Treatment Guidelines for Osteoporosis in Adults.

Background

Osteoporosis is a condition characterised by a reduction in bone mass density increasing the risk of fracture. Fractures occur most commonly in the hip, spine and wrist. Vertebral fractures due to osteoporosis can cause loss of height, curvature of the spine and chronic back pain. One in three women and one in twelve men over 50 are affected by osteoporosis and almost half of all women experience an osteoporotic fracture by the time they reach the age of 70.¹

In October 2008 NICE produced TA 160 and TA161 for the primary and secondary prevention of osteoporotic fractures. This guidance is restricted to postmenopausal women with osteoporosis as defined by a bone mineral density T-score of ≤-2.5, and does not include men with osteoporosis or individuals treated with glucocorticoids. In addition, NICE guidance for second line options demands different combinations of bone density and risk factors for different treatments which is complicated to operate in a primary care setting. Several recently introduced interventions, including ibandronic acid, zoledronic acid and more recently denosumab (separate NICE TA204) are not included in the guidance. The National Osteoporosis Guideline Group (NOGG) was launched in October 2008 to address these deficits. It is endorsed by many scientific and professional organisations including the National Osteoporosis Society and the Royal College of Physicians.

Areas of agreement between NICE and NOGG include recommendations to treat elderly postmenopausal women with a fragility fracture and the use of generic alendronate as a first line option. There is also agreement that bone mineral density measurements may be useful in reaching treatment decisions in younger postmenopausal women with a fragility fracture. However, whereas NICE requires a T-score ≤-2.5 in most women for either primary or secondary prevention, NOGG recognises the added contribution of independent clinical risk factors to fracture prediction and recommends the use of the WHO-supported fracture risk algorithm FRAX®.

Many cost-effectiveness studies of bone-sparing therapy use the Fracture Risk Assessment tool FRAX® to identify fracture risk thresholds where drugs become cost effective. The recent short NCGC Clinical Guideline 146 (August 2012), Osteoporosis: assessing the risk of fragility fracture, aims to provide guidance on the selection and use of such risk assessment tools in the care of people who may be at risk of fragility fractures. It suggests all women over 65yrs are assessed and all men over 75yrs and concurs with the algorithm on the following page suggesting patients over the age of 50yrs should be assessed for risk in the presence of certain risk factors. FRAX® combines the major risk factors of age, fracture history and BMD with parental hip fracture, rheumatoid arthritis, alcohol, smoking and chronic disease history to calculate 10-year absolute risk of major osteoporotic fracture and hip fracture. This absolute risk is deemed more appropriate than relying on single risk factors.

In order to provide comprehensive and practical guidance for the management of osteoporosis in primary care setting, the following guidelines suggest a combination of NICE and NOGG that retains the main principles of NICE guidance but incorporates the greater workability of NOGG. It also incorporates NOGG guidance for men with osteoporosis, individuals treated with glucocorticoids, and the use of more recently introduced interventions.

For the purpose of these guidelines, in line with NICE, intolerance of alendronate or risedronate is defined as persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment, and that occurs even though the instructions for administration have been followed correctly. An unsatisfactory response following treatment for secondary prevention of osteoporosis ie after a fragility fracture is defined as occurring when a woman has another fragility fracture despite adhering fully to treatment for 1 year and there is evidence of a decline in BMD below her pre-treatment baseline.

¹ National Service Framework for Older People, Department of Health, 2001
Surrey Rheumatology Network April 2014, updated virtually Nov 2014 and approved by the Prescribing Clinical Network Dec 2014
Acknowledgments to North of the Tyne PCT for use of their Osteoporosis Treatment Guidelines.
Treatment Guidelines for Osteoporosis in Adults

Osteoporosis treatment

- Falls assessment
- Lifestyle advice
- Calcium and Vitamin D supplement
  (Adcal D3 / Accrete D3 preferred products)

Treatment options:

Post menopausal women:
- Alendronic acid 70mg weekly or
- Risedronate 35mg weekly or
- Ibandronic acid 150mg monthly (note: more expensive therefore reserved for patients who experience problems taking oral bisphosphonates: alendronic acid £0.90/month / risedronate £1.16 /month, ibandronic acid £3.02/month based on prices in Feb 2014 Drug Tariff)

If intolerant to initial chosen bisphosphonate trial of another listed bisphosphonate would be the next appropriate treatment of option or
bisphosphonate contraindicated / intolerant to two bisphosphonates consider denosumab 60mg SC (see prescribing information sheet)

Based on NICE TA160 Osteoporosis - Primary Prevention and TA161
http://guidance.nice.org.uk/TA161/Guidance/pdf/English

Note: In line with the EMA guidance April 2014 strontium has been restricted to patients with severe osteoporosis who cannot be treated with other medicines approved for osteoporosis (see page 5)

For men and prevention / treatment of corticosteroid induced osteoporosis refer to table for summary of licensed indications

Fragility fracture

Postmenopausal women > 75yrs

No Fragility fracture

Postmenopausal women OR men > 50 yrs with > 1 clinical risk factor

Independent risk factors:
- Alcohol > 4 units a day
- Rheumatoid arthritis
- Parental history of hip fracture

Indicators of low bone mineral density (BMD)
- Low BMI < 22kg/m²
- Taking an oral glucocorticosteroid for ≥ 3mths
- Ankylosing spondylitis
- Crohn’s disease
- Conditions resulting in prolonged immobility
- Untreated premature menopause

Secondary care treatment options:
The following are red drugs on the traffic light system refer to PAD

Refer For:
- Patients unable to tolerate / respond to oral bisphosphonate and / or denosumab treatment.
- Osteoporosis with complex medical problems
- Fragility fractures due to other bone disease

Medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronic acid</td>
<td>5mg annual IV infusion</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>20mcg daily by subcutaneous injection (max. duration 18 months, not to be repeated)</td>
</tr>
<tr>
<td>Strontium</td>
<td>2g once daily in water</td>
</tr>
</tbody>
</table>
### Table Summarising NHS Surrey treatment options for osteoporosis

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Indication / dose</th>
<th>Contra-indications</th>
<th>Side-effects</th>
<th>Counselling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronic acid tablets 10mg</td>
<td>Treatment of postmenopausal osteoporosis 10mg daily or 70mg once weekly.</td>
<td>Abnormalities of oesophagus, factors which delay gastric emptying</td>
<td>Abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer, melaena, dysphagia, abdominal distension, acid regurgitation, musculoskeletal pain, headache</td>
<td>Take on an empty stomach at least 30 minutes before breakfast or other medicines. Swallow whole with plenty of water while sitting or standing and remain upright for at least 30min after taking.</td>
</tr>
<tr>
<td>Alendronic acid 70mg once weekly</td>
<td>Treatment of osteoporosis in men 10mg daily</td>
<td>Avoid if eGFR less than 35ml/minute/1.73m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prevention and treatment of corticosteroid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy 10mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risedronate sodium 5mg tablets</td>
<td>Treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures 5mg daily or 35mg weekly</td>
<td>As for alendronic acid tablets</td>
<td>Constipation, dyspepsia, nausea, abdominal pain, diarrhoea, headache, musculoskeletal pain</td>
<td>Swallow whole with full glass of water on rising. Take on an empty stomach at least 30mins before first food or drink of the day. Stand or sit upright for at least 30mins. Do not take tablets at bedtime or before rising.</td>
</tr>
<tr>
<td>Risedronate sodium 35mg once weekly tablets</td>
<td>Prevention of osteoporosis (including corticosteroid induced osteoporosis) in postmenopausal women 5mg daily</td>
<td>Avoid if eGFR less than 30ml/minute/1.73m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibandronic acid 150mg tablets once a month</td>
<td>Treatment of osteoporosis in postmenopausal women at increased risk of fracture</td>
<td>As for risedronate</td>
<td>Hypocalcaemia, hypophosphataemia, influenza like symptoms, bone pain, diarrhoea, nausea, vomiting, gastritis, abdominal pain, dyspepsia, headache, rash, hypersensitivity reactions, urticarial, very rarely osteonecrosis of the jaw</td>
<td>Swallow whole with full glass of water on rising. Take on an empty stomach at least 30mins before first food or drink of the day. Stand or sit upright for at least 30mins. Do not take tablets at bedtime or before rising.</td>
</tr>
<tr>
<td>Zolendronic acid intravenous infusion 5mg once a year</td>
<td>Treatment of postmenopausal osteoporosis and osteoporosis in men (including corticosteroid-induced osteoporosis)</td>
<td>Hypersensitivity to the active substance, to any bisphosphonates or to any of the excipients Patients with hypocalcaemia Severe renal impairment with creatinine clearance &lt; 35 ml/min Pregnancy and breast-feeding</td>
<td>Hypophosphataemia, anaemia, myalgia, arthralgia, GI disturbances, AF, headache, dizziness, renal impairment, Rarely osteonecrosis of the jaw</td>
<td>Single infusion once a year administered over at least 15 minutes</td>
</tr>
</tbody>
</table>

Note: Alendronic Acid Oral Solution 70mg/100ml is also available - the information above applying to the solid oral dosage form also applies to the liquid formulation.

2 For further detailed information please refer to BNF/latest edition) and www.emcmedicines.org.uk
| **Denosumab** | • Treatment of osteoporosis in postmenopausal women at increased risk of fractures  
• Treatment of osteoporosis in men at increased risk of fractures | Hypersensitivity to the active substance or to any of the excipients  
Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy.  
No dose adjustment is required in patients with renal impairment, however, if patient creatinine clearance < 30 ml/min or receiving dialysis there is greater risk of developing hypocalcaemia. | Mild, transient decreases in serum calcium.  
Skin infections predominantly cellulitis.  
Other common undesirable effects (incidence of 1-10%) were urinary tract infection, upper respiratory tract infection, cataracts, constipation, sciatica, rash, pain in extremity.  
There have been no reports of anaphylaxis with the injection of denosumab to date. | To report any adverse events to the doctor who administered the injection.  
To attend the GP surgery every 6 months for the denosumab injection. |
| **Strontium 2g sachet** | • Treatment of severe osteoporosis in postmenopausal women / adult men at high risk of fracture, for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance.  
• Prescribers are advised to: Assess patients’ risk of developing CVD before starting treatment  
Monitor patients’ CVD risk on a regular basis, generally every 6-12 months  
Stop treatment if the patient develops IHD, PAD, CVD or if hypertension is uncontrolled  
• The decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks  
• Treatment should only be initiated by a physician with experience in the treatment of osteoporosis | Hypersensitivity to the active substance or to any of the excipients  
Current or previous venous thromboembolic events (VTE), including deep vein thrombosis and pulmonary embolism.  
Temporary or permanent immobilisation due to e.g. post-surgical recovery or prolonged bed rest.  
Established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.  
Uncontrolled hypertension | Nausea, diarrhoea, venous thromboembolism, headache, dermatitis, eczema, very rarely hypersensitivity reactions including rash, pruritus, urticarial and angioedema. Also reported gastrooesophageal reflux, dyspepsia, abdominal pain, vomiting, constipation, flatulence, stomatitis, peripheral oedema, bone marrow suppression, alopecia. Severe allergic reactions including drug rash with eosinophilia and systemic symptoms (DRESS) have been reported | The absorption of strontium ranelate is reduced by food, milk and derivative products and therefore, strontium should be administered in-between meals. Given the slow absorption, strontium should be taken at bedtime, preferably at least two hours after eating |
| **Teriparatide** | • Treatment of osteoporosis in postmenopausal women and men at increased risk of fractures  
• Treatment of corticosteroid induced osteoporosis | Pre-existing hypercalcaemia, skeletal malignancies, metabolic bone disease including Pagets and hyperparathyroidism, previous radiation to the skeleton | Gastro-intestinal disorders (including nausea, reflux and haemorrhoids); palpitations, dyspnoea, headach, fatigue, depression, dizziness, vertigo, anaemia, increased sweating, muscle cramps, sciatica, myalgia, arthralgia | By subcutaneous injection daily |

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Atypical femoral fractures have been reported rarely with bisphosphonate therapy, mainly in patients receiving long-term treatment for osteoporosis.

- Atypical femoral fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture.
- Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered while they are evaluated, and should be based on an assessment of the benefits and risks of treatment for the individual.
- During bisphosphonate treatment, patients should be advised to report any thigh, hip, or groin pain. Any patient who presents with such symptoms should be evaluated for an incomplete femur fracture.
- The optimum duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of bisphosphonate therapy for individual patients, particularly after 5 or more years of use.

Adherence with bone protection treatments

The key factors that affect adherence to treatment are adverse events, lack of understanding of the condition / disease being treated, lack of information about the treatment (including potential side effects) and lack of follow up. The following measures should be implemented to help improve adherence with treatment:

- Ensure patients understand what is being treated (fracture risk/osteoporosis)
- Give patient detailed information about the treatment (how it works, potential side effects)
- Follow up the patient – a telephone follow up 3 to 6 months after starting treatment
- Encourage patients to contact GP practice if any side effects / problems

Additional local guidance:

Currently there is limited national guidance surrounding a number of key questions in relation to the ongoing management of osteoporosis. The following advice is based on current available guidance and local specialist opinion.

How long should treatment be continued and when to switch treatment?

Year 1 & 2: Patients should continue to receive the same treatment for osteoporosis during the initial 2 years of treatment even if they experience a fragility fracture. NICE guidance recommends that an unsatisfactory response following treatment for secondary prevention of osteoporosis is defined as occurring when a woman has another fragility fracture despite adhering fully to treatment to 1 year and there is evidence of a decline in BMD below her pre-treatment baseline, however, in some cases there will be no baseline BMD for reference. Treatment should not be routinely switched and a DEXA scan is not routinely recommended. It is important that patients should always be counselled regarding compliance.

Year 3, 4 & 5: if a patient has a fragility fracture after 2 years of being on the same treatment then consider changing therapy. If compliance is an issue with oral bisphosphonates then a suitable alternative could be IV bisphosphonate therapy. A DEXA scan is not routinely required at this stage. (Note if a change of therapy is considered appropriate then the patient will start at the beginning of year one of treatment again for the purpose of this guidance).
At year 6: Patient taking bisphosphonate therapy: advice from National Osteoporosis Society and National Osteoporosis Guideline Group Osteoporosis Clinical guideline for prevention and treatment (Supported by the Royal College of General Practitioners)

- Because of concerns over possible adverse effects of long-term bisphosphonate therapy treatment review should be performed after 5 years for oral treatment (and after 3 years for zolendronic acid)
- In view of the long half-life of alendronate it is possible to stop it for 2-3 years and still maintain its anti-fracture efficacy. Risedronate and ibandronate have a shorter half-life and therefore should be stopped for 1-2 years.
- The rationale for giving bisphosphonate holidays is that bone inertia develops with prolonged use and may lead to atypical fractures. However, there is no evidence that bone suppression gets more severe with time. The risks of atypical fractures appear to be higher in patients treated for longer duration with bisphosphonates but as yet there is no definitive causal relationship association between bisphosphonates and atypical fractures.
- Atypical fractures occur rarely and are not restricted to bisphosphonate users. They are subtrochanteric fractures, often bilateral and usually present with thigh pain. The fractures are commonly transverse and may be identified on X-rays and MRI scans. Continuation of treatment without the need for further assessment can generally be recommended in the following group as the benefits of osteoporotic fracture prevention outweigh the risks of atypical fractures:
  o High-risk individuals
    ▪ Those aged 75 years or more
    ▪ Those who have previously sustained a hip or vertebral fracture
    ▪ Those who are taking prednisolone
  o Individuals who sustain one or more low trauma fracture during treatment, after exclusion of poor adherence to treatment (for example less than 80% of treatment has been taken) and after causes of secondary osteoporosis have been excluded
  o If the total hip or femoral neck T-score is ≤ 2.5
- It is important to select the right patient. A DXA scan needs to be done before stopping bisphosphonates in patients who do not meet any of the above continuation criteria to ensure the BMD is improving and is no longer in the osteoporotic range. See below algorithm:

Patient taking other treatment:
The effects of other anti-osteoporosis treatments (denosumab, raloxifene, strontium, teriparatide) wear off more rapidly when treatment is stopped and there is no clear case for drug holidays in patients receiving these drugs. Review patient and ensure compliance with continuation of treatment. **If a patient has a new fracture, during their treatment break, they should be reassessed immediately.**
Calcium
Unnecessary calcium supplementation should be avoided given the recent data which suggest that calcium supplementation might raise MI risk. Patients who are at low risk of osteoporosis, have a normal bone density or who are osteopenic should be given dietary advice and only treated with calcium if overtly dietary deficient (ref EPIC-Heidelberg study from Heart 2012,98:920-92)

Other medicines which can increase the risk of osteoporosis:
- Taking corticosteroid tablets for other medical conditions for over three months
- Anti epileptic drugs
- Breast cancer treatments such as aromatase inhibitors
- Prostate cancer drugs that affect either the production of the male hormone testosterone or the way it works in the body.

Corticosteroid-induced osteoporosis:
To reduce the risk of osteoporosis doses of oral corticosteroids should be as low as possible and courses of treatment as short as possible. The risk of osteoporosis may be related to cumulative dose of corticosteroids; even intermittent courses can therefore increase the risk. The greatest rate of bone loss occurs during the first 6–12 months of corticosteroid use and so early steps to prevent the development of osteoporosis are important. Long-term use of high-dose inhaled corticosteroids may also contribute to corticosteroid-induced osteoporosis.

Patients taking (or who are likely to take) an oral corticosteroid for 3 months or longer should be assessed and where necessary given prophylactic treatment - those aged over 65 years or with a previous fragility fracture should routinely be offered bone protection as they are at greater risk. Patients over 40 but under 65 can be offered a DXA scan and should be considered for treatment if T-score < -1.5. It is difficult to interpret DXA scans and apply this guidance to patients under 40. Bisphosphonates should be used with caution in patients under 40 and pre-menopausal women. It is therefore suggested that specialist advice is sought with regards to these patients.

The therapeutic options for prophylaxis and treatment of corticosteroid-induced osteoporosis are the same:
- a bisphosphonate
- hormone replacement (HRT in women, testosterone in men [unlicensed indication])
- teriparatide (specialist use only)

Aromatase inhibitors and osteoporosis:
Aromatase inhibitors reduce oestrogen levels which increase the rate of bone turnover and can cause significant and very rapid bone density loss of up to 8 per cent per year in younger women.


Patients with early invasive breast cancer should have a baseline dual energy X-ray absorptiometry (DEXA) scan to assess bone mineral density if they:
- are starting adjuvant aromatase inhibitor treatment
- have treatment-induced menopause
- are starting ovarian ablation/suppression therapy

Do not offer a DEXA scan to patients with early invasive breast cancer who are receiving tamoxifen alone, regardless of pretreatment menopausal status.


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