



Osteoporosis – diagnosis, treatment and management

BACKGROUND Osteoporosis is common, asymptomatic and usually undetected until a fracture occurs. Fracture, particularly hip fracture, can be associated with significant mortality, morbidity and loss of independence.

OBJECTIVE This article presents a practical case based approach to identify and manage osteoporosis.

DISCUSSION The major risk factors for osteoporosis in men and women are known, and case finding by dual X-ray absorptiometry and treatment with effective medications are subsidised by the commonwealth government. At the menopause, symptomatic women considering oestrogen replacement should assess their individual risk of osteoporosis, cardiovascular events and breast cancer. Men also develop osteoporosis and this should be on the health agenda along with cardiovascular disease, prostate and colon cancer, and diabetes. Treatment should include supplemental calcium and occasionally vitamin D. There is strong evidence for the benefits of bisphosphonates, the selective oestrogen receptor modulators and oestrogen replacement.

Osteoporosis is asymptomatic until it strikes people down. It has been estimated that in the average Australian general practice of 1000 patients, there are approximately 100 patients at risk of having or developing osteoporosis. Unfortunately, people at risk (and their doctors) often don't recognise this risk. Fortunately, we do have evidence based guidelines for diagnosis and effective treatment.

Case history – Betty

Betty is 78 years of age and lives with her partner Eric. Over the past few years Betty has become a bit forgetful but she functions perfectly well in her environment and visits, and is visited by, her friends and family. One day at the supermarket she slips, falls and breaks her hip. The hip is pinned but in hospital Betty is confused, mobilisation is difficult and she is discharged to a private hospital for rehabilitation. Betty never leaves institutional care and dies 8 months later in a nursing home.

The burden of osteoporosis

Betty's tale is a common one. Older people, particularly older women, often have osteoporosis, are prone to falls, break hips, and are susceptible to complications that kill or leave them dependent on others. The cost to the individual and family is obvious – loss of independence and the loss of a loved one and the cost to the community are considerable (*Table 1*).

The case for case finding

It is clear that 30 years ago Betty was very likely to develop osteoporosis. She had several major risk factors



Patrick Phillips,
MBBS, MA (Oxon),
FRACP, MRACMA,
GradDipHealthEcon,
is Senior Director of
Endocrinology, The
Queen Elizabeth
Hospital, Woodville,
South Australia.

Jody Braddon,
BPharm, is a clinical
pharmacist, Drug and
Therapeutics
Information Service,
South Australia, and
National Prescribing
Service Therapeutics
Advice and Information
Service (SITE 6).

Table 1. Australian burden of osteoporosis, 2003²³

- Lifetime risk of osteoporotic fracture after 50 years of age
 - women 42%
 - men 27%
- 2 million Australians affected by osteoporosis
- 20 000 hip fractures per year in Australia (increasing by 40% each decade)
- Total costs relating to osteoporosis Australia are \$7.4 billion per year of which \$1.9 billion are direct costs

Table 2. Risk factors in osteoporosis

Those that render the patient eligible for DEXA rebate:

- Prolonged glucocorticoid therapy
- Conditions associated with excess glucocorticoid secretion
- Male hypogonadism
- Turner syndrome
- Amenorrhoea lasting more than 6 months before the age of 45 years
- Primary hyperparathyroidism
- Chronic liver disease
- Chronic renal disease
- Proven malabsorption disorders
- Rheumatoid disorders
- Conditions associated with thyroxine excess

Others including:

postmenopause, family history, slight body build (BMI <18), previous low trauma fracture, smoking, high alcohol intake

(Table 2) including impending perimenopause and family history, with her mother having suffered wrist and vertebral fractures. She was of slender stature (height 178 cm, weight 60 kg, body mass index [BMI] 18.9 kg/m²) and was a smoker. Unfortunately, even if she or her doctor had recognised her risk, there was little that could be done 30 years ago. X-rays could identify fractures but were insensitive in detecting osteoporosis. The only recognised preventive treatment in the 1970s was oestrogen replacement but this was not widely prescribed because of concern about endometrial cancer.

In 2004 it is a different story. The Osteoporosis Foundation suggests it is cost effective to find and treat high risk postmenopausal women. The recommendations are that women not taking oestrogen replacement should have bone mineral density

assessed at the age of 60 years, if they have a fracture after the age of 40 years and/or have a family history of osteoporotic fracture, weigh less than 58 kg or smoke. There are no similar guidelines for case finding in men despite the fact that osteoporotic fractures are common in older men, climbing after the age of 80 years. However, there is agreement on the major risk factors for osteoporosis in men and women (Table 2) and the commonwealth government has acknowledged the importance of these risk factors by subsidising testing by dual X-ray absorptiometry (DEXA). The recommended response to DEXA measurement is outlined in Figure 1.

Case history – Elizabeth

Betty's daughter Elizabeth, 55 years of age, presents with symptoms of hot flushes, irritability and loss of energy. Her menopausal symptom score suggests oestrogen deficiency. Elizabeth clearly has one of the osteoporotic risk factors (family history) and, like her mother, has a slight build (height 176 cm, weight 58 kg, BMI 18.7 kg/m). She stopped smoking at 40 years of age and apart from a range of health foods (including phyto-oestrogens) she takes no medication. This visit was prompted by one of her friends who had similar symptoms that were controlled by oestrogen. Other friends have told her that oestrogen causes breast cancer and heart attacks. She asks your advice.

Osteoporosis risk at menopause

The Women's Health Initiative Study¹ (WHI) has had a major impact on the use of oestrogen to reduce osteoporosis risk. The 'good news' was that for the first time continuous oestrogen/progestin (EP [conjugated equine oestrogens 0.625 mg/day, medroxyprogesterone acetate 2.5 mg/day]) was shown to reduce fractures. The 'bad news' was that combined EP was associated with an increased risk of breast cancer and cardiovascular events (relative risk 1.2 and 1.3 respectively).¹

Perhaps the best advice to Elizabeth is to consider her individual benefits and risks. The immediate likely benefit is control of her distressing symptoms. Longer term there is the benefit of reduced fractures and the risk of increased breast cancer and cardiovascular events. Right now these absolute benefits and risks are not high. Unless Elizabeth has other risk factors, the likelihood of osteoporotic fracture, breast cancer or a cardiovascular event is approximately 0.3–0.4% per year. This would be decreased (fracture) or increased (breast cancer, cardiovascular event) by approximately

0.08% per year by EP therapy (her absolute risk 0.3% x the relative increase of 0.25). Elizabeth might like to check her risk herself by accessing various independent websites (see *Resources*).

Usually in the short term the perceived benefits for symptomatic women outweigh the perceived risks. Moreover the risk of breast cancer in the WHI occurred in previous users of oestrogen replacement and only became significant after several years, suggesting the relative safety of short term use. This does not apply to women with clinical coronary heart disease (angina, history of coronary event) where the risk of cardiovascular mortality appears to increase even during the first year of treatment.²

Elizabeth might also consider stopping some or all of her health foods which have unknown risks, benefits and composition and only take medications where risks, benefits and composition are known. If Elizabeth is one of the 25% of perimenopausal women who have had a hysterectomy, it is worth noting that the WHI study using unopposed oestrogen continues and that the risks of unopposed oestrogen may be less than those for combined oestrogen and progestin.¹

Elizabeth might also consider taking supplemental calcium and checking bone mineral density (BMD) since she is in the high risk category. The BMD results might prompt further assessment and intervention. Calcium intake should ideally be assessed in all patients with, or who are at risk of, osteoporosis, and supplementation should be considered where intake is inadequate. The recommended daily calcium intake is 800 mg for adults, 1100–1200 mg during pregnancy and lactation and 1500 mg in postmenopausal women.³

Response to osteoporotic fracture

Elizabeth took EP therapy for approximately 4 years. She then reduced and ceased treatment over 4 weeks. She decided to continue taking her health foods but added a calcium supplement. Now aged 59 years, Elizabeth asked for a referral to a physiotherapist. At an impromptu netball game she tripped and broke her left ankle. Now the cast is off she wants to strengthen both her left and right ankles. As you write the referral it strikes you that her fracture occurred with minimal trauma (from standing height) and is an indicator of osteoporosis. How should you respond?

Fracture risk is dramatically increased in those who have had a fracture (*Figure 2*). The commonwealth government acknowledges this by subsidising BMD and

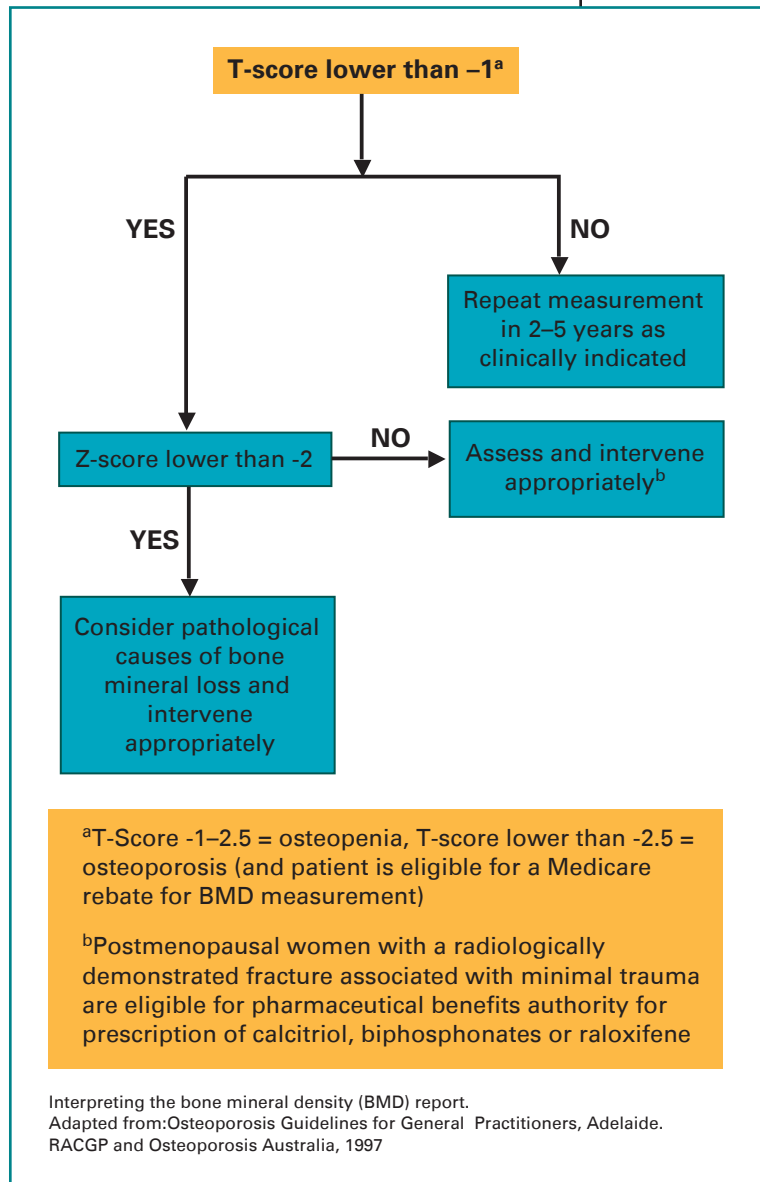


Figure 1. Response to DEXA

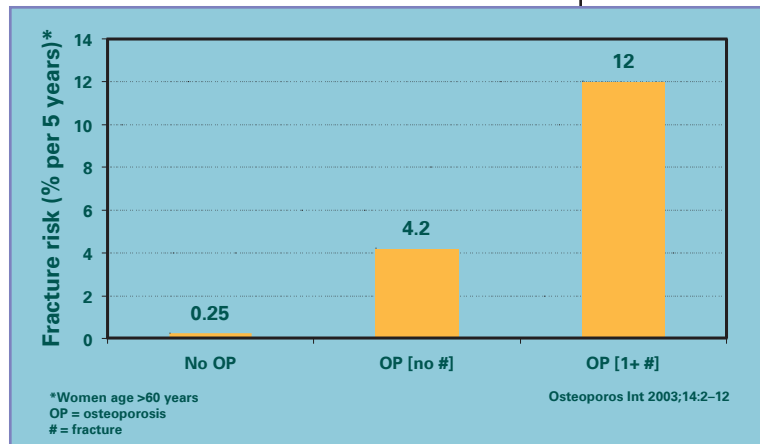


Figure 2. Fractures and future fracture risk

anti-

Table 3. Medications increasing fall and fracture risk

Medication	Danger
Osteolytics	
Anticonvulsants/ alcohol	Bone loss/ataxia
Glucocorticoids	Central hypogonadism Calcium malabsorption Calciuresis
Excess thyroxine	Bone resorption
Loop diuretics	Calciuresis
Long term heparin	Bone loss
Ataxiagenics	
Psychotropics	Neurological: confusion, ataxia, sedation Cardiovascular: postural hypotension
Hypotensives	Postural hypotension
Stopping some drugs may be as important in treatment as starting others	

osteoporotic medications for both men and women with a history of fracture associated with minimal trauma.

Most osteoporotic fractures are vertebral and are unrecognised by the people affected or by their health professionals. The fracture caused by minimal trauma should prompt assessment of medical causes of osteoporosis and consideration of lifestyle and medication changes that might reduce progression of osteoporosis and further fractures.

In those with osteoporosis (BMD T-scores 2.5 standard deviations or more below the young normal mean) a lateral X-ray of the spine will often show a previously unrecognised fracture (vertebral height reduction of 20% or more in comparison to the height of another part of that vertebra or of an adjacent vertebra – *Figure 3*). Both vertebral and nonvertebral fractures should prompt assessment, intervention and monitoring. A BMD Z-score two standard deviations or more below the age and sex matched mean strongly suggest an underlying pathological cause of bone loss and should be followed up. Whatever the BMD, calcium level, renal and liver function should be checked.

Assuming Elizabeth has no underlying cause requiring specific treatment your response might include:

- reinforcing her decision to increase her strength and reduce her risk of future fracture
- evaluating and managing her risk factors where possible including reviewing her current medication in

case she is taking something that might increase the risk of falls or fracture (*Table 3*)

- considering medications that might reduce her fracture risk.

Osteoporosis in residential care

With any luck Elizabeth will retain her independence and mobility but if she were dependent or bed/chair bound, three interventions might reduce her risk of fracture:

- hip protectors (*Figure 4*) – these halve fracture risk immediately and have no side effects)
- vitamin D supplements – Australians get vitamin D by sunlight dependent skin vitamin D synthesis. Deficiency is common in those confined indoors or in patients who ‘cover up’ for cultural reasons (especially in those with pigmented skin which absorbs UV light and reduces vitamin D synthesis)
- vitamin D levels should be assessed in patients who may be at risk of deficiency and either increased sunlight exposure or vitamin D supplementation initiated in the presence of a deficiency
- review medication – many patients in residential care are often taking one or more medications that increase fall and fracture risk (*Table 3*).

Osteoporosis – in men

Although osteoporosis and osteoporotic fractures are more common in women - partly because of lesser bone strength and partly because there are more older women - men get osteoporosis and osteoporotic fractures as well (*Table 1*).

Osteoporosis should be on the health agenda along with risk of cardiovascular disease, prostate and colon cancer and diabetes. The risk of clinical fracture climbs after 75 years of age but osteoporosis and subclinical fractures (vertebral) may precede this by many years. The major risk factors for osteoporosis in men are hypogonadism, corticosteroids, excess alcohol consumption and multiple myeloma.

A man with osteoporotic risk factors or osteoporotic fracture is eligible for similar subsidised assessment and medication as a woman (BMD,

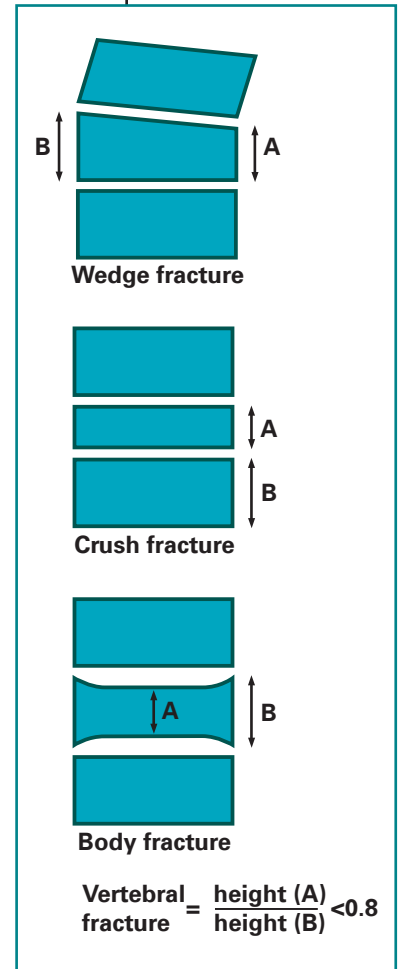


Figure 3. Vertebral fractures

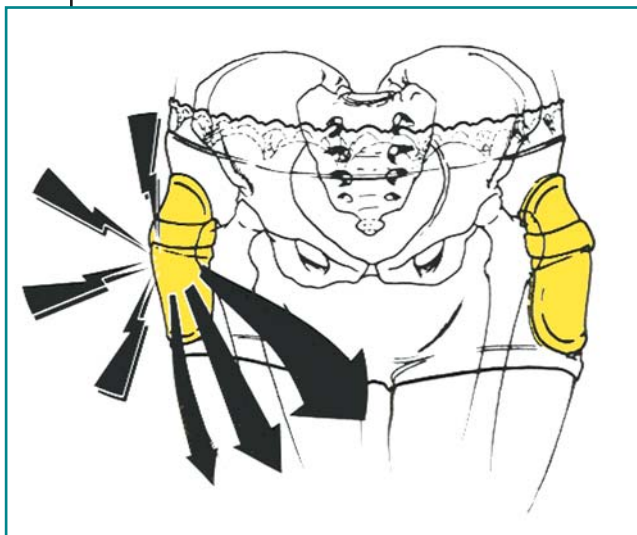


Figure 4. Hip protectors

Osteoporosis treatment options

Choosing between options

The following factors should be considered when deciding on the most appropriate treatment for individual patients:

- Evidence for efficacy: the gold standard trial is a randomised controlled trial with fracture rates as the endpoint. *Table 4* summarises evidence for the main osteoporosis treatments available in general practice today
- Availability: the greatest benefits in prevention of fractures in clinical trials have been in post-menopausal women with existing vertebral fractures. As a result most of the currently available treatments are only subsidised through the Pharmaceutical Benefits Scheme (PBS) for patients who have established osteoporosis with evidence of a fracture due to minimal trauma. The only agent subsidised through the PBS for prevention of osteoporosis in patients with no fracture history is oestrogen replacement therapy
- Concurrent medical conditions: eg. in a patient with oesophageal stricture a bisphosphonate would be contraindicated and oestrogen replacement therapy (ERT) is not recommended in patients with established coronary heart disease or with a history of venous thromboembolism or breast cancer
- Adverse effect profile of the drug or drug class (see below)
- Potential for drug interactions (see below).

Current options

Calcium and vitamin D

As described above, calcium intake should be assessed in all patients with, or who are at risk of, osteoporosis and calcium supplementation given where appropriate. In addition, vitamin D supplementation may be necessary for some patients.

Bisphosphonates

Bisphosphonates are generally considered first line therapy for the treatment of osteoporosis. There are currently three bisphosphonates available in Australia for the treatment of osteoporosis – etidronate, alendronate and risedronate. Alendronate and risedronate are generally preferred in osteoporosis because the evidence for efficacy is more extensive and the treatment schedule is less complex than etidronate. There is little to choose between alendronate and risedronate. Both

Table 4. Evidence for current osteoporosis therapies

Drug	Evidence of fracture reduction in clinical trials
Calcium and vitamin D	Trial results conflicting – one trial found reduction in hip fractures in elderly institutionalised women taking the combination. ²⁴ In trials of newer agents calcium supplementation is routinely given to all patients and vitamin D supplementation is given where vitamin D levels are low ²⁵
Bisphosphonates	Evidence shows reduction in vertebral fractures for etidronate, ²⁶ alendronate, ²⁷ and risedronate, ²⁸ and a reduction in hip fractures for alendronate ²⁷ and risedronate ²⁹ in patients with a fracture history. Evidence in patients with no previous history of fracture is limited but a reduction in fractures has been seen with alendronate in patients with T-score ≤ -2.5 . ^{30,31}
Raloxifene	Evidence shows reduction in vertebral fractures in women with a fracture history and in women without fracture history who met the WHO criteria for osteoporosis ⁷
Calcitriol	Evidence shows reduction in vertebral fractures ^{32,33} but studies are limited. Substantially less evidence than for bisphosphonates and raloxifene
ERT	Data from the WHI study showed a significant reduction in overall fractures with ERT, but this study was stopped early due to an unfavourable risk/benefit ratio. ¹ Most other controlled trials with ERT have assessed BMD and not fracture incidence as an endpoint.

gonadal hormone replacement if deficient, bisphosphonate, calcitriol). One in four hip fractures occur in men, and fractures result in the same morbidity, mortality and loss of independence as in women.

drugs have excellent evidence particularly for reducing fracture risk in patients with a history of fracture. Both drugs require strict administration instructions to ensure efficacy and safety and both are available in either a once per day tablet or a once per week preparation.

Bisphosphonates are contraindicated in patients with abnormalities of the oesophagus that delay oesophageal emptying such as stricture or achalasia, in patients who are unable to stand or sit upright for at least 30 minutes after taking a tablet, and in patients with hypocalcaemia. There has been suggestion that risedronate may have less risk of upper gastrointestinal effects,³ however, further studies are clearly needed to confirm this. Alendronate is excreted unchanged mainly by the kidney and there is limited data in patients with renal impairment. It is generally advised that alendronate and risedronate be avoided in patients with severe renal impairment (eg. creatinine clearance <35 mL/minutes).

The main interaction is binding interactions in the gut decreasing absorption and therapeutic benefit of bisphosphonates (eg. food, beverages other than water, calcium supplements, antacids, iron, magnesium, aluminium, zinc and other oral medications). To avoid these binding interactions patients need to take alendronate and risedronate with plain water only, after an overnight fast and at least 30 minutes before any other food, drink or other medication.

Long term effects on bones due to skeletal retention of the bisphosphonates are yet to be determined.⁴ There are theoretical risks of long term inhibition of bone turnover and mineralisation abnormality.⁵ Alendronate has been shown to be safe and effective for a period of 7 years,⁶ but longer term data are not yet available.

Alendronate and risedronate can be given as a once per week preparation. While there is no convincing evidence of better tolerance with this preparation it may be favourable for some patients to improve compliance. Alendronate, risedronate and etidronate with calcium are only subsidised through the PBS on authority prescription for initial and continuing treatment of established osteoporosis in patients with fracture due to minimal trauma.

Raloxifene (Evista®)

Raloxifene is a selective oestrogen receptor modulator which acts as an oestrogen agonist on bone and liver and an oestrogen antagonist on both uterine and breast tissue. Raloxifene appears to be less effective at increasing BMD than ERT, but has been demonstrated to reduce the risk of vertebral fractures in women with osteoporosis.⁷ In the MORE trial, raloxifene decreased the risk of estrogen

receptor positive breast cancer.⁸ In addition, there was no increase in cardiovascular events with raloxifene compared to placebo and in a subpopulation of patients at high risk of cardiovascular disease, events decreased.⁹ Note that breast cancer and cardiovascular outcomes were not primary endpoints in the MORE trial⁹ and further studies are needed to confirm these findings.

Raloxifene may be useful to treat established osteoporosis, particularly in younger women (<60 years) or where bisphosphonates cannot be used (eg. because of gastrointestinal side effects). It may be particularly useful for women concerned about the risk of breast cancer with ERT. Raloxifene has a similar risk of thromboembolism to ERT, does not relieve the symptoms of menopause and hot flushes may occur. Raloxifene is contraindicated in women with active or a past history of venous thromboembolic events. It is also contraindicated in men, premenopausal women and in pregnancy.¹⁰ Raloxifene is only subsidised through the PBS for initial and continuing treatment for established postmenopausal osteoporosis in patients with fracture due to minimal trauma.

Calcitriol (Citrihexal®, Kosteo®, Rocaltrol®, Sitriol®)

Calcitriol is the biologically active metabolite of vitamin D. Evidence for calcitriol in osteoporosis treatment is less robust than evidence for bisphosphonates and raloxifene and it would be generally considered a third line agent for the treatment of osteoporosis where other treatments are contraindicated or not tolerated.

The main risk with calcitriol is the potential for hypercalcaemia. An adequate supply of calcium is needed for efficacy and calcitriol should be given against a background intake of 800–1000 mg of elemental calcium per day.¹¹ This should be achieved preferably through dietary modification, and calcium supplements only considered when dietary intake remains clearly inadequate. Serum calcium should be monitored at the start of therapy, at 4 weeks and at 2–3 monthly intervals thereafter.

For osteoporosis, calcitriol is only subsidised through the PBS for initial and continuing treatment for established postmenopausal osteoporosis in patients with fracture due to minimal trauma.

Oestrogen replacement therapy

As described above it is important to discuss the benefits and harms of ERT and its alternatives for preventing osteoporotic fractures. Oestrogen replace-

ment therapy may be considered in postmenopausal women who are at low risk of cardiovascular disease or breast cancer to reduce the risk of fractures.

Tibolone

Tibolone is a synthetic steroid with weak oestrogenic, progestogenic and androgenic properties. It is thought to act as an oestrogen on the vagina, bone and thermoregulatory centres in the brain and have progestogenic and antioestrogenic effects on the breast and endometrium³. Tibolone has been shown to relieve symptoms associated with menopause and therefore is an alternative to ERT in this setting. Unlike ERT however, there is a lack of large long term trials to assess safety and efficacy with tibolone, so whether it has similar risks to ERT in the long term is currently unclear. Tibolone has been demonstrated to prevent postmenopausal bone loss and increase BMD, however, currently no trials have evaluated whether tibolone decreases the risk of fracture. Further trials are clearly needed to determine the role for tibolone in the prevention and treatment of osteoporosis.

Other therapies

Anabolic steroids

Anabolic steroids should not be used in osteoporosis management in women because of a lack of documented efficacy in preventing fractures and the risk of serious adverse effects.¹²

Complementary therapies

A number of women have turned away from ERT to complementary therapies (eg. Promensil®, Remifemin®, wild yam) in an attempt to relieve the symptoms of menopause. Of concern is the lack of studies assessing whether these agents are beneficial for prevention and treatment of osteoporosis. Controlled studies assessing whether any of these therapies can reduce fracture risk are currently lacking and, hence, their use cannot be recommended for osteoporosis management.

Corticosteroid induced osteoporosis

Doses equivalent to oral prednisolone 7.5 mg per day for 3 months or more are thought to be associated with bone loss. To minimise the risk of corticosteroid induced osteoporosis use the lowest effective dose of corticosteroids for the shortest possible time, use topical or inhaled products where possible, supplement with calcium and vitamin D if required, and implement strategies to minimise the risk of falls.

In men, assess for the presence of hypogonadism and treat with testosterone when necessary. There is some evidence that calcium plus vitamin D,¹³ calcitriol,¹⁴ HRT,^{15,16} etidronate,^{17,18} risedronate¹⁹⁻²¹ and alendronate²² can prevent the bone loss associated with corticosteroid therapy. However, trials assessing efficacy in fracture prevention are limited. Some recent studies suggest risedronate decreases risk of vertebral fractures in patients commenced on high dose corticosteroids.¹⁹⁻²¹ Therefore, if drug therapy is needed to treat corticosteroid induced osteoporosis a bisphosphonate would be first line therapy, used in conjunction with calcium and vitamin D where necessary.

SUMMARY OF IMPORTANT POINTS

- Risedronate is available on RPBS prescription for patients with osteoporosis (T-score -1 to -20) who have been taking prednisolone 7.5 mg per day or more for 3 months.
- Osteoporosis is silent, lethal, measurable and treatable and should be actively sought in men and women with risk factors for osteoporosis and fracture.
- At menopause, women should assess their individual risks of osteoporosis, cardiovascular events and breast cancer when considering oestrogen replacement.
- A fracture with minimal trauma should prompt assessment of potential underlying conditions and lifestyle and medication changes to reduce future progression of osteoporosis and fracture risk.
- Patients at risk of developing osteoporosis and those with established osteoporosis should receive supplemental calcium and in some cases, vitamin D.
- The bisphosphonates (alendronate and risedronate), raloxifene and oestrogen replacement have been shown to reduce future fracture risk. The evidence for other osteo protective medications is less robust.

Resources

- Osteoporosis Australia Risk Test
www.osteoporosis.org.au/html/aboutosteomain.php#areyouatrisk
 International Osteoporosis Foundation Risk Test
www.osteofound.org/osteoporosis/risk_test.html
 National Osteoporosis Foundation (USA)
www.nof.org/prevention/risk.htm
 Patient education page 140 this issue.

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Email: patrick.phillips@nwahs.sa.gov.au

AFP