as the result of a force equivalent to the force of a fall from a height equal to, or less than, that of an ordinary chair’. She should now be treated according to NICE guidance for secondary prevention of osteoporotic fragility fractures. However, this guidance recommends drug therapy only in women who have sustained a clinically apparent osteoporotic fragility fracture and who have confirmed osteoporosis. As Sandra is 74 years old, it is necessary to recheck her BMD to identify whether she now has osteoporosis and fits the NICE criteria for drug treatment due to a change in the balance of her likely risk of fracture and subsequent benefits of treatment. If Sandra had been older, measuring BMD may have become unnecessary as NICE recommends that in women aged ≥75 years, BMD assessment is not essential if the clinician considers it inappropriate or unfeasible. However, an absence of a pre-treatment BMD value has implications if patients later suffer a further fracture while on first-line treatment (see below).

Following a DXA scan Sandra’s T-score at the hip was –2.5 SD.

This, together with Sandra’s recent medical and family history suggests she is at increased risk of further fractures. She has suffered a fracture and has confirmed osteoporosis. It would, therefore, be appropriate to consider drug therapy according to NICE guidance.

**What would you prescribe for Sandra?**

Alendronate is recommended as drug of first-choice for secondary prevention of osteoporotic fragility fractures in the NICE guidance.

The Table (page 4) summarises the efficacy data from the systematic review used by NICE during the development of the two technology appraisals. Reductions in relative risk associated with treatment were pooled regardless of whether treatment was for primary...
Management of osteoporosis in a post-menopausal woman

Table: Relative risk of fracture with bisphosphonates versus placebo

<table>
<thead>
<tr>
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<th>Relative risk (RR) of fracture (95%CI) versus placebo</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Vertebral*</td>
</tr>
<tr>
<td>Alendronate</td>
<td></td>
</tr>
<tr>
<td>Benefit</td>
<td>0.56 (0.46 to 0.68)</td>
</tr>
<tr>
<td>Etidronate</td>
<td></td>
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<tr>
<td>Benefit</td>
<td>0.40 (0.20 to 0.83)</td>
</tr>
<tr>
<td>Risedronate</td>
<td></td>
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<tr>
<td>Benefit</td>
<td>0.61 (0.50 to 0.75)</td>
</tr>
</tbody>
</table>

* This includes both symptomatic and asymptomatic (radiographically determined) fractures.

The absolute benefit of treatment with bisphosphonates will depend on the baseline risk of fracture.

- are unable to comply with alendronate treatment or have a contraindication to, or are intolerant of, alendronate and
- have a specified combination of T-score, age and number of independent clinical risk factors for fracture (see NICE technology appraisals on primary and secondary prevention for details).

Generally, patients must have lower BMD measurements, or more risk factors, to be eligible for treatment with risedronate or etidronate. This is due to the higher cost of these second-line treatment options, which means it is necessary to identify higher-risk people in order for treatment to remain cost-effective. This approach also means that a woman not meeting NICE criteria for second-line use of risedronate or etidronate, who cannot take, use or tolerate alendronate, would not be recommended to use any other therapy beyond a calcium and vitamin D supplement.

The evidence for the effectiveness of alendronate and risedronate is more robust than that for etidronate, with benefit being demonstrated both in vertebral and non-vertebral fractures. However, there would appear to be no adequate studies comparing these two drugs in terms of patient-oriented outcomes. These drugs also seem to be similar in terms of safety and tolerability. The lower acquisition cost of alendronate, however, makes this an obvious first choice. Currently, the least costly preparation of alendronate is generic alendronic acid 70mg tablets given once weekly.

Calcium and vitamin D are generally recommended for co-administration with bisphosphonates unless clinicians are confident that women have an adequate calcium intake and are vitamin D replete. Discussion with Sandra regarding her diet and lifestyle may reveal whether she could be deficient in calcium and vitamin D. If there is any doubt, then calcium and vitamin D supplements should be prescribed.

Risedronate and etidronate are recommended as second-line alternatives for the primary or secondary prevention of osteoporotic fragility fractures in postmenopausal women who:

- have a specified combination of T-score, age and number of independent clinical risk factors for fracture (see NICE technology appraisals on primary and secondary prevention for details).

A few years later Sandra suffers a hip fracture in another fall at home despite being prescribed alendronate.

Would you change her treatment?

NICE defines an unsatisfactory response to treatment as occurring when a woman has another fragility fracture despite adhering fully to treatment for one year and there is evidence of a decline in BMD below her pre-treatment baseline. This can present a number of practical problems, especially when no other options are feasible.
pre-treatment BMD is available. Therefore, the decision to start treatment in patients aged 75 years or older without a pre-treatment BMD must be taken carefully.

It is thought that between a third and a half of all medicines prescribed for long-term conditions are not taken as recommended.12 In the third year of treatment studies of bisphosphonates, adherence was between 51% and 89%.1,2 So, it is worth exploring whether Sandra has been taking the medicine as prescribed. The NICE clinical guideline on medication adherence makes recommendations about how healthcare professionals can support patients to adhere to prescribed medicine, and help them to make informed decisions by facilitating their involvement in the decision to prescribe.13 It may be that Sandra has suffered side effects to alendronate. For example, bisphosphonates commonly cause gastrointestinal side effects. In people with oesophageal abnormalities and other factors that delay oesophageal transit or emptying, risendronate should be used cautiously and alendronate is contraindicated (see SPCs for full details of side effects and contraindications).1,2 Alternatively, she may be struggling to follow the complex administration requirements. For example, alendronate and risendronate should be taken with 200ml and 120ml of water, respectively, and patients should not eat or drink before or immediately after administration and should remain upright for stipulated time periods.1,2

Even if Sandra has adhered to the treatment regimen, a fracture while taking treatment can still occur. Bisphosphonates, or indeed any intervention, can only reduce the risk of fracture: they cannot abolish it. In the best clinical trials, alendronate and risendronate reduced the relative risk of a fracture by around 20–40% (see Table, page 4).1,2 This means that all patients, even if they adhere strictly to their prescribed regimen, and also change their lifestyle, still have a residual risk of fracture. If a fracture occurs, it does not necessarily mean the treatment has not been beneficial. A BMD measured and compared with the baseline may indicate to some degree if this is likely to be the case. Sandra may still benefit from continuing to take alendronate despite her fracture because the treatment may already have prevented and earlier fracture at this site or other fractures at different sites.

So, while second-line agents such as raloxifene, strontium ranelate and teriparatide may be an option for those who go on to have a fracture while on a bisphosphonate, practitioners should carefully assess the risks and benefits before switching to these agents.

When the risks and benefits of the various treatment options are discussed with Sandra, she decides to continue taking once-weekly alendronate.
References

1. NICE. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. Technology Appraisal 160. October 2008


12. NICE. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. CG76. January 2009