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Invited Review

# Osteoporosis: Spotlight on current approaches to pharmacological treatment

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***ABSTRACT***

Despite the availability of safe and effective anti-osteoporosis treatments, osteoporosis continues to be undertreated. The increase in fragility fractures, which is the main clinical consequence of osteoporosis, is a major problem for healthcare systems of countries. A broad range of drugs including antiresorptive and anabolic agents are used in the pharmacological treatment of osteoporosis. Fracture risk assessment in drug selection is of utmost importance in terms of guiding treatment. The recommended thresholds for osteoporosis treatment decision making are based on major osteoporotic and hip fracture probabilities from the Fracture Risk Assessment Tool (FRAX®). Currently, antiresorptive agents are usually the first choice to increase bone mineral density (BMD) and reduce the fracture risk. Bisphosphonates and antiresorptive drugs such as denosumab, a nuclear factor kappa-B ligand (RANKL) inhibitor, are the most widely used drugs in the treatment of osteoporosis. Bisphosphonates alone are unlikely to provide long-term protection against fracture and restore BMD in patients with severe osteoporosis and high fracture risk. In such patients, treatment with an anabolic agent such as teriparatide, abaloparatide, or romosozumab should be ideally initiated to achieve maximal gain in bone mass and preserve the microarchitecture. Ideally, an antiresorptive drug should be continued to maintain gain in bone mass.

***Keywords:*** Anabolic agents, antiresorptive agents, osteoporosis, treatment.

Osteoporosis (OP) was defined by the World Health Organization (WHO) in 1994 as a systemic skeletal disease characterized by low bone mass and deterioration of the microarchitecture of bone tissue, resulting in increased bone fragility and increased fracture probability.[1] In 2001, the National Institute of Health (NIH) further expanded the definition of OP with the addition of the concept of bone strength, that is largely, dependent on bone mineral density (BMD).[2] Currently, BMD-based diagnostic criteria for OP remain important.[3] Osteoporosis is one of the main clinical, social, economic health issues worldwide.[4] Currently and in the future, OP-related fractures are expected to increase gradually in the aging population of industrialized countries, leading to increased medical and socioeconomic burden on the countries.[4-6] In a scorecard and economic model study conducted to define the burden of OP in Türkiye, about 255,183 fragility fractures occurred in 2019 with 455 million USD for OP-related health expenditures. In this study, it was concluded that OP was undertreated in Türkiye and worldwide, and it is estimated that 1.35 million fractures would occur from 2019 to 2023 with a cost of 2.42 billion USD.[6] Overall, it is estimated that one in three women and one in five men over the age of 50 years worldwide would experience and OP-related fracture in their life.[7]

A central fracture, an index fracture, is an important risk factor for the development of a new fracture. The risk of a subsequent fracture is

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particularly high in the first two years after the first fracture, which is called imminent risk.[7-10] When the index fracture site overlaps with the subsequent fracture site, the fracture risk increases even more.[11] In such cases, early intervention is needed to prevent further fractures.[12,13]

Pharmacological and non-pharmacological treatments are used in the prevention and management of OP fractures. Pharmacological treatment includes a wide range of drug groups such as antiresorptive and anabolic agents.[5,10,14] Fracture risk assessment in drug selection is of utmost importance for guiding treatment.[13] In accordance with the recommendations of the current guidelines, antiresorptive agents are the first choice to reduce the fracture risk in patients with moderate-to-high fracture risk in the treatment of OP.[15] Anabolic agents are recommended in only patients with a very high risk of fracture, due to high drug costs.[9,16-19] Low calcium intake and vitamin D deficiency are positively associated with the OP prevalence.[20] The use of dietary calcium and vitamin D alone in the treatment of OP is insufficient, and vitamin D and calcium deficiency should be corrected before pharmacological treatment.[18,21]

## Current approach to osteoporosis treatment

All patients who are candidates for OP treatment should be first informed about the OP risk factor reduction, and the role of calcium and vitamin D intake, and exercise as a part of the OP treatment program should be explicitly stated and the patients should be evaluated for secondary OP.[5,22] Dietary and calcium and vitamin D supplementation alone are not sufficient in the OP treatment and they should be used with other agents to maintain a healthy bone physiology.[18] In addition, fracture risk assessment in drug selection is of utmost importance for guiding treatment.[13] Many individuals at risk of OP fractures are unable to be still diagnosed and treated properly and timely. Therefore, based on the data from large cohort series, the WHO developed an algorithm, namely the Fracture Risk Assessment Tool (FRAX®), which is used to identify the risk of fracture, considering clinical risk factors and femoral neck BMD. Despite certain drawbacks of the tool, using these risk factors, the FRAX calculates the probability of hip fracture or major OP fracture within 10 years and is used in making treatment decisions.[13,23]

Furthermore, considering the current evidence-based diagnostic and therapeutic guidelines, an individual treatment program should be tailored for each patient and comorbidities, drug interactions, treatment compliance, and special conditions of the healthcare system should be scrutinized. There are different doses and methods of administration of antiresorptive and anabolic agents used in the treatment of OP.[10,16-18,24,25] The dose scheme of current treatment options, methods of administration, and indications approved by the United States Food and Drug Administration (FDA) for the treatment of OP are summarized in Table 1.[5,10,18] Randomized-controlled studies (RCTs) have shown that all these agents reduce the risk of vertebral fractures in OP patients, while some others further reduce the risk of hip and/or non-vertebral fractures (Table 2).[16,21,25,26]

The main goals of targeted treatment in OP are to tailor treatment according to the risk of fracture, to reduce the risk of treatment-related side effects, and to improve adherence to treatment.[27] Initial treatment is chosen as monotherapy or combined therapy to achieve the goal. The decision on how long to continue treatment, switch or discontinue treatment is made according to the progress toward the goal.[28]

## Who should be treated with pharmacological therapy?

Women at the highest risk of fractures benefit most from OP medications. Therefore, patient selection should be based on the fracture risk considering a combination of clinical risk factors and BMD.[3,29,30] Although current evidence-based diagnostic and therapeutic guidelines differ slightly from country to country, pharmacological treatment is indicated if postmenopausal women and men aged ≥50 years have the following characteristics:[10,16,21,31]

1. Having a fragility fracture of the hip or spine
2. Spine, femoral neck, or total hip T-score ≤-2.5
3. In case of low bone mass with T-score between -1 and -2.5, 10-year risk of hip fracture ≥3% or 10-year risk of major OP fracture ≥20% based on FRAX scoring

Although country-adapted fracture prediction algorithms and national recommendations provide clinical guidance, OP treatment should be tailored individually, through joint decision-making between the patient and clinician.[29] In addition to the guideline recommendations, comorbidities of the patient, drug interactions, treatment compliance, and special conditions of the healthcare system play a critical role in the development an individual treatment program. Considering the reimbursement policy in Türkiye,

**TABLE 1**
Commonly used anti-osteoporotic agents[5,10,18]

| Agent name | Dosing/form/frequency | Approval (by FDA) |
|---|---|---|
| Antiresorptive agents | | |
| Alendronate | 10 mg/PO/daily[1]<br>70 mg/PO/weekly | PMO prevention and treatment<br>GIOP<br>Male OP |
| Risedronate | 5 mg/PO/daily[1]<br>35 mg/PO/weekly<br>150 mg/PO/monthly | PMO prevention and treatment<br>GIOP treatment and prevention<br>Male OP |
| Ibandronate | 2.5 mg/PO/daily[1]<br>150 mg/PO/monthly<br>3 mg/IV/every 3 months | <br>PMO prevention and treatment (PO)<br>PMO treatment (IV) |
| Zoledronic acid | 5 mg/IV/once yearly | PMO prevention and treatment<br>GIOP prevention and treatment<br>Male OP<br>Prevention of new fracture after hip fracture |
| Denosumab | 60 mg/SC/every 6 months | PMO treatment<br>GIOP treatment<br>Male OP<br>Men with nonmetastatic prostate cancer receiving androgen deprivation therapy<br>Women with breast cancer receiving aromatase inhibitor therapy |
| Raloxifene | 60 mg/PO/daily | PMO treatment and prevention<br>Prevention of breast cancer |
| Anabolic agents | | |
| Teriparatide | 20 µg/SC/daily | PMO treatment<br>GIOP treatment<br>Male OP |
| Abaloparatide[1] | 80 µg/SC/daily | PMO treatment |
| Romosozumab | 210 mg/SC/monthly | PMO treatment |

FDA: Food and Drug Administration; PO: Peroral; PMO: Postmenopausal osteoporosis; GIOP: Glucocorticoid-induced osteoporosis; OP: Osteoporosis; IV: Intravenously; SC: Subcutaneously; [1] Not available in Türkiye.

**TABLE 2**
Anti-fracture efficacy of anti-osteoporotic agents[16,21,25,26]

| | Reduction of fracture risk | | |
|---|---|---|---|
| Agent name | Vertebral | Non-vertebral | Hip |
| Alendronate | Yes | Yes | Yes |
| Risedronate | Yes | Yes | Yes |
| Ibandronate | Yes | NAE | NAE |
| Zoledronic acid | Yes | Yes | Yes |
| Denosumab | Yes | Yes | Yes |
| Raloxifene | Yes | NAE | NAE |
| Teriparatide | Yes | Yes | NAE |
| Abaloparatide | Yes | Yes | NAE |
| Romosozumab | Yes | Superior to alendronate[1] | Superior to alendronate[1] |

NAE: No available evidence; [1] Non-vertebral and hip fracture reductions were significant in patients receiving romosozumab for 12 months followed by 12 months of alendronate compared to patients receiving alendronate for 24 months[67]

screening for OP and making the decision to initiate treatment are critical considerations for clinicians, patients, and the public.[32]

### Calcium and vitamin D

Minimum 700 to 1000 mg of calcium and 600 to 800 IU of vitamin D are recommended for men and women over 50 years of age for the prevention and treatment of OP.[5,10,16,24,25,33] In recent years, there are many controversies regarding calcium supplementation and its safety and appropriate dose of calcium and vitamin D; however, calcium and vitamin D supplementation still remains to be important nutrients for the bone health.[5,15,20] In cases where adequate calcium intake cannot be achieved with diet, supplementation as the supportive treatment should be provided. Calcium carbonate and calcium citrate are the most common forms of calcium in supplements. The former has a lower solubility in individuals with low gastric acid levels, which can reduce calcium absorption from calcium carbonate supplements, unless taken with meals. The latter is less dependent on gastric acid for absorption than calcium carbonate and, therefore, it can be taken without meals. However, calcium supplements are usually more absorbed when taken with meals, regardless of the level of gastric acid. Absorption from supplements is the highest at doses of ≤500 mg.[10,16,34] In patients requiring more than 600 mg daily calcium supplementation, the dose should be divided.[16] Calcium supplementation above 2,000 mg daily is not recommended after the age of 50.[9,35]

Vitamin D is necessary for calcium absorption from the gut. Serum 25(OH)D vitamin level ≥20 ng/mL may be sufficient in healthy individuals, but ≥30 ng/mL is more appropriate in case of known or suspected metabolic bone disease.[10] The preferred range for patients with OP is >30 to 50 ng/mL.[16] In general, it is difficult to get enough vitamin D from foods alone. The majority of individuals in the world meet at least some of their vitamin D needs from exposure to sunlight. However, older adults are at risk of developing vitamin D deficiency, partly as the ability of the skin to synthesize vitamin D decreases with age.[36] Vitamin D supplementation should be administered in amounts than can increase and maintain serum 25(OH)D levels to about 30 ng/mL (75 nmol/L). Adults with vitamin D deficiency are usually treated with 50,000 units of vitamin D2 or vitamin D3 (or equivalent daily dose of 7,000 units of vitamin D2 or vitamin D3) once a week for 5 to 8 weeks. This regimen should be followed by maintenance therapy of 1,000 to 2,000 units daily or the dose required to maintain target serum level. Higher doses of vitamin D3 may be required in cases of pre-existing factors such as obesity, malabsorption, and advanced age.[10,16]

According to the Institute of Medicine (IOM), the safe upper limit for vitamin D intake is 4,000 IU/day in adults.[35,37] Calcium and vitamin D supplements may increase the risk of kidney stones, but do not increase the incidence of cardiovascular disease or cancer.[25] Routine intermittent administration of high doses of vitamin D (e.g. ≥60,000 IU) is not recommended, as it may increase the risk of fractures and falls.[25,37]

### Current antiresorptive drugs

### Bisphosphonates

Bisphosphonates are the most commonly used first-line drugs with proven efficacy to reduce the risk of vertebral, hip, and non-vertebral fractures.[16,17,38-42] They target the osteoclasts binding to inorganic compounds of the bone, thereby inducing osteoclast apoptosis and inhibiting bone turnover and resorption. Considering the mechanism of action, nitrogen-free bisphosphonates (etidronate, clodronate, tiludronate) act through adenosine triphosphate; nitrogen-containing alkyl-amino bisphosphonates (pamidronate, alendronate, neridronate, olpandronate, ibandronate) act through the enzyme farnesyl pyrophosphate synthetase; nitrogen-containing heterocyclic bisphosphonates (risedronate, zolendronate) do not only inhibit the farnesyl pyrophosphate synthetase, but also increase their inhibitory effects by keeping the structural changes in balance.[5,43]

Alendronate, ibandronate, risedronate, and zoledronic acid are the US FDA-approved bisphosphonates for the prevention and treatment of OP. The doses and indications for use of these bisphosphonates are listed in Table 1.[5,10,18] Studies regarding bisphosphonates have shown to increase BMD, decrease bone turnover markers, and prevent fractures in postmenopausal women and men with OP and in patients receiving glucocorticoid therapy.[5,15,26,39,44,45]

Several RCTs have demonstrated that daily oral treatment with alendronate, risedronate, and ibandronate and annual intravenous dosing with zoledronate reduces the risk of vertebral fractures by 30.7 to 70% over three years in postmenopausal

women with OP.[26,39] Alendronate, risedronate, and zoledronate have been shown to reduce the risk of hip and non-spine fractures by 25 to 50% and 20 to 38%, respectively in the long-term extension studies.[26,44,45]

### Side effects

As with all oral bisphosphonates, side effects include gastrointestinal complaints such as dysphagia, esophageal inflammation, and stomach pain and rare cases of atypical femur fracture (AFF) and osteonecrosis of the jaw (ONJ). Ocular inflammation may also occur.[10,46] With zoledronic acid, flu-like symptoms (arthralgia, headache, myalgia, fever) may develop at a rate of 32%, 7%, and 3% after the first, second, and third dose, respectively. To reduce the risk of acute phase reactions, patients should be adequately hydrated, consume two glasses of water prior to infusion and receive acetaminophen, unless contraindicated.[10]

### Contraindications

All bisphosphonates have the potential to impair renal function and are contraindicated in patients with an estimated glomerular filtration rate (GFR) below 30 to 35 mL/min. Since hypocalcemia may develop or may be exacerbated with the use of bisphosphonates, it should be corrected prior to treatment.[10,41,46]

### Denosumab

Denosumab (DMAB), a biological receptor activator of nuclear factor-kappa B ligand (RANKL) inhibitor, is a fully human monoclonal immunoglobulin G2 (IgG2) antibody which targets the RANKL.[47,48] It exerts its effects strongly reducing differentiation and activation of osteoclasts, leading to decreased bone turnover and increased BMD. Owing to its potent antiresorptive activity, it was approved by the US FDA in 2010 in the treatment of OP.[48-50] Indications for use of DMAB are listed in Table 1.[5,10,18]

The Phase III Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial investigated the effects of DMAB on vertebral fractures, non-vertebral fractures, and hip fractures in postmenopausal women with OP. The agent was administered subcutaneously at a dose of 60 mg every six months for 36 months and reduced the risk of vertebral fracture by 68%, hip fracture risk by 40%, and non-vertebral fracture risk by 20% with a relative increase in the BMD of lumbar spine and hip up to 9% and 6%, respectively.[50] In the extension phase of the trial in which the long-term efficacy and safety of the DMAB were assessed, DMAB treatment provided constant increase in BMD without plateau up to 10 years with lower adverse event rates and lower incidence of fractures, compared to those reported during the original study.[51] In this trial, no evidence of excessive suppression of bone turnover or mineralization was observed and the AFF and ONJ rates were found to be very low.[48]

Compared to bisphosphonates, the main advantages of DMAB are that it does not bind to bone mineral, its effect is reversible, it has good treatment compliance with two injections annually, and it is not excreted from the kidney. Nevertheless, the risk of hypocalcemia should be considered in patients with renal impairment.[5,50]

The antiresorptive effects of DMAB rapidly decreases after treatment discontinuation.[19] If the treatment is interrupted, switching to a different anti-OP drug class, such as bisphosphonates, may be helpful to prevent complete loss of BMD gained with DMAB and maintain its anti-fracture efficacy.[9,48] After discontinuation of DMAB (7 months after the last injection), the risk of multiple vertebral fractures increases as a result of rapid rebound in bone turnover.[19,48,52] In most cases, patients have other risk factors for fracture such as previous vertebral fracture, low spine BMD, glucocorticoid use or aromatase inhibitor treatment; therefore, DMAB should not be stopped.[17,52]

### Estrogen replacement therapy (estrogen therapy [ET]/hormone therapy [HT], raloxifene, conjugated estrogens/bazedoxifene)

These agents are effective acting on estrogen receptors in bone to prevent bone loss associated with postmenopausal OP. Estrogen therapy/HT is approved by the US FDA for the prevention of OP and the relief of vasomotor symptoms and vulvovaginal atrophy associated with menopause. If the uterus is intact, combined estrogen and progestin is used, while estrogen alone is used in patients undergoing hysterectomy.[10]

Estrogen therapy is associated with an increased risk of coronary heart disease, breast cancer, stroke, and dementia.[46] All patients should be questioned and examined for thromboembolism before ET.[21] Current recommendations are to use ET at the lowest dose, as necessary, and for the shortest possible time to relieve menopausal symptoms.[16]

Raloxifene is an estrogen agonist/antagonist and selective estrogen receptor modulator (SERM) approved by the US FDA in 1997 for the prevention and treatment of OP in postmenopausal women.[10,49] It has been shown to reduce the risk of breast cancer in high-risk postmenopausal women.[21] In an RCT including postmenopausal women with OP, raloxifene reduced the risk of vertebral fractures by 40% and increased vertebral BMD and femoral neck BMD by 2.6% and 2.1%, respectively.[53]

The recommended dose of raloxifene is 60 mg once daily with or without meals.[10] It may not be the most optimal treatment option for many patients with OP, as it has not been shown to reduce hip or non-vertebral fractures.[16] Side effects include the increased risk for deep vein thrombosis and hot flashes and leg cramps.[10]

Conjugated estrogens/bazedoxifene are used only for postmenopausal women not undergoing hysterectomy.[10]

The effects of estrogen replacement therapy diminish, when treatment is discontinued. Bone turnover markers return to pre-treatment values within a few months and BMD decreases to pre-treatment levels one to two years after treatment discontinuation. These effects can be avoided by switching to a bisphosphonate.[26]

### Calcitonin

Calcitonin is a hormone secreted by the parafollicular cells of the thyroid gland. It reduces bone resorption and increases renal calcium excretion by inhibiting mature, active osteoclasts.[5,54] Nasal spray formulations of calcitonin are approved for the treatment of postmenopausal OP. The recommended dose of calcitonin nasal spray is 200 IU once daily administered intranasally.[21] It reduces the risk of vertebral fractures by 33%.[55] However, it exerts no effects on reducing the risk of non-vertebral and hip fractures. It is not considered an alternative for the treatment of OP due to its high cost, less success in reducing the risk of fracture than other agents, and the increased risk of non-specific malignancies in recent years. It may also cause hypersensitivity as a side effect. Calcitonin forms antibodies to the drug over time. It has been shown that these antibodies are not blocking antibodies.[21]

### Calcitriol

Clinical studies of calcitriol have reported controversial results in postmenopausal OP. However, calcitriol has been shown to be effective in preventing glucocorticoid-induced and post-transplant-related bone loss. Patients treated with calcitriol should be given a low-calcium diet and followed for hypercalcemia, hypercalciuria, and renal failure. Due to these potential drawbacks and the lack of proven consistent benefit, its use is limited.[29]

### Current anabolic agents

Three anabolic agents are currently available for the treatment of postmenopausal women at high risk of fractures: teriparatide (TPTD), abaloparatide (ABL), and romosozumab. Anabolic agents increase bone strength and rapidly reduce the risk of fractures by stimulating new bone formation.[9,56,57]

Although osteoanabolic agents play a little role in preventing bone loss in early menopause, they are critical in the treatment of women who are at very high risk for fracture or who continue to be at a high fracture risk after bisphosphonate treatment.[13,19,58] They differ from antiresorptive agents owing to their ability to increase osteoblastic bone formation.[59] When treatment is initiated with antiresorptive agents, the loss of bone mass and microarchitecture can be slowed down with favorable results and the bone mass can be increased; however, the bone loss in the microarchitecture cannot be fully reversed. However, when anabolic agents are used in the first-line treatment, maximum gain in bone mass can be achieved and the microarchitecture can be preserved. Maintenance treatment with bone resorption inhibitors can be helpful to preserve this gain later.[5]

The order of administration of anabolic agents is critical. The benefits of these agents are reduced in patients previously treated with antiresorptive agents; however, antiresorptive agents administered after anabolic agents enhance BMD gain.[60]

Due to the high cost of drugs and limitations on reimbursement, these treatments are initiated by specialists rather than general practitioners in many countries.[58,60]

### Teriparatide and abaloparatide (parathyroid hormone [PTH] and parathyroid hormone-related protein [PTHrP] analogs)

Teriparatide (TPTD) and abaloparatide (ABL) are PTH receptor agonists which increase bone remodeling with increased bone formation more than bone resorption.[59] The former one, TPTD, is an agent which contains a sequence of the final 34 amino

acids in the human PTH [hPTH(1-84)]. The latter one, ABL, is a synthetic PTHrP analog of which the first 22 amino acids are identical to PTHrP with significantly different amino acids inserted later between residues 22 and 34.[61] Both TPTD and ABL act via PTH type 1 receptors which stimulate osteoblast activity with secondary activation of osteoclasts.[19]

Typically, TPTD is administered subcutaneously at 20 µg/day in the treatment of postmenopausal OP, male patients with OP, and patients with glucocorticoid OP and high fracture risk. In addition, ABL is administered subcutaneously at 80 µg/day in the treatment of postmenopausal OP with high fracture risk. Both agents significantly increase spine density and reduce the rate of vertebral and non-vertebral fractures; however, there is still a limited number of data on hip fractures.[19,60] Treatment is limited to 18 to 24 months and treatment is switched to an antiresorptive agent later.[17,19,30]

### Contraindications/precautions

The PTH/PTHrP analogs are contraindicated in case of primary and secondary hyperparathyroidism, hypercalcemia, Paget's disease of bone, or unexplained elevation of alkaline phosphatase, bone metastases or skeletal malignancies, history of prior skeletal radiation therapy, risk of osteosarcoma, kidney stones or kidney failure.[62]

### Side effects

Side effects of PTH/PTHrP analogs include hypercalcemia, hypercalciuria, arthralgia, headache and dizziness, hypotension, nausea/vomiting, muscle cramps, and palpitation.

Abaloparatide may lead to a greater increase in BMD and less hypercalcemia than TPTD.[62,63]

### Romosozumab

Romosozumab, a humanized monoclonal antibody to sclerotin, has the dual effect of increasing bone formation while reducing bone resorption.[59,64] It is indicated for the treatment of OP in postmenopausal women at high fracture risk, including those with previous OP fractures, multiple risk factors, or those who are intolerant or have failed other available OP treatments.[65] It is an anabolic agent approved by the US FDA in 2019 based on data showing a reduction in vertebral and non-vertebral fractures with romosozumab compared to placebo or alendronate.[29] Sclerotin is a glycoprotein which binds to the osteoblast surface, that is critical for regulation of osteoblast activity and bone formation, and inhibits the Wnt pathway signaling. Romosozumab is a humanized monoclonal antibody which binds sclerotin. It exerts its inhibitory effects via preventing sclerotin to bind to LRP-5 and LRP-6 receptors.[28]

Several studies have investigated the efficacy and safety of romosozumab in the treatment of OP.[65] In the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) and Active-Controlled Fracture Study in Postmenopausal Women With Osteoporosis at High Risk (ARCH) trials, romosozumab significantly increased the BMD in postmenopausal women and reduced the fracture risk.[66,67] In the Phase III Open-Label Study to Evaluate the Effect of Treatment with Romosozumab or Teriparatide in Postmenopausal Women (STRUCTURE) trial, romosozumab was compared with TPTD in patients in whom previous bisphosphonate therapy failed and romosozumab yielded a greater amount of increase in the BMD than TPTD.[68] In the Phase III Placebo-Controlled Study Evaluating the Efficacy and Safety of Romosozumab in Treating Men with Osteoporosis (BRIDGE) trial, romosozumab 210 mg once monthly for 12 months results in a significant increase in spine and hip BMD in male OP patients aged 55 to 90 years compared to placebo, and was well tolerated in this patient population.[69] However, romosozumab is not US FDA-approved for the treatment of OP in men and in premenopausal women.

Romosozumab was approved by the US FDA based on the results of the ARCH trial with a warning that it may increase the risk of myocardial infarction, stroke, and cardiovascular mortality. In addition, romosozumab should be avoided in patients having myocardial infarction or stroke in the year prior to or during treatment, and the risks and benefits of the agent should be considered in patients who are at high risk of cardiovascular events. Follow-up strategies are needed to maintain the high increase in BMD, as the strength of the drug decreases after repeated injections.[64,67] Although romosozumab is safe in patients with chronic renal failure, it is recommended to monitor calcium levels and adequate supplementation with calcium and vitamin D during the treatment due to the increased risk of hypocalcemia.[70]

### Other drugs: Strontium ranelate

Strontium ranelate is an anti-OP agent which exerts dual mechanism of action: it inhibits bone resorption and induces bone formation. It also increases the differentiation of preosteoblasts to

osteoblasts by stimulating calcium-sensitive receptors, and inhibits osteoclasts by increasing the synthesis of osteoprotegerin from osteoblasts. Of note, the exact mechanism of action of strontium ranelate has not been fully elucidated yet.[5,71]

Several studies have demonstrated that strontium ranelate is effective in the prevention of both vertebral and non-vertebral fractures. In the Phase III Spinal Osteoporosis Therapeutic Intervention (SOTI) trial, strontium ranelate reduced the vertebral fracture risk by 41% over the three-year study period. In the Phase III Treatment of Peripheral Osteoporosis (TROPOS) trial, strontium ranelate reduced the non-vertebral fracture risk by 16% and major fracture risk by 19%.[72,73]

The recommended dose of strontium ranelate is 2 g sachet once daily by oral administration. It is approved in the Europe for the treatment of postmenopausal OP and male OP with high fracture risk. Side effects include headache, nausea, diarrhea and, rarely, cutaneous hypersensitivity reactions and deep vein thrombosis. It is contraindicated in patients having a history of deep vein thrombosis, prolonged immobility, ischemic heart disease, peripheral artery disease, cerebrovascular disease, or uncontrolled hypertension. Its use has been restricted in many countries by the European Medicines Agency since 2013 due to the reports of serious side effects and is currently withdrawn from use in many countries, including Türkiye.[74]

## Treatment recommendations according to fracture risk

The level of fracture risk should be identified and the patients should be classified accordingly before initiating pharmacological treatment for OP, as it may affect the choice of initial treatment. In most cases, treatment is initiated due to the high fracture risk. Some patients at very high fracture risk may need more aggressive treatment to reach an acceptable level of fracture risk.[3,16]

The FRAX is the most widely adopted fracture risk assessment tool and is included in many guidelines worldwide since its launch in 2008.[3,24] Using the FRAX, major OP and hip fracture probabilities can be applied to men and women similarly.[25] Fracture risk assessment tools need intervention thresholds to be calculated for each country to guide pharmacological treatment.[3,9,25] In many countries, intervention thresholds are based not only on the T-score for BMD, but also on the presence of a prior frailty fracture.[3] The use of country-specific FRAX is recommended to evaluate the likelihood of fracture, although the Turkish FRAX model is not included in routine clinical practice across the country, since the current reimbursement policy allows prescribing of anti-OP agents without using the FRAX.[18] In the majority of guidelines, based on the US-adapted WHO algorithm, it is recommended using a fixed threshold for the treatment of OP in patients with a 10-year probability of hip fracture of ≥3% or a 10-year probability of any major OP-related fracture of ≥20%.[10,16-18] However, the National Osteoporosis Guidelines Group (NOGG) guidelines state that the intervention threshold up to age 70 years and the use of fixed thresholds above 70 years are clinically appropriate, providing equitable access to treatment.[25] Treatment recommendations of the current guidelines according to the OP risk levels are listed in Table 3.[13,16-18]

## Duration and algorithm of OP treatment

As in any lifelong chronic disease, OP is ideally managed with ongoing treatment and follow-up. Therapeutic benefits can only be maintained with treatment. When pharmacological treatment is discontinued, the BMD and fracture risk can be expected to return to baseline or even worsen. This reversal occurs gradually, when bisphosphonates are discontinued, but more rapidly with non-bisphosphonate anti-OP agents.[10]

The American Association of Clinical Endocrinology (AACE) recommends that drug holiday should be considered after five years of oral and three years of intravenous bisphosphonate therapy in high-risk patients without a history of fracture and in the absence of increased or stable BMD and fractures. It is recommended re-initiating treatment if fractures occur, BMD decreases above the least significant change, bone turnover markers increase to pre-treatment values, or the patient meets criteria for initial treatment. Treatment adherence and secondary causes of OP and factors leading to inadequate response should be evaluated thoroughly, if there is progressive bone loss or recurrent fractures. An injectable antiresorptive should be switched if an oral agent is being used, and TPTD, ABL or romosozumab should be switched if an injectable antiresorptive agent is used or there is a very high fracture risk.[16] The NOGG guidelines recommend that patients aged above 70 years with previous hip fracture or with ≥2 vertebral fractures or those

**TABLE 3**
Treatment recommendations according to the level of osteoporotic fracture risk[13,16-18]

**Very high risk: if one or more of the following**
- Major osteoporotic fracture in the last 12-24 months
- Multiple major osteoporotic fractures
- Fracture during osteoporosis treatment
- Fracture during treatment with harmful drugs for bone
- T-score ≤–3.5
- T-score ≤–2.5 and FRAX: 10-year major osteoporotic fracture risk ≥30%, hip fracture risk ≥4.5%

**Treatment**
- Anabolic agents: teriparatide, abaloparatide, romosozumab
- Antiresorptive agents: denosumab, zoledronic acid
- Calcium, vitamin D, modification of lifestyle and prevention of falls

**High risk: if any of the following**
- Hip or recent spine fracture
- T-score ≤–2.5 and one vertebral fracture
- T-score ≤–3.0
- Continuing treatment with harmful drugs for bone and T-score ≤–2.5
- Age >75 years and T-score ≤–2.5
- T-score ≤–2.5 and FRAX: 10-year major osteoporotic fracture risk ≥20%, hip fracture risk ≥3%

**Treatment**
- Anabolic agents: teriparatide, abaloparatide, romosozumab
- Antiresorptive agents: alendronate, risedronate, zoledronic acid, denosumab
- Calcium, vitamin D, modification of lifestyle and prevention of falls

**Moderate risk: if any of the following**
- T-score ≤–2.5 and no fracture
- T-score between -1 and -2.5 and FRAX: 10-year major osteoporotic fracture risk ≥20%, hip fracture risk ≥3%

**Treatment**
- At any age: alendronate, risedronate
- If the patient is <65 years old: raloxifene, ibandronate, hormone-replacement therapy
- Calcium, vitamin D and modification of lifestyle

**Low risk: if any of the following**
- Age <65 and T-score >–2.5 and no major risk factors
- T-score between -1 and -2.5 and FRAX: 10-year major osteoporotic fracture risk <20%, hip fracture risk <3%

Treatment
- Calcium, vitamin D and modification of lifestyle

FRAX: Fracture Risk Assessment Tool.

receiving high-dose glucocorticoids (≥7.5 mg/day prednisolone or equivalent) can be administered bisphosphonates up to 10 years.[25] In addition, DMAB can be used up to 10 years without any interruption.[18] There is no evidence-based data to guide treatment decisions beyond 10 years and the management of these patients should be evaluated on an individual basis.[25]

## Combination therapy

Combination therapy is not recommended due to the lack of proven additional fracture benefit, although it provides an increase in BMD in postmenopausal OP.[9,10,18,29]

Among combination therapies, TPTD plus DMAB is the most promising treatment investigated so far. In the Denosumab and Teriparatide Administration (DATA) trial, the patients were randomized to either TPTD alone, DMAB alone, or TPTD plus DMAB for 24 months. The BMI significantly increased in the combined arm than monotherapies and approved treatments. However, in this trial, no data regarding the fracture are available. As a result, combination of these two agents seems to be a feasible alternative in patients with high fracture risk.[75]

Bisphosphonate, DMAB, or TPTD can be administered as add-on treatment to patients receiving

estrogen to treat menopausal symptoms or raloxifene to reduce the risk of breast cancer, if they are at high fracture risk.[18]

### Treatment adherence and treatment success

Considering the long-term nature of the treatment, treatment adherence is an important issue for OP patients.[18] Good adherence is defined as receiving medications correctly at least 80% of the prescribed days (medication possession ratio) with a non-adherence rate of <80%. Adherence to OP medications is usually poor and suboptimal, ranging from 34% to 75% in the first year of treatment.[76] About 25 to 30% of OP patients do not start taking their prescribed medication due to forgetfulness or the complexity of the treatment regimen. The main reasons for deliberate non-compliance with the recommended treatment are limited knowledge of OP, fear of side effects, distrust of physicians or drugs, and lack of knowledge regarding the drug and/or the necessity of the drug. The incidence of fracture is 30% higher in patients who do not comply with the treatment.[10]

There is a great need to improve persistence and adherence to OP medications. Persistence and adherence are higher with parenteral treatments. Previous studies have shown higher adherence to parenteral drugs requiring reduced dosing frequency than oral drugs.[77] In addition, collaboration between the patient and healthcare provider for each individual patient should be a part of the process to improve persistence and adherence to OP treatment.[76]

In general, patients at high fracture risk do not receive adequate treatment. To address this gap, strategies should be developed including applying combined pharmacological and non-pharmacological treatments, informing general practitioners, increasing the use of Fracture Liaison Services, improving communication on reminder systems (e.g., appointment/medication follow-up), and improving adherence to treatment.[10,14,18,19,25,30,54,78]

In conclusion, current agents used in the treatment of OP are effective and safe and are usually well tolerated. Although country-adapted fracture prediction algorithms and national recommendations provide clinical guidance, OP treatment should be tailored on an individual basis through joint decision-making between the patient and clinician. Antiresorptive agents are usually chosen in the first-line treatment; however, in patients at high and imminent fracture risk, treatment initiation with a more effective anabolic drug followed by an antiresorptive agent would likely provide fracture prevention in the longer term.

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