

Guidelines for the treatment of postmenopausal osteoporosis for general practitioners

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BACKGROUND Osteoporosis Australia has been committed to the education of general practitioners and the community with a series of updated guidelines on the management of osteoporosis. Since the last series was published in *Australian Family Physician* (August 2000), there have been further advances in our understanding of the treatments involved in both prevention of bone loss and the management of established osteoporosis.

OBJECTIVE This article represents updated guidelines for the treatment of postmenopausal osteoporosis to assist GPs identify those women at risk and to review current treatment strategies.

DISCUSSION Osteoporosis and its associated problems are major health concerns in Australia, especially with an aging population. While important principles of management are still considered to be maximising peak bone mass and preventing postmenopausal bone loss, new clinical trial data about drugs such as the bisphosphonates, raloxifene and oestrogen have recently become available and the relative role of various agents is gradually becoming clearer. The use of long term hormone replacement therapy has mixed risks and benefits that requires individual patient counselling.

What is osteoporosis?

Osteoporosis is defined as a skeletal disorder characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to an increase in bone fragility and susceptibility to fracture.^{1,2} Clinically, osteoporosis is synonymous with low bone density. An osteoporotic fracture is one that occurs with minimal or no trauma, ie. a fall from standing height or less.

Although it is generally recommended that interventions are appropriate for women with bone densities more than 2.5 standard deviation (SD) units below the young normal mean (T-score <-2.5), preventive measures should be considered before that level is reached. Accordingly,

the following intervention guidelines are suggested (Figure 1):

- consider preventive measures in postmenopausal women with significant osteopenia, ie. bone mineral density (BMD) values less than 2.0 SD below the young normal mean (T-score between -2.0 and -2.5) as osteoporosis is likely with time. As mildly osteopenic women (T-score between -1.0 and -2.0) aged 50-60 years have a low absolute risk of fracture, it is difficult to justify treatment for potentially large numbers of women³
- strongly recommend treatment in postmenopausal women with osteoporosis, ie. BMD values less than 2.5 SD below the young normal mean (T-score <-2.5) and in patients with osteoporotic fractures.

Can osteoporosis be prevented?

Although medical intervention may be required in some individuals, patients should understand that it is important to:

- maximise peak bone density in childhood and adolescence
- maintain bone density throughout adult life.

Osteoporosis prevention programs should:

- promote a diet with adequate calcium content and advocate regular weight bearing exercise in children and adolescents
- exercise in women over the age of 30 years should include resistance training to improve muscle mass, strength and balance and should be performed

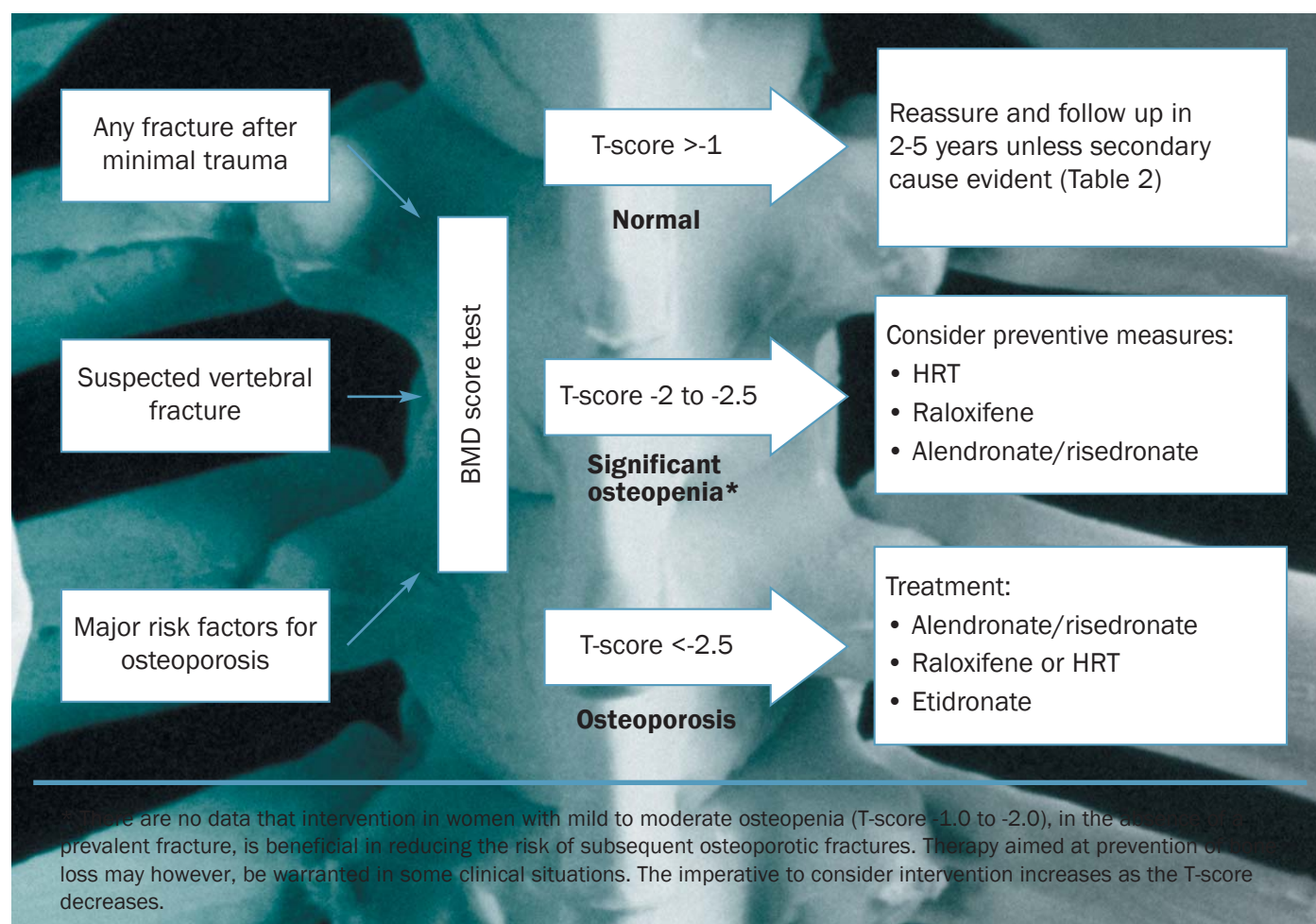


Figure 1. Intervention guidelines

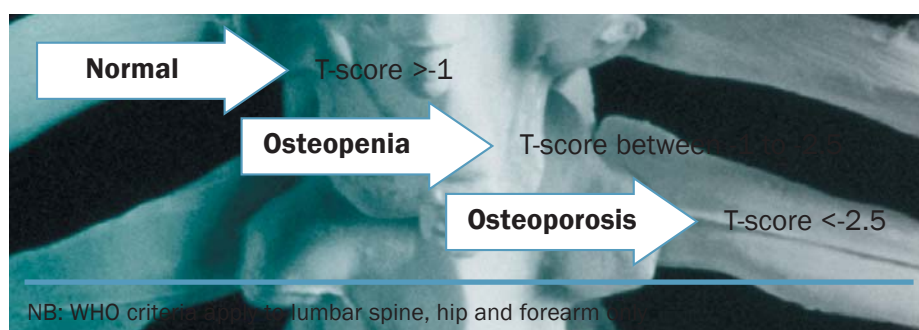
Table 1. Factors associated with increased risk of osteoporosis

- Increasing age
- Menopause (especially premature)
- Family history of osteoporosis
- Previous low trauma fracture
- Medical conditions (Table 2)
- Low calcium intake
- Low body weight (defined as BMI <20)
- Eating disorders associated with decreased weight
- Immobilisation
- Lifestyle factors including smoking, alcoholism, lack of exercise or excessive exercise

Table 2. Medical conditions associated with increased risk of osteoporosis

- Prolonged glucocorticoid therapy
- Conditions associated with excess glucocorticoid secretion
- Amenorrhoea lasting more than six months before the age of 45 years
- Primary hyperparathyroidism
- Chronic liver disease
- Chronic renal disease
- Malabsorption
- Rheumatoid arthritis
- Conditions associated with thyroxine excess

NB: A Medicare rebate is available for bone densitometry in these situations.

**Figure 2. WHO definitions of low bone density using DXA**

three times per week³

- encourage good general nutrition and ensure that vitamin D status is maintained especially in elderly patients
- discourage tobacco use.

The risk of developing osteoporosis is increased by certain factors (Table 1) and by some medical conditions (Table 2).

Although lifestyle prevention measures are important, pharmaceutical agents may be recommended for the prevention of postmenopausal bone loss. Randomised trials have shown beneficial effects of potent bisphosphonates, selective oestrogen receptor modulators, oestrogen and tibolone in prevention of

postmenopausal bone loss.^{4,7} These agents are discussed in more detail later.

Diagnosis

Dual energy X-ray absorptiometry

Dual energy X-ray absorptiometry (DXA) measures a patient's BMD, enabling fracture risk prediction. Dual energy X-ray absorptiometry is the gold standard for osteoporosis diagnosis, as it is reliable with a reported precision of approximately 1-1.5% at the spine and approximately 3% at the proximal femur. In day-to-day practice, compared with research studies, precision may be somewhat less. Postmenopausal women lose bone density at a rate of approximately 1-2% per year therefore biennial scans are generally adequate. In patients who are likely to have increased bone loss (eg. glucocorticoid treatment), more frequent scans may be indicated.³

Bone mineral density is expressed in terms of a T-score, which represents the number of SD from the young normal mean BMD (Figure 2). For every one SD decrease in BMD the relative risk of fracture increases 1.5-2.5-fold. Vertebral fracture risk is increased by a factor of 2.3 (range 1.9-2.8) for each SD reduction in lumbar spine BMD.⁸ Currently, total hip BMD is most commonly used to predict overall fracture risk, as proximal femoral measurements are less affected by osteoarthritis, which can falsely elevate spine BMD values.³ The Z-score is the number of SDs from population mean for age (ie. age matched).

Biochemical markers of bone remodelling

Serial biochemical markers of bone turnover can be measured in serum and urine, and may provide additional information for assessing fracture risk. Increased bone turnover markers in the presence of a low BMD would favour treatment of the patient. Additionally, markers may be used to assess the response to treatment and thus increase therapy adherence.³

Treating postmenopausal osteoporosis

Although osteoporosis is a common condition, a cause should be identified if possible and the specific disease processes treated appropriately. Investigations are usually normal, but are indicated to exclude other specific medical conditions (Table 2), especially where the Z-score is less than -1.5 on bone densitometry. Typical investigations might include:

- a full blood count (FBC)
- erythrocyte sedimentation rate (ESR)
- calcium
- creatinine
- total alkaline phosphatase and albumin
- thyroid stimulating hormone (TSH)
- protein electrophoresis (EPP)
- anti-endomysial antibody
- parathyroid hormone (PTH)
- 25 hydroxy vitamin D.

All patients aged 45 years and older sustaining a low trauma fracture should be considered for bone densitometry because of the high likelihood of having osteopenia/osteoporosis.

General measures

These include recommendations for lifestyle modification discussed earlier and fall prevention measures, which may be beneficial and prevent fractures. The optimal use of exercise relies upon delivery of a sustained adequate dose of the correct modality of exercise to the target population while minimising the risk of side effects.

Medication

Bisphosphonates

Bisphosphonates are potent inhibitors of bone resorption. Currently three bisphosphonates (alendronate, risedronate and etidronate) are approved in Australia on the PBS (Authority required) for the treatment of established osteoporosis in postmenopausal women with fracture due to minimal trauma. Alendronate and risedronate have been reported to reduce the risk of single, multiple and morphometric (asymptomatic) vertebral fractures in

women with osteoporosis and one or more baseline vertebral fractures.⁹⁻¹² Alendronate and risedronate have also been reported to reduce the risk of vertebral fractures by 50% in women who have osteoporosis without a pre-existing vertebral fracture.^{13,14} The risk reduction with potent bisphosphonates is usually seen within the first 6-12 months. Peripheral fracture rates are also reduced with alendronate and risedronate in patients with a prevalent vertebral fracture. Data for antihip fracture efficacy are also available. In the alendronate trials, there was consistency in hip fracture risk reduction but hip fracture was not a primary endpoint.^{10,13} In one risedronate trial, in which hip fractures were the primary endpoint, there was a 40% reduction in hip fracture risk among women aged 70-79 years with osteoporosis confirmed on DXA (baseline T-score <-3).¹⁵

The use of alendronate and risedronate has been associated with dyspepsia, abdominal pain and oesophageal ulceration and should be prescribed with caution in patients with a history of reflux oesophagitis or hiatus hernia.¹⁶ However, the overall risk of gastrointestinal events with alendronate and risedronate is very low (see Case history), and weekly bisphosphonates may further reduce the risk of this side effect.¹⁷

Etidronate is used in a cyclical regimen for osteoporosis, usually for two weeks every three months, because it can result in mineral defects if used continuously. A number of smaller controlled trials with etidronate show increases in bone density averaging 5% over 2-3 years¹⁸ and suggest a 50% reduction in vertebral fracture rate. Etidronate has been associated with lower, but not upper, gastrointestinal events.¹⁹ There appears to be no risk of mineralisation defect with the cyclical regimen.¹⁸

Bisphosphonates are polar (water soluble) drugs and when taken orally, the bioavailability is low (<1%). Calcium should not be taken at the same time of day as a bisphosphonate, since it inter-

feres with their absorption. Bisphosphonates should also be taken least 30 minutes before meals to allow adequate absorption.

The increase in BMD that occurs with prolonged use of bisphosphonates (more five years) is maintained for 2-3 years after cessation. This does not occur with hormone replacement therapy (HRT), where BMD losses commence soon after ceasing the drug.²⁰

Selective oestrogen receptor modulators

Raloxifene is a selective oestrogen receptor modulator (SERM), which acts to decrease bone resorption, like oestrogen, but without stimulating the breast or uterus. Lipid profiles are improved and breast cancer incidence has been reported to be reduced by 60-70% over four years.²¹ Controlled clinical trials with raloxifene have shown modest increases in bone density, although this is generally somewhat less than that seen with bisphosphonates or oestrogen. In women with prevalent vertebral fractures, a 36% reduction in vertebral fractures was noted using a dose of 60 mg/day for four years. In women without prevalent vertebral fractures, the relevant risk reduction is greater (55%). Peripheral fractures were not reduced, for reasons that are unclear.²² An increased risk of deep venous thrombosis has been reported with raloxifene users similar to that seen with HRT users. Treatment should be ceased if patients are immobilised for any prolonged period. Unlike HRT, raloxifene is not useful for control of, and may worsen, menopausal symptoms. Raloxifene is available on the PBS (Authority required) for established postmenopausal osteoporosis in patients with fracture due to minimal trauma. Raloxifene has also been shown to be effective for prevention of postmenopausal bone loss and should be considered as an alternative in women unable to take oestrogen for this indication (no PBS listing for this purpose).

Hormone replacement therapy

The role of long term HRT in the prevention and management of osteoporosis remains controversial following the results of the Women's Health Initiative (WHI) study of combined HRT. This study was ceased prematurely in May 2002 because of an increase in breast cancer of eight per 10 000 women years. However, this was balanced by a similar reduction in other major cancers such as bowel cancer. A possible increased cardiovascular risk was also seen in the WHI cohort, many of who had pre-established cardiovascular disease risk factors.²³ The Therapeutic Goods Administration expert committee report concluded that the continued use of combined HRT for women with established osteoporosis is an acceptable option for many, but women should discuss the benefits and risks with their treating doctors. The committee also recommended a full review of the use of combined HRT in long term treatment and prevention of osteoporosis.²⁴

Although oestrogen is effective in preventing loss of bone density when given at or near menopause, it is also effective in reducing loss of bone density over 10-15 years after menopause, with increases in bone density averaging 5% over three years.⁷ The WHI cohort experienced lower hip fracture rates (10 per 10 000 person years in the oestrogen and progestin group (E + P) versus 15 per 10 000 person years in the placebo group). Oestrogen and progestin treatment led to statistically significant reductions in fracture rates compared with placebo for hip and clinical vertebral fracture rates, other osteoporotic fractures and total fractures.²³

The data relating to increased risk of breast cancer with long term HRT use from observational studies remains inconclusive. Some studies have shown an increased relative risk of breast cancer of up to 1.5 in long term HRT users, other studies show minimal or no increase in risk.²⁵ In the WHI study with combined

HRT the invasive breast cancer rate showed a hazard ratio (adjusted 95% CI) of 1.26 (0.83-1.92). This rate reached the (conservative) predetermined cut off point in the trial protocol for breast cancer and the combined HRT arm of the trial ceased. The risk found, to that point, was half the increased risk (RR: 1.53) predicted in the Lancet re-analysis of observational studies by Beral et al²⁶ for combined HRT preparations. The absolute increase seen in the WHI data was 38 versus 30 cases per 10 000 women years commencing only after four years. No significant difference was observed for in situ breast cancers. There were no differences in mortality or cause of death between the groups.²³

A parallel trial of the WHI investigating oestrogen alone in women who have had a hysterectomy is being continued. The NIH states there is currently no evidence of increased risk of breast cancer in the oestrogen only arm of the WHI study although data from this arm is not yet available. This is planned to be complete in 2005 with an average follow up of 8.5 years. If the same significant reduction in hip and vertebral fractures is seen in that arm without significant breast cancer risk then the risk/benefit ratio for oestrogen alone therapy in hysterectomised women may appear favourable at the end of the trial, although the effects on cardiovascular disease will also need to be considered.²³ In a similar but larger, long term HRT study, The Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) (conducted in the United Kingdom, New Zealand and Australia) the Data Monitoring Committee and the WISDOM Steering Committee have recommended that it is ethical and scientifically valid to continue. Until the data becomes conclusive caution is needed; for each individual patient the potential benefits must be rationally considered against the possible small increase in risk.

Ideally, oestrogen therapy should be continuous (ie. without a break in

therapy). Adjuvant progestogens are necessary in women who still have a uterus, to protect against endometrial cancer. They may be given cyclically for 10-14 days each month in perimenopausal women or as continuous therapy combined with oestrogen in postmenopausal women. The latter is more suitable for women more than two years post-menopause to avoid the initial irregular bleeding, normally seen with this regimen, being unduly prolonged.

The minimum effective dose of oestrogen therapy has yet to be clearly established, but many routes of administration can achieve the beneficial effects of oestrogen therapy and lower doses can be used in combination with calcium supplements especially in elderly women. The optimal dose of oestrogen therapy required to prevent perimenopausal BMD loss may vary from woman to woman. As with any therapy for osteoporosis, repeat bone density should be considered after two years to check that the therapeutic regimen is efficacious.²⁷

Calcium

Calcium is weakly antiresorptive and supplementation may reduce negative calcium balance, especially in older age. Most studies suggest the required daily intake is between 1000 mg and 1500 mg in postmenopausal women not taking oestrogen replacement therapy. This can be obtained from dairy products. For example, an average glass (250 mL) of milk contains 300 mg of calcium, two slices (40 g) of cheddar cheese contains 300 mg of calcium and one tub (200 g) of yoghurt contains 340 mg of calcium. For those who are unable to tolerate dairy products, calcium enriched soy milk and a large variety of calcium supplements are currently available from pharmacies and health food stores. However, patients need to understand the varying calcium content of different supplements and that the recommended daily intake relates to elemental calcium. Controlled trials have found small effects of calcium on bone

density averaging 1-2%, associated with a modest reduction in fracture risk in some studies.^{28,29}

In patients using bisphosphonates, calcium must not be taken at the same time of day as the bisphosphonate or the calcium will impair absorption of the drug. Calcium may also cause mild constipation or upper gastrointestinal upset. It should be avoided in patients with a history of renal calculi in the presence of hypercalciuria. Calcium citrate is now available in Australia as an option for these patients.

Vitamin D

Vitamin D undergoes metabolism in the liver and kidney. Simple vitamin D is mainly available in Australia as ergocalciferol (Ostelin 1000 IU per capsule) or cod liver oil tablets (approximately 400 IU). Smaller amounts of vitamin D are also contained in some calcium and vitamin supplements (eg. Caltrate + D contains 200 IU per tablet). One French study involving largely vitamin D deficient institutionalised elderly patients, showed simple vitamin D, when used with calcium supplements, reduced hip fractures.³⁰ In Australian populations with limited exposure to sunlight (eg. the housebound elderly, the institutionalised, dark skinned or veiled women) subclinical vitamin D deficiency and osteomalacia are also common. Accordingly, long term vitamin D supplementation (1000 IU/day) is recommended in patients with a poor diet or limited sunlight exposure.

Since several of the controlled trials of antiresorptive agents previously described have used concomitant calcium and vitamin D, it is appropriate to add a calcium supplement to most therapies, except calcitriol.

Calcitriol (active vitamin D metabolite)

Calcitriol has a therapeutic profile distinct from vitamin D, and should not be used in the treatment of vitamin D deficiency.³¹ Calcitriol is available on the PBS

Table 3. When to consider referral to a specialist

Referral to specialist bone centres is appropriate in the following circumstances:

- When patients experience problems or side effects with treatment
- When patients have other complex medical conditions
- When GPs do not have access to appropriate bone densitometry
- When patients show inadequate response to therapy
- When patients have a vertebral fracture - a one visit assessment by a specialist is prudent
- When young patients (age <50) have osteoporosis
- When a secondary cause is identified
- Patients who continue to fracture with 'normal' bone densitometry

(Authority required) for the treatment of postmenopausal osteoporosis. The evidence on efficacy in fracture prevention is confusing with studies showing both increased and decreased numbers of fractures.³ Calcitriol should not be used as a sole therapy for the treatment of osteoporosis.

Parathyroid hormone

Parathyroid hormone (PTH) stimulates osteoclasts and osteoblasts in the bone, however, when presented to bone intermittently, such as in daily subcutaneous administration, it has a net anabolic action. Its major action is to prevent osteoblast apoptosis and thereby prolonging the bone formation cycle. Parathyroid hormone increases the uptake of calcium from the gut and reduces its excretion in the kidney. It reduces the relative risk of vertebral fractures (up to 65% in women with osteoporosis and one or more baseline fractures) as well as peripheral fractures. When it becomes available in Australia, PTH is anticipated to become a treatment option in severe osteoporosis due to its bone structure modulation.³²

Monitoring therapy

After therapy has been initiated, it is important to monitor patients to ensure that bone loss is controlled. Bone densitometry using DXA measurements can be used for monitoring the efficacy of therapy because of their excellent precision, and they can be performed rapidly

and conveniently. It should be noted, that changes of less than 5% are within the precision error of most machines and therefore should be regarded as representing no significant change. It is often recommended that a repeat DXA be performed within one year of commencing osteoporosis treatment. However, a measurement at two years is likely to be a more accurate representation of the effects of an antiresorptive drug. Thereafter, biennial DXA assessments are usually carried out to monitor response to therapy. Repeat measurements should generally be performed on the same machine for monitoring, assuming the DXA provider has good quality control with acceptable precision error. Biochemical measures of bone turnover may become useful in the management of the individual patient but their role has yet to be established. In certain instances a referral to a specialist may be able to fine tune therapy (Table 3).

Preventing falls

Interventions to reduce the risk of falling include:

- modifying the environment to reduce the risk of slipping and tripping by eliminating slippery surfaces, loose rugs, narrow passageways, dangerous furniture. Most people report trips, slips and loss of balance as the cause of the fall, whereas only a small proportion report dizziness or feeling faint
- modifying living habits:

Table 4. Osteoporosis support services available in Australia

- Osteoporosis Australia: Osteoporosis Australia has a range of education materials available for patients and healthcare professionals, which cover different aspects of osteoporosis and its management. There are regular courses on osteoporosis and self management to teach people how to maintain bone mass, avoid falls and fractures, and live more comfortably with osteoporosis.

Helpline 1800 242 141

Website: www.osteoporosis.org.au

- State affiliates of Osteoporosis Australia
- Specialist colleagues with an interest in osteoporosis
- Teaching hospitals
- Services for people with a disability (community help and welfare services)
- Community home care services

- by wearing appropriate footwear
- taking care when walking up or down steps, especially if patients wear bifocals
- taking care at night and in poorly lit conditions
- installing appropriate aids (eg. using supportive hand rests, rails and nonslip bathmats)
- modifying medications such as sedatives or certain antihypertensives that might predispose patients to falls
- correcting poor vision
- involving community agencies to:
 - provide support services to help implement the modifications required to reduce risk of injury
 - ensure nursing and physiotherapy services are provided when needed.

Specific exercise programs that emphasise muscle strengthening and balance retraining (eg. Tai Chi) may also be effective.³³

Where to get more help

Most states and territories have branches of support services for people with medical conditions, including osteoporosis (Table 4).

Conclusion

The management of postmenopausal osteoporosis should be based on an individual risk/benefit analysis, time since menopause, presence or absence of oestrogen withdrawal symptoms, history

of traumatic fractures and other medical conditions.

Oestrogen therapy remains appropriate for women at the time of menopause for those with symptoms, those with a premature menopause or surgical menopause. The duration of use should be reviewed with each woman after 2-5 years. Tibolone is an alternative to oestrogen therapy, and its effect on BMD appears to be similar (however, there are no antifracture data available).

Raloxifene and bisphosphonates are alternatives for prevention of bone loss after the menopause when symptoms of oestrogen withdrawal are no longer a consideration, although their use in this fashion before a fracture is currently not subsidised by the PBS.

In older women especially those with a previous osteoporotic fracture and high risk of further fracture, bisphosphonates should be considered as first line therapy because they prevent both nonvertebral and vertebral fractures.

All women should have an adequate calcium intake. Simple vitamin D supplementation should be considered in those groups at risk of vitamin D deficiency and osteomalacia, either as monotherapy or in combination with other treatments.

Case history

A 72 year old women presents following a fall, in which she sustained a forearm frac-

SUMMARY OF IMPORTANT POINTS

- The cause of osteoporosis should always be defined and specific disease processes should be treated appropriately.
- Whereas primary prevention of fracture remains crucial, treatment to ensure further fractures do not occur is equally as important.
- Any patient aged 45 years and older presenting with a low trauma fracture should undergo bone densitometry (Medicare rebate available for these patients).
- Women at high risk of osteoporosis (Table 1, 2) should undergo DXA for diagnosis (although only Table 2 attract a Medicare rebate).
- The role of long term oestrogen as first line therapy to prevent bone loss at the time of menopause is controversial. The potential benefits must be rationally considered and discussed with patients, balanced against the possible small increased risk of breast cancer.
- In older patients with previous fractures, the rank order of treatments is alendronate or risedronate, followed by raloxifene and then etidronate.
- Simple vitamin D should be considered in the housebound or institutionalised elderly.
- Lifestyle changes relating to dietary calcium, the correct modality of exercise and fall prevention are also important.

ture. Her risk factors for osteoporosis include a positive family history, use of inhaled corticosteroids for airways disease and an early menopause at 45 years of age. Bone densitometry confirms a low spine and hip T-score of -2.6 and -3.0 respectively. Her sister died of breast cancer at the age of 60 years. She suffers from mild dyspepsia, for which she takes antacids.

The first treatment choice in this woman, who has so called 'established' osteoporosis, based upon her previous fracture, is between the bisphosphonates

(alendronate or risedronate) and raloxifene. Alendronate or risedronate would be considered first choice and the history of dyspepsia is not a contraindication. If she did suffer from significant reflux or hiatus hernia, alendronate or risedronate once weekly may be an option. Raloxifene requires further study of its efficacy in reducing risk fracture at sites other than the spine.

Acknowledgments

This paper was developed by the authors as a committee on behalf of Osteoporosis Australia.

Conflict of interest: none declared.

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