Current and Emerging Treatment of Osteoporosis

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15.1 Introduction

A fracture is a dramatic event for every patient because of pain, immobility and therefore the overall deterioration of their quality of life. Unfortunately, epidemiological data tell us that those who have suffered a fragility fracture are more at risk of suffering another in the same or other sites within a short time [1]. The goal of those treating a patient with recent fragility fracture should therefore not only be to treat the patient in the acute phase but also to prevent further fractures [2].

Interventions to increase bone mass to preventing further fragility fractures can be classified as pharmacological and non-pharmacological.

15.2 Pharmacological Treatment for All Patients with Fragility Fractures

Who are the patients that need pharmacological treatment? All European and international guidelines [3–5] do not base the need for treatment on the diagnosis of osteoporosis (based on the T-score) but on the risk of fracture, which is strongly influenced by the presence of a fragility fracture, especially vertebral or femoral fractures. A fragility fracture occurs spontaneously or following low-energy trauma in individuals with a low bone mineral density (BMD) [6].

This chapter is a component of Part 4: Pillar III.

For an explanation of the grouping of chapters in this book, please see Chapter: "The multidisciplinary approach to fragility fractures around the world—an overview".

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We do not need to apply an algorithm to decide who to treat because if our patient is a postmenopausal woman has had a fragility fracture, automatically we should consider her at high risk of further fractures. In the same way, an elderly patient with a hip fragility fracture should automatically be classified as having severe osteoporosis independently of other risk factors.

15.2.1 Bedridden Fractured Patients

Immobilisation itself causes osteopenia, indeed bedridden patients can suffer painful spontaneous fractures [7]. Secondary prevention trials usually do not include bedridden fractured patients, possibly because most common oral osteoporosis treatments are associated with esophagitis as a side effect and may increase the risk of reflux esophagitis for these patients [8]. However, a few studies on non-oral administration have shown good efficacy in patients with severe motor and intellectual disabilities [9]. Although further studies are needed, it seems to be important to treat this category of patients as well.

In conclusion, all orthogeriatric patients should start pharmacological treatment to strengthen their bone to prevent further fractures.

15.2.2 Make a Diagnosis Before Treatment

Before treatment it is important to make a differential diagnosis between primary and secondary osteoporosis because the anti-osteoporotic drug treatment would be useless if the main illness causing osteoporosis is not treated too.

In hospital, during the acute phase, it is important to investigate the osteoporosis to exclude secondary forms, by means of simple first-level blood tests (erythrocyte sedimentation rate, blood count, serum levels of protein, calcium, phosphorus, alkaline phosphatase and creatinine, 24 h urinary calcium) and some second level tests (TSH, Parathormone, 25-OH-vitamin D, serum protein electrophoresis). These tests are sufficient to exclude 90% of the secondary causes of osteoporosis. Only the evaluation of these parameters will guarantee that we are giving to the patient appropriate treatment [10].

It is important to make at any age a diagnosis of secondary causes of osteoporosis, such as hyperthyroidism and hyperparathyroidism, because these can now be treated with drugs and not only by surgery [11, 12].

15.2.3 Set Up an Appropriate and Personalised Treatment

Some studies show that anti-osteoporotic drugs are frequently interrupted within 1 month of their prescription; this happens not so much due to the occurrence of adverse events but mostly because patients have not been sufficiently informed about the importance of taking the drug and because they not receive personalised treatment [13].
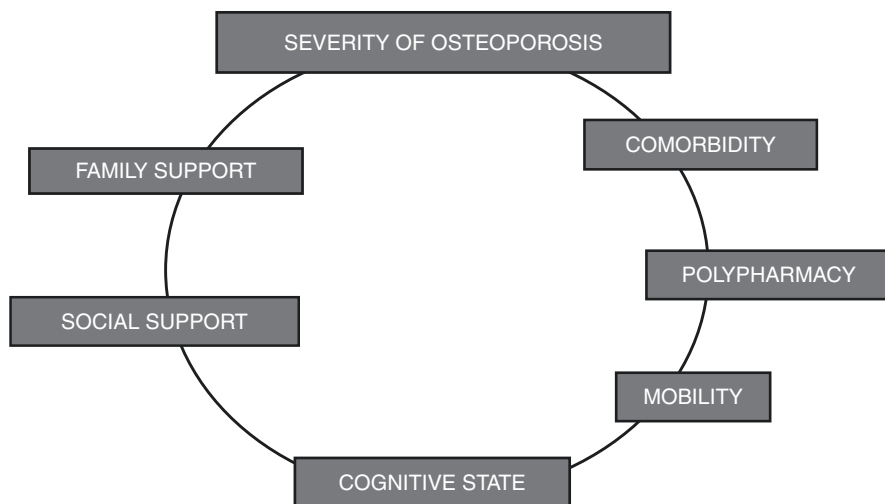
Fig. 15.1   Tailored treatment of osteoporosis in elderly people

The orthogeriatric patient with non-vertebral fracture has specific characteristics: they are normally very old (over 75 years) and present all the characteristics of frailty (reduced mobility, malnutrition, comorbidity, cognitive impairment, polypharmacy, neurosensory deficits). To improve adherence, in addition to osteoporosis severity, the degree of frailty and social family support should be considered in the choice of treatment. Osteoporosis treatment presents many choices [14], both in the route of administration and dosage frequency, so it is possible to define, together with the caregivers, a tailored treatment (Fig. 15.1). For example, subcutaneous or intramuscular administration may be easier or more complicated than oral intake depending on the patient's overall clinical and social conditions.

Sometimes, a drug recommended on the basis of severity of osteoporosis is not the most suitable for the patient. The need to renew the treatment plan every year, for an institutionalised elderly patient with a low family support, can be problematic. Depending on the complexity of the patient, a specialist management of osteoporosis therapy by a bone specialist may be necessary.

Another important point to improve adherence is that, on discharge from the orthopaedic department, the patient should be referred to a Fracture Liaison service that can also follow up the patient and change the medication in the light of the occurrence of new fractures under treatment, BMD measurement, change in clinical or social conditions and so on [15].

15.3   Non-pharmacological Treatment

15.3.1   Lifestyle and Exercise

Excessive use or abuse of alcohol should be avoided for a number of health-related risks, including bone loss. Moderate drinking during a meal (one glass of wine or beer), or only in social occasions, is harmless. Likewise, caffeine intake is harmful only when

excessive amounts are ingested, although its calciuric effect should be compensated by increasing calcium intake. On the other hand, any form of nicotine use should be discouraged, although substantial negative effects of cigarette smoking on bone health are seen only in individuals with smoking histories of 30 pack-years or above.

By and large, the most important lifestyle factor to be included in managing patients with osteoporosis is physical activity. The amount and intensity of weight-bearing physical activity in young healthy individuals is a determinant of peak bone mass. Likewise, a sedentary lifestyle and prolonged bed rest lead to increased bone loss in the involutional period. Therefore, attempts should be made to encourage physical activity and implement a moderate exercise programme to minimise bone loss in elderly people.

For the older individual with vertebral fractures and severe loss of bone mass, walking may be the only feasible exercise. Swimming, which is an excellent exercise for older individuals to condition muscle tone and strength, does not appear to alter bone loss patterns appreciably because it is not a weight-bearing exercise. Bone mineral content in the spine may be increased somewhat by more vigorous programmes, individualised for target heart-rate ranges, which depend on age and the maximum predicted pulse.

Cessation of exercise results in a gradual but progressive loss of bone. When recommending exercise regimens for elderly women of unknown cardiovascular fitness with established vertebral osteoporosis, patients should be advised about the adverse effects of strenuous exercise. Extension or isometric exercises are more appropriate for these individuals because vertebral compression fractures are more apt to occur during flexion exercise. These aerobic conditioning exercise programmes should be implemented with physician advice and should also include warm-up and cool-down intervals.

15.4   Pharmacological Interventions

A wide variety of drugs have been proposed for either preventing bone loss in high-risk populations or preventing fracture and further bone loss in individuals with a previous fracture.

15.4.1 Ca and Vitamin D to All Patients in Association with Anti-osteoporotic Therapy

There have been controversies in the literature on the efficacy of calcium and vitamin D for the prevention of osteoporosis and fractures without other drugs. However, in the oldest patients, including orthogeriatric patients, all data confirm that vitamin D deficiency is very common and calcium intake is often not adequate.

So, osteoporosis guidelines recommend:

- Older people should routinely receive vitamin D supplements [16].
- In postmenopausal women with low BMD and at high risk of fractures, calcium and vitamin D should be used as an adjunct to osteoporosis therapies, otherwise the latter will be ineffective [3].

There is broad consensus that vitamin D levels should be maintained above 20 ng/mL; this would already be a good result for orthogeriatric patients, who generally have values lower than 8 ng/mL [17]. Regarding the recommended dose of vitamin D, local guidelines should be followed; the most widespread programme for the correction of vitamin D deficiency (<10 ng/mL) consists of cholecalciferol in quite high doses of 50,000 IU per week for 1 or 2 months; then continued daily, weekly or monthly doses that guarantee 1200 IU daily. The most appropriate form of vitamin D to use (cholecalciferol, calcifediol, alfacalcidol, calcitriol) depends on the patient's condition and compliance. However, hydroxylated vitamin D metabolites increase the risk of hypercalcaemia and hypercalciuria; they may therefore need to be ruled out or monitored with serial serum and urinary calcium measurement [18].

It is difficult for older patients to have an adequate calcium intake by diet alone, but it is better to improve the dietary intake before giving a calcium supplementation. Many calcium formulations are available and the most suitable one should be recommended for each patient; for example, calcium carbonate should not be prescribed for patients with dyspepsia or who use protonic pump inhibitors (PPI)—for these patients, formulations of calcium citrate are more suitable [19].

15.4.2 Choose the Safe and Effective Drug for the Orthogeriatric Patient

We have many drugs for the treatment of patients at high risk of fracture (see Table 15.1) [14], but we should choose drugs based on efficacy and safety evidence provided by targeted studies or extrapolated data in old age subgroups.

For example, the use of oestrogen, tibolone and selective oestrogen receptor modulators (SERMs) is not recommended in orthogeriatric patients because they do not fit the patient characteristics appropriate for these drugs according to the latest guidelines. Specifically, they are not usually under 60 years of age or <10 years past menopause, with low risk of deep vein thrombosis and low cardiovascular risk. Moreover, in most countries these drugs are approved for the prevention but not the treatment of osteoporosis, nor for secondary prevention of fracture [3, 14].

We can divide osteoporosis therapies into two groups: antiresorptive and anabolic.

Table 15.1 Fracture risk reduction and route of administration of antiresorptive drugs

Antiresorptive drugs	Route of administration	Fracture risk reduction			
		Vertebral	Hip	Non-vertebral	Elderly
Alendronate	Oral once daily or weekly	Yes	Yes	Yes	Yes
Risedronate	Oral once daily, weekly, or monthly	Yes	Yes	Yes	Yes
Ibandronate	Oral once monthly or intravenous every 3 months	Yes	ND[a]	ND[a]	Yes
Zoledronic acid	Intravenous once yearly	Yes	Yes	Yes	Yes
Denosumab	Subcutaneous injection every 6 months	Yes	Yes	Yes	Yes

[a]Studies not powered to observe effect on hip or non-vertebral fracture risk

15.5   Antiresorptive Therapies

The fracture risk reduction and route of administration of antiresorptive drugs are shown in Table 15.1.
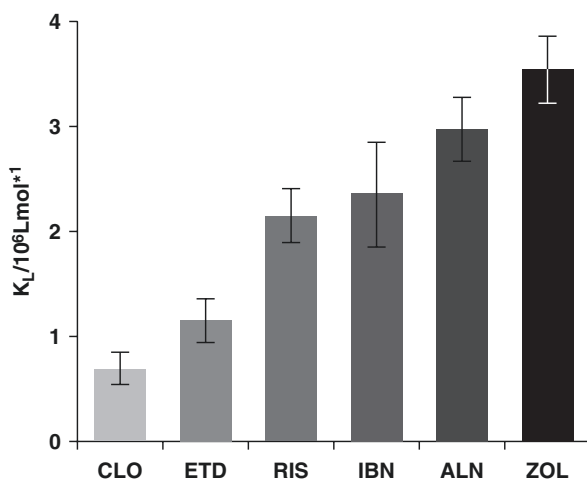
15.5.1 Bisphosphonates

Bisphosphonates are chemically related to inorganic pyrophosphate, which is a potent inhibitor of calcium phosphate crystallisation and dissolution. These compounds act primarily by inhibiting osteoclast-mediated bone resorption via a variety of mechanisms. Small changes in the basic structure of the bisphosphonate can result in extensive alterations in its biological, toxicological and physiochemical characteristics in addition to its therapeutic potential for the treatment of osteoporosis. Of the bisphosphonates that have been synthesised, etidronate, clodronate, ibandronate, zoledronate, alendronate and risedronate have been available commercially for varying periods of time for the treatment osteoporosis. Others, such as neridronate, are currently being tested for use in osteoporosis.

The bisphosphonates are not all the same; their effectiveness, long-term action and safety depend on the strength of their bond with hydroxyapatite (Fig. 15.2); because of this link they have different dosages and ways of administration so it is possible to choose a personalised treatment based on the needs of the patient [20]. Another advantage is the low cost of oral therapy which makes it accessible even to patients with low economic resources.

Clodronate is currently commercially available in a variety of international locations. Clodronate does not inhibit bone mineralisation in doses recommended for osteoporosis therapy.

Fig. 15.2 Kinetic binding affinity of bisphosphonates

Alendronate was the first bisphosphonate to be approved by the U.S. Food and Drug Administration for the prevention and treatment of postmenopausal and glucocorticoid-induced osteoporosis and osteoporosis in men. Alendronate, an aminobisphosphonate with approximately 700 times more potency than etidronate in inhibiting bone resorption, has been shown in several controlled trials to increase bone density and reduce vertebral and hip fractures among postmenopausal women with low bone density. It also increases bone density in men and women taking glucocorticoids and in men with idiopathic osteoporosis. Data on the effectiveness of alendronate are the largest currently available for any drugs used in osteoporosis treatment.

The Fracture Intervention Trial (FIT) was the first randomised, controlled trial designed with fracture reduction as the primary outcome. In the vertebral fracture arm of FIT, 2027 women with low bone mass and at least one pre-existing vertebral fracture were randomly assigned to receive a placebo or alendronate 5 mg (raised to 10 mg at month 24) daily for 3 years [21]. They were also given 500 mg of calcium and 250 IU of vitamin D. The proportion of women with new morphometrically (radiologically) defined vertebral fracture(s) was 55% lower in those taking alendronate (8%) relative to those taking placebo (15%). Likewise, the proportion of women with clinically evident (reported during the study as adverse events) new vertebral fractures was 47% lower in the alendronate (2.3%) relative to the placebo group (5.0%). The relative risk for two or more morphometric vertebral fractures was reduced by ~90% by alendronate treatment, demonstrating that the best results are obtained in subjects at the highest risk. Importantly, the incidence of hip fractures was also reduced to 51% in women taking alendronate, an extraordinary finding considering the size of the study that was not designed to detect effects on hip fracture, a much less frequent event relative to vertebral fractures [21]. These results remain a milestone observation that has revolutionised the approach to treating osteoporosis and demonstrate the efficacy of this bisphosphonate for fracture prevention.

In the non-vertebral fracture arm of the FIT trial, 4432 postmenopausal women with femoral neck T score <-1.6, but without vertebral fractures at baseline were studied in the same fashion as for the vertebral fracture arm. At the end of the study, there was an overall statistically significant 44% reduction in new morphometrically defined vertebral fractures in the alendronate group. Although clinical vertebral fractures or hip fractures were not statistically decreased in this study population, in the subgroup of women with femoral neck T-score <-2.5 there was indeed a reduction in both clinical vertebral fractures (36%) and hip fractures (56%) in the alendronate group. This result underscores the concept that, in primary prevention, therapeutic interventions are only effective in subjects at risk. When the risk is low or absent, expecting an effect may be unreasonable. Hence, a diagnosis of osteoporosis or a full estimation of fracture risk should always be made before committing a patient to long-term therapies with a bone active drug.

Risedronate. In early postmenopausal women, 5 mg daily of risedronate for 2 years produced 5.7% and 5.4% increments of vertebral and trochanter bone

density, respectively. Efficacy on vertebral fracture prevention was demonstrated in the VERT (Vertebral Efficacy with Risedronate Therapy) trial, which was conducted on 2458 postmenopausal osteoporotic (femoral neck T-score <−2.5) women with at least 1 vertebral fracture at baseline, as two separate trials in North America and in the rest of the world [22]. Relative to women receiving only vitamin D (500 IU) and calcium (1000 mg), 5 mg of risedronate daily resulted in significant increases in bone density at the lumbar spine and proximal femur, and reduced the incidence of new vertebral fractures by as much as 65% within the first year of the study and by 41% at 3 years [22]. As a secondary outcome, a significant 39% reduction in non-vertebral fractures among treated women was detected, but no significant reduction in hip fractures was noted. While the VERT trial was not powered to detect such an effect, the HIP (Hip Intervention Program) found a 30% reduction in new hip fracture in women taking risedronate (pooled data from 2.5 and 5 mg daily) [23]. In addition to the indication for prevention and therapy of postmenopausal osteoporosis, risedronate is also approved for the treatment of steroid-induced osteoporosis.

Ibandronate is a third generation, potent bisphosphonate currently available at 150 mg once a month. Bone markers of turnover were also suppressed, although with a fluctuating pattern.

Zoledronate is the most potent bisphosphonate among the ones currently available in clinical medicine. With intravenous administration, zoledronate at a yearly dose of 5 mg is currently approved for the treatment of osteoporosis, hypercalcemia of malignancy and bone metastases. The Horizon trial [24] demonstrated a 40% reduction in zoledronate-treated patients versus placebo for hip fractures, rising to more than 50% for vertebral fractures. Zoledronate treatment is also associated with 30% reduction in mortality. Recent data [25] have shown also a strong efficacy of zoledronate used every 18 months for 5 years in osteopenic post-menopausal women. Importantly, secondary analysis also proved efficacy for reducing the risk of cardiovascular diseases and mortality.

Use of zoledronate is limited by hospital setting and acute reaction symptoms.

15.5.1.1 Adverse Events

The common ones are upper gastrointestinal adverse reactions with oral dosing, acute phase reaction with intravenous dosing. The uncommon are bone, joint and muscle pain.

The rare ones are eye inflammation, femoral shaft or subtrochanteric fractures with atypical radiographic features, osteonecrosis of the jaw.

In recent years, the fear of rare side effects of bisphosphonates has increased, in particular, osteonecrosis of the jaw, an opportunistic infection with actinomyces caused by the inhibition of osteoclast activity that mostly happens after dental surgery. It is appropriate to recall the Joint Position of ASBMR which reiterates that the incidence of this event is only 1:100,000 in patients who are treated with bisphosphonates for osteoporosis while it is much higher in patients treated for bone metastases or immunosuppressed. It is however recommended to perform a dental check before starting therapy and always maintaining good oral hygiene.

Contraindications for all these drugs are hypersensitivity and hypocalcaemia. For oral drugs: oesophageal abnormalities that delay emptying, inability to remain upright; zoledronic acid should not be used in impaired renal function (creatinine clearance less than 35 mL/min).

There is a warning about the use of bisphosphonates in patients with severe renal impairment.

15.5.1.2   Technical Remark

Since their chemical structure is acidic, bisphosphonates are irritant for the oesophageal mucosa if contact is prolonged. This problem can be overcome by taking the drug with 100–200 mL of water while standing upright for 30–40 min.

An important technical remark about in patients who are taking bisphosphonates is that fracture risk be reassessed after 3–5 years:

– If the risk is still high: the patient should continue therapy.
– If the risk has become low-moderate: the patient should be considered for a temporary discontinuation of bisphosphonates (bisphosphonate holiday).

A bisphosphonate holiday should involve a reassessment of fracture risk at 2–4 year intervals and consideration of reinitiating osteoporosis therapy earlier than 5 years if there is a significant decline in BMD, a new fracture or certain other factors [3].

15.5.2 Rank Ligand Inhibitor

Denosumab is a human monoclonal antibody that specifically targets RANK Ligand, an essential mediator of osteoclast formation, function and survival. The binding of this drug to RANK ligand prevents the activation of RANK on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone [26]. This drug therefore has a completely different mechanism of action from that of bisphosphonates and does not bind to bone, which is why it was more effective than bisphosphonates in the prevention of non-vertebral fractures. The effects of Denosumab on bone remodelling, reflected in bone turnover markers, reverse after 6 months [27] so it can administered only twice per year (see Table 15.2).

The positive effects of Denosumab treatment on BMD persist for 10 years (Freedom) and there is no increase in adverse effects [28]. Denosumab advantages for hip fracture patients are that it can be administered during hospitalisation in bedridden patients and doesn't have a toxicity risk in patients affected by hepatic or renal chronic failure (even with dialysis) [29]. In countries where its prescription needs a bone specialist management, family or social support is necessary.

Table 15.2 Fracture risk and route of administration of anabolic drugs

		Fracture risk reduction			
Anabolic drugs	Route of administration	Vertebral	Hip	Non-vertebral	Elderly
Teriparatide	Subcutaneous injection daily for 2 years	Yes	ND[a]	Yes	Yes
Abaloparatide (not available in Europe)	Subcutaneous injection daily for 2 years	Yes	ND[a]	Yes	Yes
Romosozumab	Subcutaneous injection monthly for 1 years	Yes	Yes[b]	Yes	Yes

[a]Studies not powered to observe effect on hip or non-vertebral fracture risk
[b]Data available only in sequential therapy with alendronate

15.5.2.1 Adverse Events

Uncommon: skin rash; rare: cellulitis, femoral shaft or subtrochanteric fractures with atypical radiographic features, osteonecrosis of the jaw.

Contraindications for Denosumab use are hypocalcaemia, pregnancy, hypersensitivity;

Warning: multiple vertebral fractures have occurred when Denosumab has been discontinued.

15.5.2.2 Technical Remark

A drug holiday is not recommended with Denosumab, administration should be not delay or stopped without subsequent antiresorptive therapy to prevent a rebound in bone turnover [30].

15.6 Anabolic Drugs

Anabolic drugs are recommended in postmenopausal women at very high risk of fracture, such as those with severe or multiple fractures. Osteoanabolic therapy has the potential to restore skeletal microstructure and uniquely transform osteoporotic bone towards normal [31]. We have two class of anabolic drugs: parathyroid hormone receptor agonist and sclerostin antibody (see Table 15.3). Teriparatide is a current therapy, whereas abaloparatide and romosozumab should be considered emerging therapies.

The fracture risk reduction and the route of administration of anabolic drugs are shown in Table 15.2.

15.6.1 Parathyroid Hormone Receptor (PTHr) Agonists: Teriparatide and Abaloparatide

The safety and efficacy of PTHr agonists have not been established beyond 2 years of treatment so the maximum duration of therapy over a patient's lifetime is 24 months.

Table 15.3 Fundamental recommendation in secondary prevention in the elderly (modified by the American Society of Bone and Mineral Research Secondary prevention Guidelines 2019)

- Offer pharmacologic therapy for osteoporosis to people aged 65 years or older with a hip or vertebral fracture, to reduce their risk of additional fractures
  - Do not delay initiation of therapy for bone mineral density (BMD) testing
  - Consider patients' oral health before starting therapy with bisphosphonates or denosumab
  - For patients who have had repair of a hip fracture or are hospitalized for a vertebral fracture:
    Oral pharmacologic therapy can begin in the hospital and be included in discharge orders
    Intravenous and subcutaneous pharmacologic agents may be therapeutic options after the first 2 weeks of the postoperative period. Concerns during this early recovery period include:
    Hypocalcemia because of factors including vitamin D deficiency or perioperative overhydration
    Acute phase reaction of flu-like symptoms following zoledronic acid infusion, particularly in patients who have not previously taken zoledronic acid or other bisphosphonates
    If pharmacologic therapy is not provided during hospitalization, then mechanisms should be in place to ensure timely follow-up.
- Initiate a daily supplement of at least 800 IU vitamin D per day for people aged 65 years or older with a hip or vertebral fracture.
- Initiate a daily calcium supplement for people aged 65 years or older with a hip or vertebral fracture who are unable to achieve an intake of 1200 mg/day of calcium from food sources.
- Because osteoporosis is a life-long chronic condition, routinely follow and re-evaluate people aged 65 years or older with a hip or vertebral fracture who are being treated for osteoporosis. Purposes include:
  - Reinforcing key messages about osteoporosis and associated fractures
  - Identifying any barriers to treatment plan adherence that arise
  - Assessing the risk of falling
  - Monitoring for adverse treatment effects
  - Evaluating the effectiveness of the treatment plan; and
  - Determining whether any changes in treatment should be made, including whether any antiosteoporosis pharmacotherapy should be changed or discontinued

In the registration study the hip fracture reduction for both agents was not statistically significant, probably because the numbers of hip fracture were small and the studies were inadequately powered for this endpoint; however, increased bone strength in the hip has been reported with longer term treatment [32].

These agents are much more expensive than other antiosteoporotic drugs, for this reason, they are used only in secondary treatment.

Teriparatide is a fragment of full-length PTH, it is recommended for postmenopausal women with osteoporosis at very high risk of fracture (severe or multiple fractures) [33].

In comparator studies, teriparatide was significantly more effective in:

- Protecting postmenopausal women with osteoporosis from vertebral fracture than was risedronate [34].
- Preventing new vertebral fractures in glucocorticoid-induced osteoporosis than was alendronate [35].

Its use is limited to 24 months due to a significant increase in osteosarcoma in rats given the drug for longer than this period but, since the introduction of

teriparatide in 2002, in more than 1 million patients the rate of osteosarcoma has not been greater than expected [36].

Abaloparatide is a PTH-related protein analogue (PTHrP). It has a mechanism of action similar to teriparatide, but it showed a little more efficacy in preventing vertebral fractures compared with placebo, and milder adverse events than teriparatide [37].

Abaloparatide is not available in Europe because EMA refused its commercialisation on grounds of doubts about its effectiveness in reducing non-vertebral fractures and a tendency to tachycardia and palpitations.

15.6.1.1   Adverse Events

Common: nausea, dizziness, muscle cramps, increased serum or urine calcium or serum uric acid; uncommon: orthostatic hypotension. Abaloparatide causes less hypercalcemia but causes palpitations [38].

Contraindications: Hypercalcemia, hypersensitivity, nephrolithiasis.

Warnings: should not be used in children or adolescents with open epiphyses, or patients with Paget's disease of bone, previous external beam or implant radiation involving the skeleton, bone metastases, history of skeletal malignancies, other metabolic bone diseases or hypercalcaemic disorders.

15.6.2 Anti-Sclerostin Antibody: Romosozumab

Romosozumab is a monoclonal antibody that binds and inhibits sclerostin. It exerts a dual effect on bone: increased bone formation and decreased bone resorption [39]. During 2019 it was approved by FDA and EMA and in Japan for the treatment of osteoporosis in postmenopausal women at high risk of fracture.

The sequence of Romosozumab followed by an antiresorptive therapy may provide significant benefits for the treatment of osteoporosis in women at high risk for fracture [40].

Another study demonstrated that 1 year of Romosozumab followed by 1 year of Denosumab treatment in the FRAME trial led to BMD changes similar to 7 years of Denosumab treatment [41]. An increased risk of cardiovascular events was observed compared with alendronate but not compared with placebo.

15.6.2.1   Adverse Events

Common: Injection-site reaction (pain (1.6% of patients), erythema (1.3%), pruritus (0.8%), haemorrhage (0.5%), rash (0.4%) and swelling (0.3%).

Contraindications: hypersensitivity.

15.6.2.2   Technical Remark for Anabolic Agents

In patients who have completed a course of anabolic agents, it is recommended to switch to treatment with antiresorptive therapies, to maintain bone density gains [3].

15.7 Influence of Osteoporosis Medication on Fracture Healing

Pharmacologic agents that influence bone remodelling are an essential component of osteoporosis management. Because many patients are first diagnosed with osteoporosis when presenting with a fragility fracture, it is critical to understand how osteoporotic medications influence fracture healing. Vitamin D and its analogues are essential for the mineralisation of the callus and may also play a role in callus formation and remodelling that enhances biomechanical strength. In animal models, antiresorptive medications, including bisphosphonates, denosumab, calcitonin, oestrogen and raloxifene, do not impede endochondral fracture healing but may delay remodelling. Although bisphosphonates and denosumab delay callus remodelling, they increase callus volume and result in unaltered biomechanical properties. Parathyroid hormone, an anabolic agent, has demonstrated promise in animal models, resulting in accelerated healing with increased callus volume and density, more rapid remodelling to mature bone and improved biomechanical properties. Clinical data with parathyroid hormone have demonstrated enhanced healing in distal radius and pelvic fractures as well as postoperatively following spine surgery [42].

There is currently no evidence that osteoporosis treatments are detrimental for bone repair and some promising experimental evidence for positive effects on healing, notably for agents with a bone-forming mode of action, which may translate into therapeutic applications [43].

15.8 Conclusion

There is a range of good pharmacological options and indications for sequential therapy to reduce the risk of further fracture in orthogeriatric patients; despite this they are frequently undertreated. The literature shows that treatment can be started even in very old patients at high risk of fracture and may be continued for as long as the developing evidence shows efficacy and safety.

Undertreatment of patients following hip fracture is an important age-related health disparity that must be addressed by both health systems and individual clinicians. The challenge for the multidisciplinary approach to fracture patients is to abolish undertreatment, thereby enabling a real improvement of quality of life for our patients.

New guidelines on secondary fracture prevention have been recently released by an international coalition led by the American Society of Bone and Mineral Research and should be followed by treating physicians and health care providers [44] (see Table 15.3).

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