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Welsh Medicines Resource Centre
Canolfan Adnoddau Moddion Cymru

Bulletin

"Independent prescribing information for NHS Wales"

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Management of post-menopausal osteoporosis

This bulletin focuses on the pharmacological management of patients with post-menopausal osteoporosis – both those with clinically evident disease (e.g. prior osteoporotic fracture) and those who are identified as being at high-risk of fracture. It does not discuss pre-menopausal, glucocorticoid-induced, or male osteoporosis.

Background

Osteoporosis is a progressive, systemic skeletal disease characterised by "low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture".[1] The condition may have a primary or secondary cause, or in some cases both. Primary osteoporosis, the more common form, describes post-menopausal, age-related, and idiopathic disease. Secondary osteoporosis has another identifiable cause, such as glucocorticoid therapy, or is linked to a separate disease process, such as hyperthyroidism.

One in three women over the age of 50 years is affected by osteoporosis and nearly half of all women will experience an osteoporotic fracture by the age of 70 years.[2] Fractures of the vertebrae, hips, and wrists are most typical but fractures of certain other bones, such as the ribs and pelvis, are not uncommon.

In Wales, more than 12,000 osteoporotic fractures occur annually; over 4,200 of these are hip fractures.[3] Hip fracture is associated with a significant increase in mortality and morbidity with up to 25% of patients dying within 1 year and 50% of survivors remaining incapacitated. Many other patients fail to ever regain their earlier levels of independence.[3] Vertebral fractures are more common but it is estimated that less than a third of cases are clinically diagnosed.[4] They are associated with significant morbidity, including pain, further fracture, and death.

Summary

- The burden of osteoporosis and associated morbidity and mortality is substantial (as discussed on page 1).
- Factors which contribute to a woman's risk of fracture are known, however, thresholds for intervention are the subject of ongoing expert debate. NICE guidance and other tools currently available for informing decisions about treatment are outlined on page 2.
- Appropriate lifestyle interventions should be considered in all women (see page 3).
- Where supplementation of calcium and/or vitamin D is required, adequate doses should be provided (see page 3).
- The most commonly used pharmacological therapies are discussed on pages 3 to 6. Relevant NICE guidance is also detailed where applicable. There are other therapies that may be used in specialist settings.

Diagnosis

Bone mineral density (BMD)

Osteoporosis is diagnosed on the basis of BMD (see Table 1).[2] BMD can be measured in several ways, but at present the use of dual energy x-ray absorptiometry (DXA) at the hip (femoral neck) and/or lumbar spine is considered to be the most reliable for diagnosis.[5]

Table 1. General diagnostic categories of BMD measured by DXA (standard deviation from mean).

Category	T-score (SD)
Normal	≥ -1
Low bone mass (osteopenia)	< -1 and > -2.5
Osteoporosis	≤ -2.5
Severe osteoporosis	≤ -2.5 *
*together with one or more fragility fractures	

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Assessing fracture risk – thresholds for intervention

Using BMD to predict fracture risk is similar to using blood pressure measurements to predict stroke.[5,6] BMD does not have a high sensitivity for predicting fractures, i.e. many women not diagnosed with osteoporosis are still at increased risk. Therefore, routine screening of all post-menopausal women using BMD measurement is not recommended. However, women identified with lower BMD are more likely to benefit from pharmacological (bisphosphonate) therapy.

Thresholds for intervention to prevent fractures should be informed by clinical risk factors, with or without BMD measurements. Some risk factors are independent of BMD (e.g. women with the same T-scores but different ages have different fracture risks), whereas others are associated with low BMD (e.g. prolonged immobility).[7]

Weighing the relative importance of separate, and sometimes interdependent risk factors can be difficult (e.g. the risk of falls is more important in older patients - see the section on preventative strategies).[3] An integrated diagnostic tool to predict an individual's 10 year absolute fracture risk (FRAX®) has been developed.[8] The 'risk calculator' encompasses age, gender, low body mass index ($\leq$19kg/m^2), previous fragility fracture, parental history of hip fracture, current use of corticosteroids (at any dose for $\geq$3 months), current smoking, and alcohol intake of $\geq$3 units daily. Secondary causes of osteoporosis are also taken into account and these are rheumatoid arthritis (RA), untreated hypogonadism, prolonged immobility, organ transplantation, type 1 diabetes, hyperthyroidism, gastrointestinal (GI) disease, chronic liver disease, and chronic obstructive pulmonary disease.

The probability of fracture can be calculated initially without BMD (and recalculated when BMD is known). Guidance from the National Osteoporosis Guideline Group (NOGG)[9] recommends whether reassurance, a DXA scan, or pharmacological therapy is appropriate on the basis of FRAX® results. The thresholds for therapy are set at a risk equivalent to that associated with prior fracture and, therefore rise with age. NOGG recommend that most women with a prior fragility fracture should be treated without DXA, but acknowledge that DXA is appropriate for younger post-menopausal women when considering pharmacological therapy.[9]

Current recommendations from the National Institute for Health and Clinical Excellence (NICE) for the primary or secondary prevention of fracture in patients diagnosed with osteoporosis are based upon age and T-score, together with the presence of the risk factors listed in Box 1.[10,11]

Box 1. Risk factors for fracture used in NICE guidance for assessment of postmenopausal osteoporosis.

Independent clinical risk factors for fracture

- parental history of hip fracture
- alcohol intake of $\geq$ 4 units daily
- presence of RA

Indicators of low BMD

- low BMI ($\leq$ 22 kg/m^2)
- presence of conditions such as ankylosing spondylitis, Crohn's disease, those resulting in prolonged immobility, or untreated menopause

To determine suitability for treatment in women who **have not** sustained a prior fracture, referral for DXA is recommended if: [10]

- aged < 65 years with an independent clinical risk factor for fracture **and** $\geq$ 1 indicator of low BMD.
- aged 65-69 years with an independent clinical risk factor for fracture.
- aged $\geq$ 70 years with an independent clinical risk factor for fracture **or** $\geq$ 1 indicator of low BMD.*

* *Exception 1.* In women aged $\geq$75 years with $\geq$2 independent clinical risk factors for fracture **or** $\geq$2 indicators of low BMD, a DXA scan may not be required if the clinician considers it inappropriate or unfeasible.

Women who **have** sustained a suspected fragility fracture should have a DXA scan to determine suitability for treatment ** (When patients present with a vertebral fracture it is important to exclude bony secondaries or other underlying causes such as myeloma.)

** *Exception 2.* In women $\geq$75 years, treatment can commence without DXA if the clinician considers it inappropriate or unfeasible.[11]

The thresholds for intervention to prevent fracture in women with post-menopausal osteoporosis have been the subject of much expert debate. NICE is undertaking further review of its published guidelines and is also developing guidance on assessment of fracture risk and prevention in individuals who are at high risk.

Preventative strategies

It is important to provide post-menopausal women with appropriate **lifestyle advice** that may include encouraging weight-bearing activity, promoting a healthy diet including adequate calcium and protein intake, and supporting smoking cessation. Vitamin D deficiency should also be addressed.[9,12]

Falls are a major cause of disability and are the leading cause of mortality due to injury in people aged over 75 years. Up to 90% of all hip fractures occur from a simple fall from standing height or less (the definition of a fragility fracture).[13] Individuals at higher risk can be identified by screening for balance, gait, or mobility problems; visual impairment; postural hypotension; impaired cognition, or depression; and for taking four or more medications (especially sedatives and antihypertensives).[12] Falls risk assessment and prevention plays a large role in the prevention of fracture and is incorporated in the standards of the National Service Framework for Older People.[14]

Studies of hip protectors to prevent fractures from falls have shown that they can marginally reduce the possibility of fractures in institutional care settings; they have not been helpful in other settings and long-term compliance is low.[15] Hip protectors cannot be prescribed on the NHS.

Pharmacological intervention

The aim of pharmacological management is the **primary prevention** of osteoporotic fractures in patients at high risk or **secondary prevention** in patients who have already sustained a fracture. Discussed below are those medicines that are considered to be the main interventions.[9-11]

Non-adherence and lack of persistence with oral treatment are significant problems associated with osteoporosis. At least 50% of patients discontinue their medication during the first year of therapy and 80% of patients do so by 3 years. However, many instances of inadequate adherence occur within the first 3 months of therapy.[16] NICE has recently published a clinical guideline that offers advice on best practice for involving patients in decisions about prescribed medicines and for supporting their adherence with therapies.[17] This is particularly relevant to managing osteoporosis.

Calcium and Vitamin D

Calcium and/or vitamin D supplements (at doses of ≥ 1 g and 800 IU, respectively)[9] should be considered for every patient treated for post-menopausal osteoporosis unless the clinician is confident that they have an adequate dietary calcium intake and are vitamin D replete.[10,11] Such supplementation given alone results in a decreased rate of hip fracture in frail, institutionalised, elderly women without previous fracture,[18] but does not reduce the risk of fracture among healthy post-menopausal women.[19] Further treatment is indicated to reduce fracture rates in relevant populations, as detailed below.

Bisphosphonates

Bisphosphonates have been shown to reduce fracture risk in patients with osteoporosis. They act by reducing the rate of bone resorption. Nitrogen-containing bisphosphonates, such as alendronate, risedronate, ibandronic acid, and zoledronic acid may suppress bone resorption more potently and by a different mechanism from that of etidronate.

For optimal treatment, oral bisphosphonates must be taken with a large glass of tap water on an empty stomach after an overnight fast. Food and other medication must be avoided for a specified period after dosing. Details vary slightly between the different medicines (see relevant Summary of Product Characteristics).

All oral bisphosphonates have the potential to cause adverse GI effects. Sometimes these can be severe – oesophagitis, oesophageal ulcers, stricture, and erosion have been reported. The incidence of such effects can be reduced if the patient is counselled to follow the dosing instructions carefully and to remain upright, sitting, or standing, for 30-60 minutes after dosing. Patients should also be advised to stop taking the tablets and to seek medical attention if they develop any symptoms of oesophageal irritation such as pain or difficulty swallowing, new or worsening reflux, or retrosternal pain.[20]

Box 2. Intolerance of oral bisphosphonates.

NICE defines intolerance of oral bisphosphonates as persistent severe upper GI disturbance warranting discontinuation, despite the correct dosing instructions being followed.[10,11]

A serious adverse effect of bisphosphonate therapy is osteonecrosis of the jaw. It occurs rarely or very rarely (<1/1000 to <1/10000) in patients taking oral therapy and is more commonly associated with higher-dose intravenous (IV) therapy used in cancer treatment. Patients should maintain good oral hygiene during and after treatment. Those with concomitant risk factors for osteonecrosis (such as cancer, or treatment with chemotherapy or corticosteroids) should receive remedial dental work before starting therapy.[20]

Alendronate

Weekly alendronate is first-line therapy for the primary and secondary prevention of post-menopausal osteoporotic fracture.[10,11] In women given alendronate for **primary prevention** the rate of vertebral fracture is significantly reduced. The rate of non-vertebral fracture has not been shown to be affected.[21]

NICE states that alendronate is a treatment option for the primary prevention of an osteoporotic fracture in post-menopausal women diagnosed with osteoporosis (T-score ≤-2.5):

- aged ≤65 years with an independent clinical risk factor and an indicator of low BMD.[10]
- aged 65-69 years with a clinical risk factor.
- aged ≥70 years with a clinical risk factor or an indicator of low BMD (see **Exception 1*).

When used for **secondary prevention**, alendronate has been shown to significantly reduce the incidence of both vertebral and non-vertebral fracture.[21] NICE recommends use of alendronate for the secondary prevention of osteoporotic fractures in post-menopausal women with T-score ≤-2.5 (see ***Exception 2*).[11]

Risedronate

There is an absence of evidence of a significant decrease in the fracture rate at any site in women given risedronate for **primary prevention**.[22] NICE does recommend risedronate as an alternative to alendronate for primary prevention if the woman is unable to comply with the special instructions for taking alendronate, or if she has a contra-indication to, or is intolerant of alendronate.[10] The woman must also have a combination of T-score, age, and other independent risk factors for fracture as shown in Table 2 (see **Exception 1*).[10]

Table 2. T-score at (or below) which risedronate is recommended for **primary prevention.**

	Number of independent risk factors		
Age (years)	0	1	2
65-69	n/a	-3.5	-3.0
70-74	-3.5	-3.0	-2.5
≥75	-3.0	-3.0	-2.5

When used for **secondary prevention**, risedronate reduces vertebral and some non-vertebral fractures. This includes fractures of the hip but not those of the wrist.[22] NICE recommends the use of risedronate as an alternative to alendronate in the same circumstances as for primary prevention but following the instructions in Table 3 (see ***Exception 2*).[11]

Table 3. T-score at (or below) which risedronate is recommended for **secondary prevention**.

	Number of independent risk factors		
Age (years)	0	1	2
50-54	n/a	-3.0	-2.5
55-59	-3.0	-3.0	-2.5
60-64	-3.0	-3.0	-2.5
65-69	-3.0	-2.5	-2.5
≥70	-2.5	-2.5	-2.5

As can be seen from the criteria above, there may be some patients who will qualify for treatment with alendronate, find themselves unable to tolerate the agent, and then be ineligible for further treatment until their bone health deteriorates. This element of the NICE guideline is controversial; it may lead to difficult decisions for patients and ethical dilemmas for prescribers since such women remain at increased risk of fracture.

Etidronate

Alendronate and risedronate are considered the bisphosphonates of choice in osteoporosis but etidronate may be considered when those agents are unsuitable or not tolerated.[20] When used for primary prevention, etidronate (administered cyclically with calcium carbonate over 90 days) has not been shown to reduce fractures at any site.[23] When used for secondary prevention vertebral, but not non-vertebral, fracture rates are reduced with cyclical etidronate.[23]

NICE recommends the use of etidronate in both **primary** and **secondary prevention** of osteoporosis in the same circumstances as risedronate but notes that clinicians and patients should balance the effectiveness and tolerability profiles of the two medicines.[10,11]

Zoledronic acid ▼ and Ibandronic acid ▼

Zoledronic acid has been shown to reduce vertebral and hip fractures.[24] It is available as an annual IV infusion. Ibandronic acid has been shown to reduce the risk of vertebral but not non-vertebral fracture.[25] It is available as a once-monthly oral formulation and as a three-monthly IV injection.

For those unable to tolerate oral therapy, IV dosing is an effective alternative that has the advantage of eliminating adherence problems. It is not currently clear how the cost effectiveness of ibandronic acid and zoledronic acid preparations compare with other, less expensive options such as weekly alendronate. Although there is evidence that a switch to weekly formulations rather than daily treatment with oral bisphosphonates results in improved adherence,[26] there is conflicting evidence from numerous small studies as to whether moving to less frequent treatment improves this further.

Strontium ranelate ▼

There is evidence that treatment with strontium ranelate reduces vertebral fracture rates in post-menopausal women with established osteoporosis and/or prevalent vertebral fractures. There is also some evidence to support a reduction in grouped non-vertebral fractures in these groups.[27]

Strontium ranelate is recommended by NICE for the **primary prevention** of post-menopausal osteoporosis if the woman is unable to comply with the special instructions for taking alendronate and either risedronate or etidronate, or if there is a contraindication to, or if she is intolerant of alendronate, and either risedronate or etidronate.[10] The woman must also have a combination of T-score, age, and number of independent risk factors for fracture as shown in Table 4.[10]

Table 4. T-score at (or below) which strontium ranelate is recommended for **primary prevention**.

	Number of independent risk factors		
Age (years)	0	1	2
65-69	n/a	-4.5	-4.0
70-74	-4.5	-4.0	-3.5
≥75	-4.0	-4.0	-3.0

For **secondary prevention**, NICE recommends strontium ranelate as for primary prevention but following the criteria in Table 5. In women aged ≥75 years with ≥1 independent clinical risk factor for fracture or ≥1 indicator of low BMD, a DXA scan may not be required if it is clinically inappropriate or unfeasible.[11]

Table 5. T-score at (or below) which strontium ranelate is recommended for **secondary prevention**.

	Number of independent risk factors		
Age (years)	0	1	2
50-54	n/a	-3.5	-3.5
55-59	-4.0	-3.5	-3.5
60-64	-4.0	-3.5	-3.5
65-69	-4.0	-3.5	-3.0
70-74	-3.0	-3.0	-2.5
≥75	-3.0	-2.5	-2.5

Strontium is taken daily as a single 2 gram sachet of powder dissolved in water, usually at night at least two hours after food or, if taken during the day, in the middle of a 4 hour fast.[20]

The most common adverse effects of strontium ranelate are nausea and diarrhoea, although this does not appear to affect adherence over a number of years.[27] Rarer effects include venous thromboembolism and severe allergic reactions.[20] Drug rash with eosinophilia and systemic symptoms (DRESS), which can be fatal, has been reported. Patients should be counselled to discontinue treatment and contact their doctor immediately if a skin rash develops.[20]

Raloxifene

Raloxifene is a selective oestrogen reuptake modulator (SERM). SERMs mimic the action of oestrogen on certain organs or tissues in the body while simultaneously blocking the effect of oestrogen in others. The use of raloxifene for post-menopausal osteoporosis results in a significant reduction in vertebral, but not non-vertebral, fracture rates.[28]

NICE does not recommend the use of raloxifene in any patients for **primary prevention**.[10] For **secondary prevention** it recommends that raloxifene is a therapeutic option in the same circumstances as strontium ranelate. In deciding between these two medicines, clinicians and patients should balance their overall effectiveness against their tolerability and other effects in the individual.[11]

The risk of venous thromboembolism is increased with the use of raloxifene; however, the risk of oestrogen-receptor-positive breast cancer is decreased.[28] Its use does not result in the reduction of menopausal vasomotor symptoms and may in fact increase these.[20] The medicine may be taken at any time of day without restriction.

Teriparatide▼ (Recombinant Human Parathyroid Hormone (1-34))

Human parathyroid hormone (hPTH) stimulates bone formation and resorption and can either increase or decrease bone mass depending on the mode of administration. (High levels of hPTH in hyperparathyroidism cause significant bone loss.) Daily injections cause only transient increases in serum hPTH concentration and induce an increase in bone mass.[29]

Teriparatide▼ comprises the first 34 amino acids of hPTH, which produce its chief biologic effects.[30] Treatment with teriparatide, compared with placebo, reduces the risk of vertebral fractures and grouped non-vertebral fractures in post-menopausal women with osteoporosis.[30] It is administered by daily subcutaneous injection with a pen device, similar to an insulin pen injector, into the abdomen or thigh and may be used for a maximum of 24 months.

NICE does not recommend the use of teriparatide in any patients for **primary prevention**.[10] For **secondary prevention** it recommends that teriparatide is used in women with severe osteoporosis who cannot comply with the special instructions for taking alendronate and either risedronate or etidronate, or who have a contraindication to, or are intolerant of alendronate and either risedronate or etidronate, or have had an unsatisfactory response to alendronate, risedronate, or etidronate.[11]

The woman must also be:

- aged 55-64 years and have a T-score of ≤-4.0 and >2 fractures.
- aged ≥ 65 years and have a T-score of ≤-4.0, or a T-score of ≤-3.5 plus >2 fractures.

The Summaries of Product Characteristics should be consulted for full prescribing information

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