Osteoporosis is a worldwide health issue, with a high prevalence of disease not only in western countries but also in Asia and Latin America. Of various fragility fractures, which represent the major complication of the disease, vertebral and hip fractures are associated with pronounced morbidity and excess mortality. Thus, the prevention and treatment of osteoporosis should be aimed at reducing substantially this risk of fracture. Although many agents have been suggested for the treatment of osteoporosis, only in the past 10 years have large double blind placebo controlled trials been done in postmenopausal women with the condition, with incident vertebral and non-vertebral fracture as a primary endpoint. Results of these trials have shown that several agents reduce greatly (by 30–50%) the risk of fractures (panel 1). This review will focus on such trials whenever available.

Because a low bone mass is the major risk factor for fractures, the treatment of osteoporosis focuses on agents that prevent bone loss or even increase bone mass. Osteoporosis, however, is a multifactorial disease, and skeletal fragility results from various factors. Thus, achievement of optimum bone health should be the aim throughout life, by age-specific non-pharmacological intervention.

Available treatments
Calcium and vitamin D
Calcium is an important nutrient in the prevention and treatment of osteoporosis. Although calcium supplied in the form of dairy products is as effective as calcium supplements, supplements are necessary in most countries to achieve an adequate calcium intake. Calcium slows the rate of bone loss, especially in elderly women and in those with a low calcium intake. Findings of some studies suggest a reduction in the frequency of fractures in patients who receive calcium supplements. Calcium is generally prescribed as an adjunct to other drugs for osteoporosis, and in most trials active and placebo groups receive the mineral (500–1000 mg daily). Thus, calcium supplementation is useful but not sufficient to treat individuals with osteoporosis. Calcium supplementation of about 500–1500 mg per day is safe, though mild gastrointestinal disturbances such as constipation are often reported. The risk of kidney-stone disease related to increased urinary calcium excretion does not seem to be raised in those who take supplements. Bioavailability is greatest during meals and varies with different calcium salts, though these factors are probably of little clinical significance.

Vitamin D is also given as a treatment for osteoporosis. In a French study of 3270 elderly women (mean age 84 years) who lived in care homes and were treated for osteoporosis IV
3 years with calcium (1200 mg daily) and vitamin D (800 IU daily), the probability of hip and all non-vertebral fractures was significantly reduced by 29% and 24%, respectively, compared with placebo. The findings of two other smaller studies suggest a trend for a reduction in non-vertebral fractures in elderly men and women treated with annual intramuscular injection of vitamin D or a daily supplement of calcium and vitamin D. Conversely, in a Dutch study of 2578 elderly but fairly healthy women with a high calcium intake, daily supplementation with vitamin D 400 IU over 3-5 years had no effect on the risk of hip fracture. Taken together, these data indicate that vitamin D should be used routinely in individuals who live in care homes because of a high prevalence of vitamin D deficiency related to low vitamin D intake, low sunshine exposure, and impaired vitamin D synthesis in the skin. When compliance is low, vitamin D 150 000–300 000 U can be given intramuscularly twice a year. Vitamin D at this dose is safe and does not require monitoring. The efficacy of calcium and vitamin D supplementation in healthy elderly people with adequate dairy product intake and normal bone mineral density (BMD) has not been established.

**Hormone replacement therapy (HRT)**

Oestrogen stops bone loss in early, late, and elderly postmenopausal women by inhibition of bone resorption, resulting in a 5–10% increase in BMD over 1–3 years. There is growing evidence that in elderly women such an increase in BMD can be achieved with smaller doses than those often used in early postmenopausal women, in the range of 0.5–1 mg of oral 17β-oestradiol, 25 μg of transdermal 17β-oestradiol, or 0.3 mg of conjugated equine oestrogens. Calcium supplements could enhance the effect of oestrogen on BMD. When HRT is stopped, bone loss probably resumes at the same rate as after the menopause.

Findings of several case-controlled and cohort studies suggest that HRT decreases the risk of hip fracture by about 30%, and results of two small placebo-controlled studies done in women with osteoporosis suggest a 50% reduction in the risk of fractures of the spine. The results of a meta-analysis of 13 randomised placebo-controlled trials suggest a 33% (95% CI 45–98) reduction in vertebral fracture, and those of a meta-analysis of 22 randomised trials indicate a 27% (0.56–0.94, p=0.02) reduction in non-vertebral fractures in a pooled analysis, with a 40% reduction for hip and wrist fractures alone. There has been no large placebo-controlled trial of HRT in women with osteoporosis and with incident fractures as a primary endpoint, so the evidence for efficacy of postmenopausal HRT for prevention of osteoporotic fractures is much weaker than for other compounds. The fact that the reduction in fracture risk seems to be lost within 5 years of HRT withdrawal, irrespective of the duration of treatment, raises the issue of the optimum timing and duration of HRT.

HRT has several non-skeletal effects (panel 2). Women who undergo hysterectomy can be given oestrogen alone. Those with an intact uterus, however, should be given oestrogen and a progestagen in a combined cyclic regimen, in women close to menopause, or in a combined continuous regimen, especially in women who are postmenopausal by more than 5 years, to reduce the risk of endometrial cancer. With the exception of norethisterone acetate, which has an anabolic effect on bone cells, the addition of a progestagen does not affect the effect of oestrogen on bone metabolism. Results of several observational studies have shown a small increase in the risk of breast cancer after 10 years of HRT use. Findings of observational studies have suggested a reduction in risk of coronary heart disease in women taking HRT, but this finding has not been confirmed in a randomised secondary prevention trial: HRT increases the risk of deep vein thrombosis and pulmonary embolism. A beneficial effect on cognitive function has been suggested in retrospective analysis of HRT users, but not in randomised controlled studies.

**Selective oestrogen receptor modulators (SERMs) and other oestrogen analogues**

SERMs act as oestrogen agonists or antagonists, dependent on the target tissue. Tamoxifen, which has long been used as an adjuvant treatment in breast cancer, is an oestrogen antagonist in breast tissue but a partial agonist in bone, cholesterol metabolism, and the endometrium. Tamoxifen does not wholly prevent bone loss in postmenopausal women but it does increase the risk of endometrial cancer, precluding its widespread use in healthy postmenopausal women.

Raloxifene is a benzothiophene that competitively inhibits the action of oestrogen in the breast and the endometrium, and that acts as an oestrogen agonist on bone and lipid metabolism. In early postmenopausal women, raloxifene prevents postmenopausal bone loss at all skeletal sites, reduces markers of bone turnover to premenopausal concentrations, and reduces serum cholesterol concentration and its LDL fraction without stimulating the endometrium. Results of the MORE study (Multiple Outcomes of Raloxifene Evaluation), which involved 7705 women with osteoporosis, indicate that a 30% and 50% reduction of incident vertebral fractures in women with and without prevalent vertebral fractures, respectively, happens after treatment with raloxifene. However, no effects on non-vertebral fractures were noted (table). In the MORA study, raloxifene also lowered the frequency of breast cancer by 70%, although the RUTH study will ascertain whether or not the decrease in LDL cholesterol and fibrinogen, seen in individuals taking raloxifene, can result in a reduction in coronary heart disease in the high-risk population of postmenopausal women as shown in the MORA study. Raloxifene does not impair cognitive function in postmenopausal women and might even slow age-related cognitive deterioration; raloxifene-treated women did better than controls in two tests of verbal memory and attention. Although rare, thromboembolic disease (venous thrombosis and pulmonary embolism) is increased in individuals treated with raloxifene, with a relative risk similar to that seen in osteoporosis IV
endometrium,50 and does not induce breast tenderness, but reduces menopausal symptoms, does not seem to affect the on fracture risk have not been investigated. The drug Bisphosphonates51 are stable analogues of pyrophosphate effect on cardiovascular disease is also unknown. studied in large long-term placebo controlled studies. Its (dyspepsia, abdominal pain, diarrhoea). Rare instances of the side chain. Bisphosphonates have a strong affinity for identified. The oral bioavailability of bisphosphonates is impaired by food, calcium, iron, coffee, tea, and orange juice. These drugs are quickly cleared from plasma, with a half-life of bisphosphonates in bone is several years. about 50% deposited in bone and 50% excreted in urine. The oral bioavailability of bisphosphonates is osesophagitis have also been reported with alendronate. Furthermore, etidronate, but not other bisphosphonates, can induce a mineralisation defect of bone after long-term use, especially in patients with renal insufficiency. The table shows their effects on fractures.

Tibolone is a synthetic steroid that acts on oestrogen, progesterone, and androgen receptors either directly or indirectly through its metabolites, with a different pattern according to the target tissue. Tibolone prevents bone loss in early and late postmenopausal women,44,45 but its effects on fracture risk have not been investigated. The drug reduces menopausal symptoms, does not seem to affect the endometrium,36 and does not induce breast tenderness, but its overall effect on the uterus and the breast should be studied in large long-term placebo controlled studies. Its effect on cardiovascular disease is also unknown.

Bisphosphonates
Bisphosphonates41 are stable analogues of pyrophosphate characterised by a phosphorus-carbon-phosphorus (P-C-P) bond. By substituting for hydrogens on the carbon atom, various bisphosphonates have been synthesised, the potency of which depends on the length and structure of the side chain. Bisphosphonates have a strong affinity for bone apatite, which is the basis for their clinical use. They are potent inhibitors of bone resorption, reducing the recruitment and activity of osteoclasts and increasing their apoptosis through a molecular mechanism recently identified. The oral bioavailability of bisphosphonates is low, between 1% and 3% of the dose ingested, and is impaired by food, calcium, iron, coffee, tea, and orange juice. These drugs are quickly cleared from plasma, with about 50% deposited in bone and 50% excreted in urine. The half-life of bisphosphonates in bone is several years. The safety profile of bisphosphonates is favourable; mild-to-moderate gastrointestinal discomfort that rarely results in discontinuation of medication has been reported for all (dyspepsia, abdominal pain, diarrhoea). Rare instances of these who take HRT. Other SERMs are under development.

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Etidronate was the first bisphosphonate developed. Administered intermittently (400 mg per day for 2 weeks, repeated every 3 months), etidronate increases the BMD of the spine by about 4%, with a reduction of vertebral fracture rate at 2 years53,54 that was no longer significant after 3 years of treatment in one of two studies.55 Findings of a meta-analysis56 of trials of controlled etidronate done over 1–4 years suggest a reduction of vertebral fractures with a relative risk of 0.63 (95% CI 0.44–0.92), but no effect was noted for non-vertebral fractures.

Alendronate prevents postmenopausal bone loss.57,58 Results of a study57 in 2025 women with osteoporosis and at least one prevalent vertebral fracture who were treated with alendronate 5 mg daily for 2 years followed by 10 mg daily in a third year showed a 50% reduction of vertebral, wrist, and hip fractures compared with placebo. Women with low BMD but without vertebral fracture at baseline58 were given alendronate for 4 years with the same placebo controlled design. There was a small though insignificant decrease in frequency of clinical fractures with alendronate (p=0.07), whereas the frequency of new vertebral fractures was significantly reduced by the treatment.59 When the analysis was restricted to patients with osteoporosis diagnosed according to the WHO criteria—ie, with a BMD less than 2.5 SD below the mean value of healthy premenopausal women (T score <-2.5)—the reduction of all types of clinical fractures was significant.60 Findings of a pooled analysis61 of women with osteoporosis who were involved in both FIT studies62 indicate that the reduction of the risk of fracture with alendronate happens early, within
12–18 months. Results of another placebo controlled study in 1908 postmenopausal women with a low BMD (T score ≤−2) show a 47% reduction in the risk of non-vertebral fracture after 1 year of alendronate 10 mg daily. The optimum duration of treatment is unknown. Findings of one study suggest that 7 years of treatment with alendronate is safe, but there might not be additional benefit after 5 years, on the basis of changes of BMD and bone turnover markers. Alendronate 70 mg given once a week has a good safety profile and the same efficacy as 10 mg daily in increasing BMD and reducing bone turnover. Administration once a week rather than daily might improve long-term compliance, a challenge in such a chronic disease.

Risedronate prevents postmenopausal bone loss. Oral daily 5 mg per day significantly reduced the cumulative incidence of patients with new vertebral fractures by 41% over 3 years and by 65% after the first year in 2400 women with prevalent vertebral fractures. In another study, in 1226 patients with severe osteoporosis (at least two prevalent vertebral fractures), treatment with risedronate resulted in a 49% reduction of vertebral fracture incidence at 3 years. The overall incidence of non-vertebral fracture in two studies was reduced by 30–40%. Effects of risedronate on hip fracture have been assessed in 5445 women aged 70–79 years with osteoporosis defined by a low BMD, and in 3896 women older than age 80 years who were mainly recruited on the basis of clinical risk factors for falls, without BMD assessment in most. The overall analysis showed a 30% reduction of hip fracture (p=0.02) with risedronate over 3 years. In the first group, the reduction of hip fractures was large (40%), reaching 60% in those with prevalent vertebral fractures. By contrast, there was no significant reduction in the second group, emphasising the need to target bisphosphonates to women who have osteoporosis as confirmed by BMD measurement.

Clodronate, another bisphosphonate, was developed more than 20 years ago and is still widely used for the treatment of malignant bone diseases. In a study of 677 individuals with osteoporosis, including postmenopausal, secondary, and male osteoporosis, clodronate 800 mg daily decreased significantly the incidence of new vertebral fractures by 46%. Tiludronate is a bisphosphonate used in several countries for the treatment of Paget’s disease of bone, though its development as a possible treatment for osteoporosis has been discontinued because of absence of evidence of fracture reduction in large phase III trials. Oral daily pamidronate might be effective in osteoporosis but is associated with a high frequency of upper gastrointestinal adverse events. Intravenous infusion of pamidronate, commonly used in malignant bone disease and in Paget’s disease of bone, increases BMD at the spine and hip when infused every 3 months in patients with osteoporosis. No fracture data are available. Ibandronate and zoledronate, two new potent bisphosphonates, are in phase III trials.

Calcitonin Calcitonin, a peptide produced by thyroid C cells, reduces bone resorption by direct inhibition of osteoclast activity. When given subcutaneously or intramuscularly, tolerance is sometimes poor (nausea, facial flushes, diarrhoea), whereas intranasal administration of salmon calcitonin has no significant side-effects. The minimum intranasal dose needed for a significant effect on BMD is 200 IU daily. Calcitonin is less effective in prevention of cortical bone loss than cancellous bone loss in postmenopausal women.

OSTEOPOROSIS IV

Parathyroid hormone (PTH)

Excess secretion and continuous intravenous infusion of PTH result in increased bone resorption and bone loss. By contrast, there is compelling evidence, in a range of species made osteoporotic by gonadectomy, that intermittent PTH injection restores bone strength by stimulation of new bone formation at the periosteal (outer) and endosteal (inner) bone surfaces, thickening the cortices and existing trabeculae of the skeleton, and perhaps increasing trabecular numbers and their connectivity. In a double blind placebo controlled prospective study in 1637 postmenopausal women with previous vertebral fractures, daily treatment with subcutaneous 1–34 fragment recombinant human PTH 20 μg or 40 μg for a median of 19 months reduced greatly the incidence of new vertebral fracture (relative risk 0·35 and 0·31 for the respective doses). The incidence of non-vertebral fragility fractures was reduced by 53% with both doses (table). BMD increased by 9% and 12% at the spine, by 3% and 6% at the femoral neck, and by 2% and 4% overall after administration of PTH 20 μg and 40 μg, respectively, after 21 months of observation. High-dose PTH occasionally caused nausea and headache. There was a dose-dependent rise in serum calcium within 4–6 h after injection that was mild and transient, occurring in 11% of patients who received PTH 20 μg. In long-term toxicological studies, high doses of PTH induced osteosarcomas in rats but not in monkeys. In clinical studies in about 1000 patients, treatment with PTH or its fragments for up to 3 years has not increased the frequency of tumours in bone or other tissues. PTH 20 μg per day has been submitted for approval for treatment of osteoporosis in the USA and Europe.

Other treatments

Alfacalcidol and calcitriol are vitamin D analogues and are used in some countries for the treatment of osteoporosis. Both compounds induce a small increase in BMD that seems to be limited to the spine. Data on reduction of fracture risk are scarce and conflicting. In a large randomised study that was not placebo controlled, the rate of vertebral fracture was reduced in individuals with osteoporosis who received calcitriol compared with those who received calcium alone. This result might have been biased by an unusual increase of the annual fracture rate in the calcium group with time. No study has compared the effect of vitamin D derivatives versus calcium plus vitamin D on fracture risk. Vitamin D derivatives expose patients to hypercalcaemia and hypercalciuria. Serum and urine calcium concentrations should, therefore, be monitored in patients on these drugs, and the dose adapted when necessary.

When administered, fluoride is incorporated into the hydroxyapatite component of bone, and stimulates osteoblast recruitment and activity, thus increasing the rate of bone formation. In human beings, sodium fluoride
Vitamin D is essential for the intestinal absorption of calcium and, as discussed above, serum concentrations of 25-hydroxyvitamin D decline with age. Findings of several studies suggest that the daily intake of vitamin D should be around 400–800 IU if sunlight exposure is low. An adequate protein intake is essential in frail elderly individuals.

Exercise
Physical activity early in life contributes to high peak bone mass. Various activities, including walking, weight training, and high impact exercises, induce a small (1–2%) increase in BMD at some but not all skeletal sites, that is not sustained once the exercise programme is stopped. The results of clinical trials and observational studies suggest that load bearing exercise is more effective for increasing bone mass than other types of exercise. Fitness might indirectly protect individuals from fractures by improving mobility and muscle function, and by reducing the risk of falls. Findings of observational studies suggest that regular exercise and recreational activity reduce hip and leg fracture risk but increase the risk of wrist fracture. After a vertebral fracture, a supervised exercise programme to maintain strength and flexibility of the thoracic and lumbar spine is recommended in elderly individuals. Specific interventions aimed at preventing falls and their consequences in the elderly need to be developed. Results of controlled studies have shown that exercise can increase muscle mass and strength, and reduce the risk of falls by about 25% in frail elderly individuals. However, no controlled study has shown that such exercise programmes can reduce the risk of fracture, irrespective of age.

Orthopaedic management of fractures
Early surgical management of hip fractures is essential to decrease mortality rate and to improve perioperative morbidity, which is pronounced—especially in frail elderly individuals. The surgical treatment of peripheral fragility fractures does not require specific procedures, since the rate at which fracture heals is much the same in patients of a similar age with and without osteoporosis. In patients with major pain related to a crushed vertebra, vertebral plasty, involving injection of polymethylmethacrylate cement into the vertebral body, has been suggested. Although this procedure might have a beneficial effect on acute pain, the long-term effects on the subsequent risk of fractures of adjacent vertebrae have not been assessed in controlled studies.

Other measures
Treatments that predispose to osteoporosis—eg, chronic corticosteroid therapy—should be avoided whenever possible. In addition to an exercise programme, a strategy to decrease the risk of falls in elderly individuals should be implemented. Visual impairment and cataract should, for example, be detected and treated and, whenever possible, the use of drugs that increase the risk of falling—eg, basodiazepine, hypnotics, antidepressants, and medications that induce hypotension—should be reduced. Furthermore, patients should be instructed to avoid slippery floors and install adequate lighting at home. Finally, results of two controlled studies done in elderly individuals in care homes have shown that the risk of hip fracture could be reduced as much as 50% by use of energy-absorbing external hip protectors. However, long-term adherence with these devices is unknown.

Treatment choice
Decisions with respect to treatment of postmenopausal osteoporosis should be based on an assessment of the
patient’s risk of fracture and on the efficacy and side-effects of drugs likely to be prescribed. Fracture risk depends mainly on the magnitude of bone loss. On the basis of results of epidemiological studies, algorithms are being derived to establish the 10-year probability of all low-trauma fractures (including spine, hip, and other sites) according to age, history of fractures, degree of bone mass (assessed by dual energy radiograph absorptiometry or other relevant techniques), and degree of bone resorption (assessed by specific biochemical markers). Such algorithms will provide an absolute risk of fractures, and should help doctors to make a treatment decision. In general, patients with higher absolute risk will derive greater benefit from treatment. However, results of trials with bisphosphonate suggest that the drug will only reduce rate of non-vertebral fractures in individuals with a T score less than –2.5, irrespective of the absolute fracture risk derived from assessment of other risk factors. The decision on when and how to treat, therefore, depends on the clinical presentation.

Individuals with fractures
Vertebral fracture is probably the most common form of osteoporosis in postmenopausal women aged older than 60 years. Other causes of vertebral fractures, such as malignant disease, need to be ruled out by adequate clinical and biological investigation. Although knowledge of degree of BMD is not necessary to make a treatment decision, this index is usually measured. Individuals with a fragility vertebral fracture should always be treated, since their risk of further vertebral fractures is very high, around 20% in the 12 months after a previous break. Alendronate, risedronate, and raloxifene are the best treatment options, based on the scientific evidence.

In patients with other low-trauma fractures, the existence of skeletal fragility underlying the fracture needs to be assessed by BMD measurement. In instances of a low BMD (T score ≤–1) treatment should be considered on the basis of the type of fracture (all hip fractures should be treated, whereas fractures of the toes and fingers are usually non-osteoporotic), the age of the patient, additional risk factors, and current BMD (fracture risk doubles for every 1SD decrease in BMD).

Women without a history of low-trauma fractures
If a postmenopausal woman has osteoporosis, according to the WHO definition—ie, T score less than or equal to –2.5—at the spine or hip, or both, the risk of fracture is high enough to justify treatment. If a woman has osteopenia (T score between –1 and –2.5) preventive treatment might be considered if BMD is in the lower range—ie, less than –2—or if there are other clinical risk factors for fractures.

Choice of treatment is affected by age. Thus, HRT is the first choice to prevent bone loss in early postmenopausal women with menopausal symptoms. Raloxifene is an attractive alternative for reducing the risk of vertebral fractures in middle and late postmenopausal women, especially if they are concerned about the risk of breast cancer. Bisphosphonates have no extra skeletal benefits, but especially if they are concerned about the risk of breast cancer. Bisphosphonates have no extra skeletal benefits, but their antiresorptive nature of most treatments does not allow easy detection of responders to treatment. If a non-response—ie, a pronounced decrease of BMD—is detected, it should be confirmed by a subsequent measurement, to keep regression to the mean to a minimum. Use of biochemical markers of formation and resorption has been proposed as a good way to monitor antiresorptive therapies. Findings of several studies have shown a significant inverse correlation between the short-term (3–6 months) fall in bone turnover markers and the 2–3 year rise in BMD at various skeletal sites with HRT and bisphosphonates. Cut-off values for these decreases, for a specific marker and treatment that will identify responders and non-responders with adequate sensitivity and specificity have been proposed by the committee of scientific advisers of the International Osteoporosis Foundation. Studies are being done to correlate short-term changes in bone turnover markers with the probability of fracture in women with osteoporosis, and such an association has been reported for raloxifene and risedronate. Whether BMD measurement or bone markers, or both, are used to monitor treatment response, there remains no proof that such an approach improves long-term compliance to treatment.

Perspectives
Although there are several treatment options that reduce substantially the risk of fragility fractures, their mechanisms of action remain poorly understood. Most antiresorptive therapies induce a 2–10% increase in spinal BMD, though risk of fracture is reduced still further. Additionally, raloxifene and alendronate increase spinal BMD by 2–3% and 8%, respectively, though the differences in subsequent vertebral fracture rate are modest. The rise in BMD seems to be mainly related to an increase in the amount of mineral per unit of bone, as shown by quantitative microradiography, rather than to an increase in true bone mass. Reduced bone turnover is another determinant of fracture reduction and there are probably other mechanisms that are important, with changes in bone structure and biology that could vary according to the skeletal envelope. Our incomplete understanding of the mechanism by which antiresorptive agents improve skeletal strength at some, but not necessarily all, skeletal sites deserve further investigation.

Because the mechanism of action of PTH is totally different from that of antiresorptive therapy, combination therapy could be an option for individuals with severe osteoporosis. In animals, antiresorptive drugs seem to maintain bone mass, structure, and strength when treatment with PTH is stopped, and drugs such as bisphosphonate, raloxifene, and HRT could have the same effect in people. Concomitant therapy with oestrogen does not seem to blunt the anabolic effects of PTH in postmenopausal women, but there is no evidence that this combination produces a higher bone mass or greater bone strength than PTH alone. A combination of bisphosphonates (alendronate or risedronate) and HRT or raloxifene induces an increase in BMD slightly above that achieved with either treatment alone, but there is no evidence that it results in a greater reduction of the risk of fracture.
Conclusion

Poor awareness of the consequences means that few individuals who present with fragility fractures are treated for osteoporosis, despite availability of effective treatments. This situation needs to change, since fractures are associated with pronounced morbidity and mortality. Treatment should be offered to postmenopausal women with vertebral fractures, those with non-vertebral fractures associated with low BMD, and those with osteoporosis as defined by WHO. The most rigorously investigated drugs reported to reduce spinal fractures are alendronate, raloxifene, and risedronate, and the most thoroughly investigated drugs reported to reduce non-vertebral fractures are calcium and vitamin D in elderly individuals in care homes, and alendronate and risedronate in the community. PTH, with its ability to reduce the risk of vertebral and non-vertebral fractures, will also be an interesting alternative in patients with severe osteoporosis when approved.

Drugs are also available to prevent osteoporosis, and their prescription should be decided on a case-by-case basis, according to age, degree of BMD, and presence of other risk factors. HRT is the first choice of preventive treatment in early postmenopausal women with menopause symptoms, whereas women at distance from menopause might prefer raloxifene, or a bisphosphonate in those at high risk of non-vertebral fractures.

Conflict of interest statement

P D Delmas has been a consultant for, a member on the advisory board of, has received honoraria for speaking from, and has received research grants from some or all of: Aventis, Boehringer, Chugui, Cilag, Cis bio International, Glaxo Wellcome, HMR, Hybritech, Leras, Lilly, Merck Damstadt, MSD, Novartis, Novo Nordisk, Organon, Osteometer, Pfizer, Procter and Gamble Pharmaceutical, Rhone Poulenc Rorer, Roche, Rotta, Sanofi Recherche, Servier, SmithKline Beecham, and Wyeth-Ayerst.

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Uses of error

A developing country perspective

Buddha Basnyat

One of the joys of working in Nepal is the gratitude the patient expresses when you try to help. Yet the doctor-patient ratio is low; the potential for error is high, and we may actually be negligent and unhelpful while the patient perceives us to be useful and dedicated. The story of one patient I mismanaged several years ago illustrates this point.

As a medical consultant that night I did not have a house officer with me. It was late and I felt I had had my fill of patients for that day. Then they wheeled in a fifty-year-old gentleman with abdominal pain and a history of peptic ulcer. He was tachycardic and anxious but his blood pressure was normal, and his abdomen soft with mild epigastric tenderness. He also complained of arthralgia and some mild weakness in his legs. I read the referral note which said that the patient had some black stool and therefore needed hospital admission. I found no blood on rectal examination, and no coffee grounds on nasogastric aspiration. I concluded that the main problem was his peptic ulcer. I admitted him to the general medical ward, scheduled a gastroscopy for the following day, and started omeprazole. I did not address his arthralgia nor his mild weakness beyond checking to see that he could grossly move his legs. I thought that many Nepalese patients had vague, disjointed complaints and that he was no exception. The next morning a colleague discovered that he had a left foot drop and no tibialis posterior or dorsalis pedis pulse. Overnight, unkown to me, he had developed a more tender abdomen and a radiograph showed air under the diaphragm. His creatinine was raised and he had proteinuria. At laparotomy he was found to have a perforated ileum with extensive necrosis and polyarteritis nodosa was subsequently diagnosed.

The patient and his relatives had thanked me profusely before I went off to sleep that night, little knowing that my preconceptions about patients with vague symptoms not amounting to much and my failure to carry out a proper physical and neurological examination were not going to help them in the least.

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