



## 2013 Up-date of the consensus statement of the Spanish Menopause Society on postmenopausal osteoporosis



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### ABSTRACT

Postmenopausal osteoporosis is a major female health problem that increases morbidity, mortality and healthcare system costs. Considering that gynecologists are the primary health practitioners involved in the treatment of women with osteoporosis in our country, a panel of experts from the Spanish Menopause Society met to establish a set of criteria and procedures for the diagnosis and treatment of this disease based on the best available evidence and according to the model proposed by the GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) system to elaborate clinical practice guidelines and to classify the quality of the evidence and the strength of the recommendations. These recommendations should be a reference to gynecologist and other health professionals involved in the treatment of postmenopausal women.

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### 1. Introduction

Postmenopausal osteoporosis (PMOP) is a major female health problem that increases morbidity, mortality and healthcare system costs. Spain is a country of low risk of osteoporosis. Besides lifestyle reasons, Spanish gynecologists are very involved in the prevention of OP. Still, it is estimated that PMOP affects 35% of Spanish women over 50 years of age and 52% of those over 70 years of age and that 12–16% of all women will suffer hip fractures secondary to PMOP [1].

Considering that gynecologists are the primary health practitioners involved in the treatment of women with osteoporosis in our country [2,3], a panel of experts from the Spanish Menopause

Society met to establish a set of criteria and procedures for the diagnosis and treatment of this disease based on the best available evidence. The *Spanish Menopause Society* considers it appropriate to develop its own recommendations based on the GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) system to elaborate clinical practice guidelines and to classify the quality of the evidence and the strength of the recommendations [4].

## 2. Strategies for the prevention of osteoporotic fractures

The diagnosis of and risk stratification for PMOP are based on the detection of risk factors (RFs) and on the measurement of bone mineral density (BMD), as indicated in [Algorithm 1](#). The best-validated PMOP RFs include old age, personal history of any fragility fracture or a family history of hip fracture, use of glucocorticoids, excessive alcohol consumption, smoking, and rheumatoid arthritis [5]. We also recommend evaluating factors that increase the risk of falls; these include muscle weakness, impaired coordination, difficulty walking or standing, osteoarthritis, impaired vision, and consumption of certain drugs. Furthermore, prolonged hypoestrogenism (early menopause, anorexia nervosa, extreme physical exercise, or the use of aromatase inhibitors) is unique to women and has a great influence on bone loss. Given these RFs, various instruments and scales have been devised that aim to predict fracture risk even without the need to measure BMD [6,7].

We recommend dual-energy X-ray absorptiometry (DXA) to measure BMD; this method is considered a reference technique. Other methods (ultrasound, peripheral equipment, CT scan) are useful in predicting the risk of fracture but not for diagnosis or follow-up. Radiography is sensitive and specific for the detection of vertebral fractures but not for the assessment of bone mass [8].

Spain is a country of low risk of osteoporosis, perhaps due to lifestyle reasons that include diet and sun exposure. Observational studies have reported that our diet is linked to higher BMD and lower fracture risk [9]. They form the necessary foundation for pharmacologic approaches to the prevention or management of osteoporosis. In this sense, all patients should receive advice on how to maintain a healthy lifestyle aimed at preserving bone strength. This advice should include recommendations for following a balanced diet, getting regular exercise, and cessation of smoking and/or excessive alcohol consumption. We also recommend calcium and vitamin D supplements when these are missing in the diet and when drug treatments are prescribed for PMOP. There is a reduction in the tendency to fall and an improvement in muscle function and physical performance when dietary supplementation with 800 IU vitamin D is administered to deficient populations [10–12].

The recommended type of exercise combines resistance with weight bearing. This type of exercise improves body stability, compensates for weakness or postural abnormalities, and can be adapted to the functional capacity of each woman. The simplest exercise is walking for 30 min a day; other types of exercise that focus on balance (e.g., tai chi) should be considered for women at risk of falls [13].

## 3. Pharmacological treatment of PMOP

There is an abundance of evidence regarding the effectiveness of the available treatments for PMOP in reducing the risk of vertebral fractures. Some treatments also prevent nonvertebral fractures and reduce morbidity and mortality arising from these (see [Table 1](#)).

## 4. Hormone therapy (HT)

Hormonal treatment (HT) with estrogen alone or with estrogen combined with progestogens or tibolone is still considered the treatment of choice for menopausal symptoms. All treatments of this type have antiresorptive effects, and there is evidence that standard-dose HT reduces all types of fractures even in osteopenic women [14,15]. Improvements in BMD have been observed with low doses, but there are no trials that assess the reduction in fractures [16].

In general, the benefits of HT to bone health disappear when treatment is stopped; when this occurs, some other continuation treatment should be administered to protect bone. Similarly, women who undergo early menopause are protected from PMOP by HT until age 50 with no need for other antiresorptive drugs; at this age, evaluation of whether to continue the same therapy or change treatment is needed.

## 5. Selective estrogen receptor modulators (SERMs)

Tamoxifen is used for the prevention and treatment of breast cancer. Women who use it do not need additional drug therapy for bone protection.

Raloxifene was the first SERM approved for the treatment of PMOP; it is also effective in reducing the risk of breast cancer. Raloxifene reduces the risk of vertebral fractures and also nonvertebral fractures in women with severe pre-existing vertebral fractures, as was shown in a post hoc analysis dedicated to them. It does not stimulate the endometrium, but it increases the risk of thrombosis and causes hot flashes and cramps. Although neutral for cardiovascular disease [17,18], a post hoc analysis has suggested that raloxifene might reduce risk for coronary heart disease in women at higher risk [19].

Bazedoxifene is a third-generation SERM with high affinity for the estrogen receptor alpha. In a three-year randomized clinical trial (RCT), the incidence of new vertebral fractures was significantly lower in women treated with bazedoxifene or raloxifene versus placebo (fracture rates of 2.3, 2.5, and 2.3 vs. 4.1%) [19–21]. In a post hoc analysis and subsequent studies, bazedoxifene was shown to reduce the risk of vertebral fracture in women at high risk; its benefits extended up to seven years, and it protected against endometrial cancer. The incidence of breast fibrocystic disease was lower with bazedoxifene or raloxifene than placebo after three years of treatment, while changes in breast density and breast cancers were low and evenly distributed among the three groups [22,23]. Although there is clear evidence that raloxifene is effective in primary prevention of breast cancer in women at risk for osteoporosis, this evidence is not available for bazedoxifene at the moment. Superiority of bazedoxifene to raloxifene in terms of cost-effectiveness has been suggested based on its efficacy versus raloxifene in preventing non-vertebral fractures in women at high risk [24].

## 6. Bisphosphonates

Bisphosphonates offer great flexibility in route and schedule of administration, and some (alendronate) are also available in combination with vitamin D. Ibandronate has not been shown to reduce the risk of non-vertebral fractures or new fractures in women without prior vertebral fractures, but monthly administration of ibandronate may be advantageous for some patients [25–27].

Bisphosphonates bind tightly to hydroxyapatite crystals and exert an antiresorptive action for years, so we must be cautious in using them in young women over long periods. In recent years, concerns have been raised about some of their long-term effects (ONJ

**Table 1**  
Features of major marketed drugs for osteoporosis in Spain (according to technical data sheet, updated April 2013)<sup>a</sup>

Active principle	Dosage and administration	Indications	Contraindications	Adverse effects <sup>b</sup>
Estrogens	Dose: 1–2 comp Route: oral Freq: daily	PMOP prevention in postmenopausal women and ↑ fracture risk for patients who are intolerant of or have contraindications for other approved treatments for PMOP prevention	Allergy to estrogens/excipients Personal history of past or suspected breast cancer Malignant or suspected estrogen-dependent tumors Undiagnosed vaginal bleeding Untreated endometrial hyperplasia Idiopathic venous thromboembolism or history Known thrombophilic alterations Active or recent arterial thromboembolic disease Pregnancy and lactation Acute liver disease or a history of liver disease with abnormal liver function tests Porphyria	Common: vomiting, abdominal pain, anorexia, depression, vaginal bleeding, breast secretions, gynecomastia, breast pain, amenorrhea, dysmenorrhea, cholestatic hepatitis, jaundice, endometrial hyperplasia, dizziness, alopecia, headache, ↑ weight Uncommon: libido and mood changes, edema, abnormal menstrual bleeding, dizziness, venous thromboembolism, migraine headaches, breast cancer, vaginitis Rare: pancreatitis, stroke/ictus, ovarian cancer, allergic reactions, glucose intolerance, asthma exacerbation, hirsutism
Tibolone	Dose: 2.5 mg Route: oral Freq: daily Administer preferably at the same time of day. If a dose is missed, it should be taken as soon as remembered unless it has been more than 12 h since the usual time. In the latter case, the missed dose should be skipped and the next dose taken at the usual time	Treatment of estrogen deficiency symptoms such as hot flashes, sweating, and libido or mood changes in postmenopausal women (over 1 year).	Hypersensitivity Pregnancy and lactation Breast cancer, a history or suspicion of cancer. Estrogen-dependent malignant tumors (endometrial cancer) Undiagnosed vaginal bleeding Active deep vein thrombosis or thromboembolic disorders; untreated endometrial hyperplasia; known thrombophilic alterations Arterial thromboembolic disease (angina, myocardial infarction, CVA or transient ischemic attack) Acute liver disease or a history of acute liver disease Porphyria	Common: lower abdominal pain, abnormal hair growth; vaginal discharge, endometrial wall thickening, postmenopausal bleeding, breast pain to palpation, genital itching, vaginal candidiasis, vaginal bleeding, pelvic pain, cervical dysplasia, genital discharge, vulvovaginitis; weight gain, abnormal cervical smear Uncommon: acne, breast tenderness, yeast infection, vaginal mycosis, sore nipples
Raloxifene	Dose: 60 mg Route: oral Freq: daily It can be given at any time of day without regard to meals	Treatment and prevention of osteoporosis in postmenopausal women	Allergy to raloxifene/excipients Women who may become pregnant, pregnancy or nursing History/current episode of venous thromboembolism (DVT, pulmonary embolism, retinal vein thrombosis) Hepatic failure, including cholestasis Severe renal failure Unexplained uterine bleeding Patients with signs or symptoms of endometrial cancer or who are receiving treatment for breast cancer	Very common: vasodilation (flushing), flu-like syndrome Common: leg cramps, peripheral edema Uncommon: venous thromboembolism (VTE) (DVT, pulmonary embolism, retinal vein thrombosis, superficial vein thrombosis) Rare: thrombocytopenia, nausea, vomiting, abdominal pain, dyspepsia, headache, rash, arterial thrombosis, ↑ blood pressure, breast pain
Bazedoxifene	Dose: 20 mg Route: oral Freq: daily It can be given at any time of day without regard to meals	PMOP in postmenopausal women with ↑ risk of fracture	Allergy to bazedoxifene/excipients Presence or history of VTE (DVT, pulmonary embolism, and retinal vein thrombosis) Women of childbearing age Unexplained uterine bleeding Patients with signs or symptoms of endometrial cancer	Very common: hot flashes, muscle cramps Common: hypersensitivity, drowsiness, dry mouth, rash, peripheral edema, ↑ triglycerides, GOT, GPT Uncommon: DVT, pulmonary embolism

Table 1 (Continued)

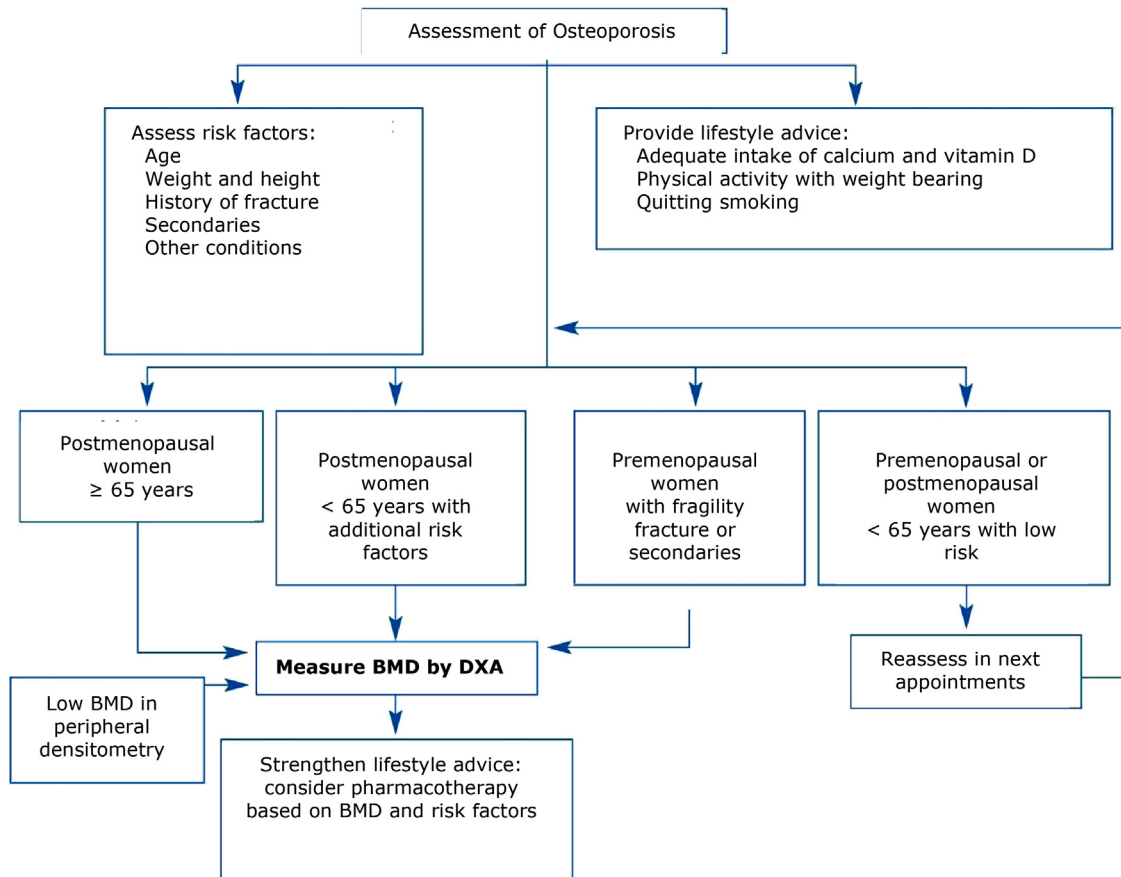
Active principle	Dosage and administration	Indications	Contraindications	Adverse effects <sup>b</sup>
Alendronate	Dose: 70 mg/2800 IU vit. D and 70 mg/5600 IU vit. D Route: oral Freq: weekly At least 30 min before the 1st food, beverage, or medication of the day with plain water only	Postmenopausal OP	Allergy to alendronate/excipients Abnormalities of the esophagus or other factors that delay esophageal emptying (stricture, achalasia) Inability to remain upright (sitting or standing $\geq 30$ min) Hypocalcemia Severe renal failure Pregnancy and lactation	Common: abdominal pain, dyspepsia, headache, constipation, diarrhea, flatulence, esophageal ulcer, dysphagia, musculoskeletal pain Uncommon: gastritis, esophagitis, esophageal erosions, melena Rare: symptomatic hypocalcaemia, uveitis, esophageal stricture, PUH, ON jaw
Risedronate	Dose/frequency: 5 mg/day, 35 mg/wk. 2 days followed by 75 mg/month Route: oral At least 30 min before the first food, beverage or medication of the day with plain water only	Postmenopausal OP to $\downarrow$ the risk of vertebral and hip fractures PMOP prevention in women and $\uparrow$ risk of osteoporosis Maintain/ $\uparrow$ bone mass in postmenopausal women and prednisone or equivalent $>3$ months and $\geq 7.5$ mg/day PMOP in men and $\uparrow$ risk of fractures	Allergy to risedronate/excipients Hypocalcemia Severe renal failure Pregnancy and lactation Special attention if: esophageal abnormalities or other factors that delay esophageal emptying (stricture, achalasia), active or recent upper gastrointestinal or esophageal disorders, or inability to remain upright (sitting or standing) $\geq 30$ min	Common: headache, constipation, dyspepsia, abdominal pain, diarrhea, musculoskeletal pain Uncommon: iritis, gastritis, esophagitis, dysphagia, duodenitis, esophageal ulcer Rare: glossitis, esophageal stenosis, abnormal liver function tests
Ibandronate	Dose: 150 mg Route: oral Freq: monthly After night fasting (at least 6 h) and 1 h before breakfast or 1st drink (other than water) of the day or other medications or supplements by mouth, including calcium	Postmenopausal OP/ $\uparrow$ risk of fracture	Allergy to ibandronate/excipients Abnormalities of the esophagus or other factors that delay esophageal emptying (stricture, achalasia) Inability to remain upright (sitting or standing) $\geq 60$ min Hypocalcemia Severe renal failure Pregnancy and lactation Special attention if: esophageal abnormalities or other factors that delay esophageal emptying (stricture, achalasia), active or recent upper gastrointestinal or esophageal disorders	Common: headache, rash, esophagitis, gastritis, GERD, dyspepsia, diarrhea, abdominal pain, musculoskeletal pain, flu-like illness Uncommon: esophagitis with ulcerations or strictures and dysphagia, vomiting, flatulence, fatigue Rare: duodenitis, urticaria, angioedema
Strontium ranelate	Dose: 2 g Route: oral Freq: daily Between meals, preferably at bedtime or at least 2 h after dinner	Postmenopausal OP to $\downarrow$ risk of vertebral and hip fractures	Ranelate Allergy/excipients Pregnancy and lactation Severe renal failure Special attention if: $\uparrow$ risk of venous thromboembolism or heart problems	Common: headache, disturbances of consciousness, memory loss, diarrhea, dermatitis, venous thromboembolism, $\uparrow$ blood creatine Uncommon: seizures Unknown frequency: arthromyalgia, fever, peripheral edema, $\uparrow$ transaminases, abdominal pain, vomiting, airway hyperresponsiveness
Denosumab	Dose: 60 mg Route: sc Freq: 6 months	PMOP in postmenopausal women with $\uparrow$ risk of fractures Bone loss associated with hormone suppression in men with prostate cancer and $\uparrow$ risk of fractures	Allergy to denosumab/excipients Hypocalcemia Pregnancy and lactation	Common: extremity, urinary and respiratory tract infection, sciatica, cataracts, constipation, rash Uncommon: diverticulitis, cellulitis, otitis, eczema Rare: hypocalcemia

Teriparatide	Dose: 20 µg Route: sc Freq: daily	PMOP in postmenopausal women and men with ↑ fracture risk PMOP by use of corticosteroids in women and men with ↑ fracture risk	Allergy to teriparatide/excipients Pregnancy and lactation Preexisting hypercalcemia Severe renal failure Metabolic bone diseases (hyperparathyroidism, Paget) other than PMOP, primary or corticosteroid-induced Unexplained elevations in alkaline phosphatase History of external radiation or localized radiotherapy to the skeleton Bone tumors or bone metastases	Very common: pain in the extremities Common: palpitations, anemia, dizziness, muscle cramps, sciatica, dizziness, dyspnea, GERD ↑ sweating, fatigue, hypercholesterolemia, hypotension, chest pain, reaction at the injection site, headache, depression Uncommon: tachycardia, ↑ weight, heart murmur, ↑ alkaline phosphatase, hemorrhoids, myalgias, arthralgias, hypercalcemia >2.76 mmol/l, hyperuricemia Rare: allergic reaction
Parathyroid hormone	Dose: 100g Route: sc Freq: daily	PMOP in postmenopausal women with ↑ risk of fracture	Allergy to parathyroid hormone/excipients Pregnancy and lactation Preexisting hypercalcemia and other disturbances of phosphorus-calcium metabolism Metabolic bone diseases (hyperparathyroidism, Paget) other than the primary PMOP Unexplained elevations in alkaline phosphatase History of external radiation or localized radiotherapy to the skeleton Renal or hepatic failure	Very common: hypercalcemia, hypercalciuria, nausea Common: headache, dizziness, palpitations, erythema at the injection site, asthenia, fatigue, vomiting, constipation, diarrhea, pain in extremities, cramps Uncommon: ↑ alkaline phosphatase, dysgeusia, parosmia, abdominal pain, hyperuricemia, anorexia
Zoledronic acid	Dose: 5 mg Route: iv Freq: yearly	PMOP in postmenopausal women and men with ↑ fracture risk PMOP for steroid use in postmenopausal women and men with ↑ fracture risk	Allergy to the active principle, to any bisphosphonates or any of the excipients Hypocalcemia Severe renal failure Pregnancy and lactation	Common: hypocalcemia, headache, dizziness, ocular hyperemia, atrial fibrillation, vomiting, diarrhea, arthromyalgia Uncommon: infection, drowsiness, insomnia, lethargy, paresthesia, anemia, tremors, syncope, dizziness, dysgeusia, conjunctivitis, gastritis, esophagitis, dyspepsia, GERD, abdominal pain, constipation Rare: uveitis, episcleritis, iritis Unknown frequency: ON jaw
Etidronate	Dose: 400 mg Route: oral Freq: 2 wk/3 months Empty stomach, at least 2 h before or after ingestion of food or medicines	Vertebral PMOP without hormone replacement therapy	Allergy to etidronate/excipients Severe renal failure Osteomalacia Pregnancy and lactation	Common: abdominal pain, constipation, diarrhea, flatulence, vomiting, muscle cramps in legs Rare: hypersensitivity reactions, pancytopenia, leukopenia, agranulocytosis

Tab, tablets; Freq, frequency; HBP, high blood pressure; iv, intravenous; mg, milligram; µg, microgram; wk, weekly; ON, osteonecrosis; PMOP, osteoporosis; PUB, perforation, ulcers, bleeding; GERD, gastroesophageal reflux; sc, subcutaneous; DVT, deep vein thrombosis.

<sup>a</sup> Data in this table are obtained from the data sheet of the Spanish Agency of Medicines.

<sup>b</sup> Adverse effects: very common, at least 1 in 10 patients; common, at least 1 in 100 patients; uncommon, at least 1 in 1000 and less than 1 in 1000 patients; rare, at least 1 in 10,000 and less than 1 in 1000 patients.



BMD: bone mineral density, DXA: Dual X-ray absorptiometry.

**Algorithm 1.** Recommendations for the selection of women for the assessment of bone mineral density. BMD, bone mineral density; DXA, dual X-ray absorptiometry.

osteonecrosis of the jaw, atypical femur fractures, and esophageal cancer) [28,29]. These are some of the reasons that have led us to consider sequential therapy for PMOP (see below) and have caused the FDA and the European Medicines Agency (EMA) to warn about their continuity in treatment [30,31].

## 7. Strontium ranelate

Strontium ranelate has demonstrated efficacy in all types of fractures in women of any age with any bone condition and in the treatment of knee osteoarthritis [32,33]. The EMA's Committee for Medicinal Products for Human Use (CHMP) has recently recommended a restriction in its use, following an assessment of data showing an increased risk of serious heart problems, and has been recommended that strontium ranelate should only be used to treat severe osteoporosis in postmenopausal women at high risk of fracture without heart or circulatory problems. Moreover, given the other serious risks previously identified with strontium ranelate, including blood clots and rare serious skin reactions, the Agency's scientific committees also concluded that there was a need to review all the available data on the benefits and risks of the medicine in further depth. The Agency will now carry out this in-depth review, including a detailed analysis of the latest available data on the risk of heart problems [34].

## 8. Denosumab

We suggest the use of denosumab to improve compliance in women with PMOP and multiple RFs, those with a history of

fracture or renal failure, and those who cannot tolerate or have failed other treatments. Although its cost may seem high, the need for only semiannual administration of this compound renders it equivalent in cost to other preparations that are administered daily, weekly, or monthly.

Denosumab maintains long-term effectiveness, but calcium levels should be monitored in patients predisposed to hypocalcemia. Infections can also occur, especially in the skin, and there have been reports of atypical fractures and ONJ associated with denosumab use [35].

## 9. Other therapies

There are additional therapies for PMOP that are used less often by gynecologists and/or are subjects of current research [3,36]. These include the following:

- **Parathyroid hormone and teriparatide.** These agents are indicated in women with several fragility fractures or in those who cannot tolerate other treatments. They are administered subcutaneously daily for up to two years; after this time, treatment with another antiresorptive drug should be initiated. Their most common side effects are dizziness and cramps. Their administration is contraindicated in patients with risk of osteosarcoma, Paget's disease, hypercalcemia, prior radiation therapy, or history of previous bone malignancies [10].
- **Calcitonin.** Compared to other agents, calcitonin has a weak effect on bone metabolism, and it has not shown efficacy in preventing non-vertebral fractures in patients with recent

menopause. Recently, in Spain the intranasal administration of calcitonin has been suspended because of its relationship with bone tumors [37].

- **Isoflavones.** There is heterogeneity in the results of RCTs that have examined the effect of isoflavones on BMD, and no RCTs evaluating their effects on the prevention of fractures are available. Therefore, we do not recommend them as a strategy to prevent or treat PMOP [38].
- **Androgens.** Because androgen deficiency likely plays a role in bone loss associated with aging, treatment with androgens could stimulate the production of bone and increase muscle mass. However, there is concern about the risk of virilization, dyslipidemia, hypertension and hepatotoxicity when androgen treatment is extended for more than three months. The risk of virilization would depend on the type and on the dose of androgen used.
- **Bazedoxifene/conjugated estrogens.** A combination of bazedoxifene and conjugated estrogens is under investigation for the treatment of vasomotor symptoms, vaginal atrophy, and PMOP prevention without increasing the risk of thrombosis or endometrial hyperplasia compared to the isolated use of SERMs or estrogen [39].
- **Sclerostin inhibitors.** Sclerostin is produced by osteocytes and inhibits bone formation. In animal models and in one phase I trial in healthy adults, the administration of a monoclonal antibody to sclerostin increased bone mass.
- **Integrin antagonists.** Integrins mediate adhesion of osteoclasts to the bone surface, an important initial step in bone resorption.
- **Cathepsin K inhibitors.** Cathepsin K is a protease expressed in osteoclasts that plays a role in bone resorption mediated by osteoclasts. Its inhibitors (odanacatib) prevent the dissolution of bone matrix, decrease bone resorption, and increase bone mineral density in postmenopausal women.

## 10. Safety of treatments

PMOP treatments are generally considered safe, but mild adverse reactions may compromise compliance. Some issues related to the safety of these treatments remain unresolved [40]:

- High doses of calcium supplements may increase the risk of kidney and cardiovascular events.
- Denosumab may increase the risk of cellulitis.
- Hormone therapy, SERMs, and strontium ranelate increase the risk of thrombosis.
- There have been isolated cases of serious risks (heart attack, blood clots and rare serious skin reactions).
- Teriparatide can cause hypercalciuria and hypercalcemia, usually mild and resolved spontaneously or with discontinuation of calcium supplementation.
- Bisphosphonates should be avoided in patients with impaired renal function.
- ONJ occurs particularly after intravenous bisphosphonate therapy in oncologic patients; its risk is very low in patients treated with oral preparations.
- Atypical fractures are rare and even seem to increase with the duration of treatment. The benefit/risk ratio for drugs that have been associated with these effects remains favorable.
- Given that PMOP is closely related to the occurrence of periodontitis and that some long-term treatments may be associated with periodontal effects, regular oral examinations should be recommended. If dental procedures are required, they should be as conservative as possible [41].

- There is no evidence that discontinuation of bisphosphonates prior to dental procedures reduces the risk of ONJ or increases the risk of PMOP.

## 11. Monitoring response to treatment and compliance

The primary goal of PMOP treatment is fracture risk reduction, making it necessary to monitor the patient's bone mass and to ensure compliance.

Compliance with some PMOP treatments barely reaches 50% the first year, a serious problem in women at high risk of fracture. Some strategies to improve compliance include encouraging the participation of the patient, development of a good relationship between the patient and her doctor, periodic monitoring, measurement of biochemical markers of bone remodeling, and simplifying the drug dosing schedule [42].

Despite the effectiveness of treatments for PMOP, some patients will experience bone loss while they are receiving it. For this reason, although there is no consensus for monitoring patients undergoing treatment with PMOP, we are inclined to perform densitometry every two years. The response to treatment is satisfactory when BMD increases or remains stable, while a decrease may be related to poor compliance, poor intestinal absorption, insufficient intake of calcium or vitamin D, or the appearance of another disorder with adverse skeletal effects.

### 11.1. Duration of treatment

We have no consensus to indicate the optimal duration of any of the treatments for postmenopausal bone density loss discussed above. Because the effects of each drug differ, recommendations regarding their continuity must be drug-specific.

The difficulty in making recommendations is greater in patients taking bisphosphonates because the antiresorptive effect of these drugs persists after cessation [43–46]. The use of these drugs should be reassessed periodically and on an individual basis; young women without previous fractures and with near-normal BMD are candidates for interruption of treatment after 3–5 years. In contrast, older women with previous fractures or BMD *T* scores < –2.5 may undergo treatment for more than 3–5 years [47–51].

### 11.2. Sequential treatment of PMOP

Overall, PMOP treatment should be individualized according to the risk/benefit ratio and the clinical circumstances of each patient, taking into account the non-skeletal effects of each drug. We recommend drug treatment of all women with established PMOP (*T*-score  $\leq$  –2.5) or with fragility fractures and also of osteopenic women (*T*-score between –1 and –2.5) at high risk of fracture. Additionally, we recommend that treatment be carried out in a sequential manner because perimenopause and menopause are different physiological states that require specific treatment. In this regard, it is important to establish the first agent to be used because some drugs, especially potent antiresorptives, can influence the response to the next drug and lessen the effectiveness of subsequent therapies.

- For women who have recently undergone menopause, we suggest HT as the first treatment of choice if they have vasomotor symptoms and SERMs if they do not have them.
- After HT, SERMs are preferred over other antiresorptive drugs in younger women with vertebral PMOP and in women at increased risk of breast cancer. In this phase of PMOP treatment, we recommend SERMs in preference to bisphosphonates because of the

excessive antiresorptive power and lack of long-term safety of the latter.

- In older women or women at risk of hip fracture, alendronate, risedronate, strontium ranelate, or denosumab can be used as first-line therapies. Monthly oral ibandronate may prove to be an easier dosing schedule for the patients, although RCTs have not confirmed that it reduces the risk of hip fracture. Zoledronic acid is only available for hospital use.
- There is no consensus on the optimal timing for the use of denosumab. It can be used in patients at high risk of fracture who cannot tolerate or do not respond to other treatments and in patients who are suffering kidney failure. Overall, denosumab is preferred for the prevention of bone erosion in rheumatoid arthritis patients.
- Women who fail to benefit from or do not comply with these treatments may be candidates for the use of parathyroid hormone.

## 12. Summary of recommendations

### 12.1. Non-pharmacologic measures

- We suggest that all postmenopausal women with PMOP maintain adequate calcium and vitamin D intake (Grade 2B): overall, 1200 mg of calcium and 800 U of vitamin D daily from diet and supplements.
- Additional important lifestyle measures include exercise, smoking cessation, prevention of falls, and avoidance of excessive alcohol consumption for all women with PMOP (Grade 1A).

### 12.2. Drug therapy

- It is recommended that women with PMOP ( $T$ -score  $\leq -2.5$ ) or fragility fractures be treated with a pharmacological agent (Grade 1A).
- Some patients with osteopenia ( $T$ -score between  $-1.0$  and  $-2.5$ ) will require drug treatment if any of the predictive scales indicate a high risk of fracture (Grade 2B).
- Standard-dose HT is the most effective treatment for the relief of menopausal symptoms (Grade 2A) and is a reasonable choice for the prevention of PMOP (Grade 2A).
- HT can be recommended at low doses for the symptomatic relief of menopausal symptoms (Grade 2A); data are available showing that BMD is maintained, although it is unclear whether these doses are efficacious in the prevention of POMP.
- We suggest SERMs as first-line treatment in recent postmenopausal women with PMOP and without fragility fractures (Grade 2B).
- **Raloxifene** has been the most widely used SERM, and its effectiveness in reducing the risk of vertebral fracture is well described (Grade 2A).
- **Bazedoxifene** has shown an efficacy similar to that of raloxifene in vertebral fractures (Grade 2A) and has also shown efficacy in a subgroup of patients at high risk of nonvertebral fractures in a post hoc analysis (Grade 2C).
- Treatment with **alendronate and risedronate** should be considered to reduce the risk of vertebral, non-vertebral, and hip fractures (Grade 2A). Although **ibandronate** may offer a more convenient dosing schedule, it has not been established that it reduces the risk of hip fracture.
- Oral bisphosphonates should not be used in patients with history of gastroesophageal reflux disease, Barrett's esophagus, or peptic ulcer (Grade 2B).

- Given the potential risks, the need for continued bisphosphonate therapy should be periodically reassessed in each patient, particularly after 5 years of treatment.
- Studies have shown the ability of **strontium ranelate** to increase BMD, and reduce the risk of vertebral, non-vertebral (Grade 2A) and hip (Grade 2C) fractures.
- **Denosumab** is a highly effective and safe treatment for patients with PMOP and high fracture risk. It significantly reduces the risk of vertebral, non-vertebral, and hip fractures (Grade 2A).
- We suggest **PTH** therapy in women with PMOP and at least one fragility fracture who are unable to tolerate bisphosphonates or who have not responded to them (Grade 2B).

### 12.3. Duration of treatment

We have no consensus to guide us in defining the optimal duration of treatment with any of the drugs discussed in this review. Accordingly, we recommend periodic reassessment of each drug's use on an individual basis and changing the therapeutic option (sequential therapy) in relation to the time at which treatment was started and according to the age and characteristics of the patient.

### Contributors

A. Cano, R. Sánchez-Borrego and N. Mendoza: conception and design of the idea, data interpretation and preparation of manuscript. All authors participated in the statement and approved the final version of the manuscript.

### Competing interest

None of them have conflict of interest with.

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