Original Article

2011 Up-Date of the Consensus Statement of the Spanish Society of Rheumatology on Osteoporosis


ª Servicio de Reumatología, Hospital del Mar, Barcelona, Spain
ª Servicio de Reumatología, Hospital de Cruces, Barakaldo, Bizkaia, Spain
ª Servicio de Reumatología, Hospital de Sant Joan Despí Moisés Broggi, Sant Joan Despí, Barcelona, Spain
ª Servicio de Reumatología, Instituto de Investigación Sanitaria Hospital La Princesa, Hospital Universitario de La Princesa, Madrid, Spain
ª Servicio de Reumatología, Hospital Universitari Clinic de Barcelona, Barcelona, Spain
ª Servicio de Reumatología, Hospital Universitari La Paz, Madrid, Spain
ª Servicio de Reumatología, Hospital Universitario Miguel Servet, Zaragoza, Spain
ª Servicio de Reumatología, Hospital Universitari Son Espases, Palma de Mallorca, Spain
ª Servicio de Reumatología, Hospital Universitario Central de Asturias, Oviedo, Spain
ª Servicio de Reumatología, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain
ª Servicio de Reumatología, Hospital Universitari de Bellvitge, IDIBELL, L’Hospital de Llobregat, Barcelona, Spain
ª Servicio de Reumatología, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain
ª Servicio de Reumatología, Clínica Mediterránea de Neurociencias, Alicante, Spain
ª Servicio de Reumatología, Hospital Virgen de la Salud, Toledo, Spain
ª Servicio de Reumatología, Hospital Universitario de Salamanca, Salamanca, Spain
ª Servicio de Reumatología, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain
ª Servicio de Reumatología, Hospital Regional Universitario Carlos Haya, Málaga, Spain
ª Servicio de Reumatología, Consorcio Hospital General Universitario Valencia, Valencia, Spain
ª Unidad de Investigación, Sociedad Española de Reumatología, Madrid, Spain

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A B S T R A C T

Objective: Due to increasing improvement in the diagnosis, evaluation and management of osteoporosis and the development of new tools and drugs, the Spanish Society of Rheumatology (SER) has promoted the development of recommendations based on the best evidence available. These recommendations should be a reference to rheumatologists and other health professionals involved in the treatment of patients with osteoporosis.

Methods: Recommendations were developed following a nominal group methodology and based on a systematic review. The level of evidence and the degree of recommendation were classified according to the model proposed by the Center for Evidence Based Medicine at Oxford. The level of agreement was established through Delphi technique. Evidence from previous consensus and available clinical guidelines was used.

Results: We have produced recommendations on diagnosis, evaluation and management of osteoporosis. These recommendations include the glucocorticoid-induced osteoporosis, premenopausal and male osteoporosis.

Conclusions: We present the SER recommendations related to the biologic therapy risk management.

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Actualización 2011 del consenso Sociedad Española de Reumatología de osteoporosis

RESUMEN

Objetivo: Dado el creciente avance en el diagnóstico como evaluación y tratamiento de la osteoporosis, y la incorporación de nuevas herramientas y medicamentos, desde la Sociedad Española de Reumatología (SER) se ha impulsado el desarrollo de recomendaciones basadas en la mejor evidencia posible. Estas deben de servir de referencia para reumatólogos y otros profesionales de la salud implicados en el tratamiento de pacientes con osteoporosis.

Métodos: Las recomendaciones se emitieron siguiendo la metodología de grupos nominales. El nivel de evidencia y el grado de recomendación se clasificaron según el modelo del Center for Evidence Based Medicine de Oxford y el grado de acuerdo se extrajo por técnica Delphi. Se utilizó toda la información de consensos previos y guías de práctica clínica disponibles.

Resultados: Se realizaron recomendaciones sobre el diagnóstico, evaluación y tratamiento en pacientes con osteoporosis. Estas recomendaciones incluyen la osteoporosis secundaria a glucocorticoides, la osteoporosis premenopáusica y la del varón.

Conclusiones: Se presentan las recomendaciones SER sobre el diagnóstico, evaluación y manejo de pacientes con osteoporosis.

Introduction

Updating knowledge on the different aspects of osteoporosis (OP) is still needed because of its high prevalence, its complications, and the associated health and social spending. At a time when the rational use of resources is important, this document is, in reality, a corporate reflection in which we analyze new evidence on diagnosis, risk factors for fracture, follow up and treatment of OP.

These recommendations are intended as a reference for therapeutic decision making to rheumatologists and all professionals who, from the different levels of care, are implicated in the treatment of OP.

Methodology

Tasks were distributed for the elaboration of this document and commentary to each part. The structure of the document is based on questions relevant to clinical practice in OP.

Each panelist was first assigned one or several parts of the consensus for write up. Once completed, the whole panel was distributed for comment. After that, members of the research unit (RU) of the Spanish Society of Rheumatology (SER) reviewed, categorized, classified and summarized all of the comments for their evaluation prior to the panel getting together.

A meeting of the nominal group was carried out, moderated by members of the RU of SER. In this meeting, modification proposals in relation to format and content, including the recommendations, were performed.

Then, a Delphi survey was performed and consensus recommendations were voted on (anonymously online). The aggregated results were shown to all the panelists (modified Delphi). Recommendations with a degree of agreement (DA) of less than 70% were reedited and voted for a second time. Agreement is defined if, on a scale of 1 (complete disagreement) to 10 (complete agreement), the vote is 7 or more. The level of evidence (LE) and degree of recommendation (DR) are classified according to the model proposed by the Center for Evidence Based Medicine of Oxford by members of the RU of SER.

With all of this information the definite document was written up.
Table 1
Risk Factors for Fracture.

<table>
<thead>
<tr>
<th>High risk (≥2)</th>
<th>Moderate risk (1 &lt; 2)</th>
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</thead>
<tbody>
<tr>
<td>1. Advanced age (65 years)</td>
<td>7. Tobacco and/or alcohol consumption</td>
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<tr>
<td>2. Low weight (BMI &lt; 20 kg/m²)</td>
<td>8. Early menopause (45 years)</td>
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<tr>
<td>3. Personal history of fractures</td>
<td>9. Primary and secondary amenorrhea</td>
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<tr>
<td>5. Steroids</td>
<td>11. Diseases and drugs with a capacity to reduce BMD: rheumatoid arthritis and other inflammatory arthropathies, inflammatory intestinal disease, celiac disease, malabsorption, liver disease, hyperparathyroidism, hyperthyroidism, anorexia and bulimia, patients with solid organ transplants, use of hydantoins, antiretrovirals, antiepileptics, etc.</td>
</tr>
<tr>
<td>6. Falls</td>
<td>12. Factors related to falls: visual disturbances, psychopharmacology, stroke, Parkinson’s disease</td>
</tr>
</tbody>
</table>

| a | More than 5 mg/prednisone/day for over 3 months. |
| b | More than 2 falls in the past year. |
| c | Tobacco use and alcohol consumption > 3 units a day: one unit of alcohol is equivalent to 8–10 g. |
| d | If untreated it may be considered as a risk factor for fracture. |

high risk for fracture when there are at least 2 high risk factors (Table 1). Having a tool for the calculation of osteoporotic fracture risk would permit the identification of persons with a high risk who would merit early intervention and reduce the number of unnecessary treatments administered to low risk patients.

Different instruments that estimate the risk of fracture based on risk factors have been developed (Table 2). Of them, the most important is the FRAX tool, a software tool sponsored by the WHO, which can be applied with and without BMD. The FRAX® algorithms calculate the absolute 10 year probability of fracture into a group of “major fractures” (clinical vertebral, forearm, hip and humeral fractures) and isolated hip fractures. It is currently the most recommended instrument used to calculate the risk of osteoporotic fracture. However, as everything, it has limitations and the medical judgment of the clinician is still fundamental. The risk of a major fracture calculated by FRAX® in the Spanish population over 15 years is very specific for osteoporosis.

There is no consensus in the medical literature on the threshold above which the risk for a fracture would be considered “high” in the Spanish population. An approximation would be:

<table>
<thead>
<tr>
<th>Absolute 10 year risk of fracture</th>
<th>Moderate</th>
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<tbody>
<tr>
<td>&lt;10%</td>
<td>high</td>
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<td>≥10% and &lt;20%</td>
<td>moderate</td>
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<tr>
<td>≥20%</td>
<td>low</td>
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</tbody>
</table>

If FRAX® is employed, its systemic application is recommended in patients in whom: (a) the indication of a BMD is being evaluated; (b) the onset of treatment is being evaluated for OP, and (c) they are over 65 years of age.

What History and Examination Data Are Important?

If OP is suspected, with the aim of evaluating the risk of fracture and the cause of OP, we recommend obtaining the following data: age, ethnicity, history of toxic habits (tobacco, alcohol), dietary intake of calcium and vitamin D, degree of exposure to sunlight, menstrual history (age at menopause and menarche), obstetric history (interventions, surgical menopause, hypogonadism), osteopenia associated diseases and drugs, previous trauma, family or personal history of fragility fractures and conditions associated to falls, as well as data regarding recent or prior fractures (LE 5; DR D; DA 95%).

The presence of present or prior fractures should be evaluated determining episodes of acute and/or chronic back pain, progressive reduction in height, etc.13,14 It is important to remember that OP is asymptomatic and that more than half of the vertebral fractures are also asymptomatic.15

It is recommended that physical examination record weight, height, the existence of skeletal deformities and palpation/percusión of the spine be carried out (LE 5; DR D; DA 90%).

The relationship between the body mass index and BMD is well known.16 The possible existence of skeletal deformities should be established by the presence of dorsal kyphosis, a reduction of the space between the ribs and the pelvis, etc., and palpation/percusión should be directed to the localization of painful zones of the locomotor system.14 General physical examination may provide data on other diseases associated to a reduction in bone mass.

What Laboratory Data Is Important?

Laboratory tests are performed to identify associated processes and perform a differential diagnosis with other diseases associated to bone fragility.17–21

When OP is suspected, one should request: complete blood count, alkaline phosphatase, creatinine, serum proteins, erythrocyte sedimentation rate, serum calcium and phosphorus and 24h urinary calcium excretion (LE 5; DR D; DA 100%).

It is advisable to determine during the initial visit what the levels of 25-hydroxyvitamin D (25-[OH]-D3), parathyroid hormone (PTH) and thyroid stimulating hormone are (LE 5; DR D; DA 80%).

In case an associated disease is suspected, pertinent laboratory tests should be performed (LE 5; DR D; DA 95%).

The systematic determination of bone markers is not recommended for the diagnosis and evaluation of patients with OP. Their measurement is useful to identify subjects with a greater risk of fracture and especially to evaluate in an early manner response to both antiresorptive as well as bone forming treatments (LE 2c; DR C; DA 80%).

Bone remodeling markers provide additional and complementary information to the study of BMD. Osteocalcin, bone alkaline phosphatase and type I procollagen aminoterminal propeptide stand out as bone formation markers and pyridinolines, carboxy and aminoterminal telopeptides of type I collagen (serum CTX and urine NTX) and tartrate 5b resistant acid phosphatase stand out among those associated to resorption. These are more sensitive and specific than classic markers such as total alkaline phosphatase and hydroxyproline. It is important to take into account biological variability and circadian rhythm in their correct interpretation and therefore establish an adequate schedule to obtain samples.22–24

When Is it Advisable to Request Spinal X-rays?

Spine radiographs are not useful to assess the decrease in BMD, but allow the diagnosis of fractures, including asymptomatic ones. We must remember that the presence of prior vertebral fracture is a significant risk factor for new fractures, both vertebral and non-vertebral.25–29

In patients with suspected or diagnosed OP, it is recommended to perform an initial spinal X-ray for detecting fractures (LE 2b; DR B; DA 95%).

If there is suspicion of vertebral fracture during follow up, a spinal X-ray is recommended (LE 2b; DR B; DA 100%).

The panel believes that for the diagnosis of spinal fractures, lateral, dorsal and lumbar spine X-rays, with focus on D8 and L2, respectively30 are sufficient (LE 2a; DR C; DA 100%).
Table 2

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<th>Fracture Risk Scales (1, 2, 3)</th>
<th>Fracture</th>
<th>Catalan Agency</th>
<th>EPESE</th>
<th>Community of Madrid</th>
<th>Diez</th>
<th>WHI</th>
<th>NORA</th>
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<td>h Peripheral densitometry: distal forearm, fingers, calcaneus, by DXA or ultrasound.</td>
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<td>l Thyazide diuretics have osteoprotective effects.</td>
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Anteroposterior projections are not essential for diagnosis but can provide additional information.

When Is it Indicated to Perform a Bone Densitometry?

A densitometric survey of the general population is not cost-effective and there is great variability regarding indications for densitometry. Until today there are no validated tools that satisfactorily quantify the risk of fracture or a consensus on the definition of risk of fracture that helps determine a therapeutic intervention. The evaluation of BMD along with other risk factors is useful for the diagnosis and follow up of patients.

The indication for performing a densitometry should be based on clinical criteria that allow the selection of patients in whom the use of this technology is efficient (LE 2b; DR B; DA 95%).

Before requesting for it is essential to be certain that the result will help determine the therapeutic decision to be taken. A baseline densitometry is recommended in the following (LE 5; DR D; DA 75%):

1. Women with early menopause and any major risk factors for fracture.
2. Postmenopausal women of any age and men over 50 with at least one major risk factor for fracture.
3. A history of fragility fracture in patients over 50.
4. Underlying disease or chronic treatment with medication associated to bone loss, especially glucocorticoids.
5. Women over 65 years of age and men >70 without known risk factors at least in one occasion if patient request it.
7. If the FRAX® is employed, a densitometry is recommended in women 65 and older and those younger but with a major risk factor for fracture according to the FRAX®, equivalent to a 65 year old woman with no risk factors de riesgo (Spanish FRAX 3.6%),38,40

To detect significant changes with a confidence interval (CI) of 95%, these should be, at least, 2.8 times the variation coefficient (minimum significant change). In clinical practice its application is difficult because very strict precision measures are needed. The use of another concept is more practical, “the smallest detectable difference” which is established in 2% (change in lumbar BMD > ±0.05 g/cm², total femur ± 0.04 g/cm²). Although major changes in BMD are detected on the lumbar spine, it is also useful to monitor the hip because it is less dependent on artifacts produced by degenerative change.

Which Densitometric Technique Is the Most Adequate?

Dual energy X-ray absorciometry (DXA) is recommended as the reference technique for measuring BMD (LE 2b; DR B; DA 100%).

DXA is a technique that has good precision, low radiological exposure and allows for measurement of BMD both in the axial as well as in the peripheral skeleton. It is considered the best technique to evaluate BMD.41

What Is Dual Energy X-ray Absorciometry Good for?

Results of BMD obtained through DXA predict the future risk of fracture due to OP, both in postmenopausal women as in elderly males.43-49 But in addition, according to WHO, to diagnose OP it is necessary to know the value of the BMD in the femur and lumbar spine through a central DXA.50,51 Currently, central DXA is the only validated technique to follow up and for evaluation of therapeutic response.

To perform a diagnosis of OP, we recommend carrying out a DXA, as long as it is possible on the hip and lumbar spine (LE 2b; DR B; DA 95%). A lateral projection of the spine should not be used for the diagnosis of OP.

If DXA of the lumbar spine or hip is impossible, it is recommended that DXA be performed on the distal third of the radius of the non-dominating forearm (LE 2b; DR B; DA 90%).

This may occur in case of anatomical alterations (scoliosis, degenerative problems, multiple vertebral fractures, morbid obesity) or technical problems (presence of metallic elements after spinal surgery, hip arthroplasty).52

When necessary, control DXA of the hip and the spine should be performed with the same equipment (LE 1b; DR A; DA 90%).

Long-term precision or reproducibility of DXA; expressed as a variation coefficient, varies according to the measurement area and the equipment used from 1 to 2%.53-55 In women undergoing treatment for postmenopausal OP, densitometric controls should be performed every 2–3 years.32 In general, codensitometric controls are not recommended before 2 years because it has been seen that some patients who lose bone mass during the first year may regain it during the second.55

Ultrasound, peripheral DXA equipment and central or peripheral quantitative computerized tomography are useful to predict an elevated risk of fracture but should not be used for diagnosis, follow up or evaluation of therapeutic response in patients with OP (LE 1a; DR A; DA 95%).

There are other techniques to measure BMD in the peripheral skeleton, such as phalangeal, knee and calcaneus DXA, and calcaneus ultrasound. They are cheaper, easier to handle and faster in comparison to central DXA but, among other limitations, their precision is low.49,52,56,57 They are useful to predict the future risk of fracture and may have some value when it is impossible to perform a central DXA.49,52,56 Peripheral quantitative computed tomography is a rapidly developing imaging technique. It allows for volumetric BMD measurement of the lumbar spine, hip and distal radiums, but its results are not comparable to those obtained through DXA.58

How Is Osteoporosis Diagnosed?

Diagnosis of OP is based on the densitometric criteria established by WHO for white postmenopausal women (BMD values under –2.5 standard deviations (SD) (T-score inferior to –2.5) and/or the presence of fragility fractures (LE 2c; DR B; DA 90%).

Cutpoints for BMD measured by DXA on the lumbar spine and hip correspond to normal, values of BMD > –1 SD in relation with the mean of young adults (T-score > –1); osteopenia or low bone mass, BMD values between –1 and –2.5 SD (T-score between –1 and –2.5); OP, BMD values of ≤ –2.5 DE (T-score ≤ –2.5), and established OP when the previous condition is associated to ≥ 1 osteoporotic fracture. The same cutpoints have been proposed for adult males.60

Treatment

What Non-pharmacologic Methods Should we Use?

The following general measures should be recommended to all of the population, with special emphasis on osteoporotic patients: physical exercise, elimination of toxic habits, balanced diet, adequate intake of calcium and vitamin D, preventing falls (LE 1a; DR A; DA 100%).

Moderate to intense physical exercise increases bone mass in young patients, as well as in adults, although less intensely. There is no consistent evidence on the effect over bone mass in elderly patients, but performing it reduces the risk of fractures, probably by reducing falls.85-70

Avoidance of sedentarism and the performance of moderate physical activity are recommended, taking into account the
patients’ age, physical status and other diseases (LE 5; DR D; DA 100%).

A balanced diet with an adequate consumption of proteins, avoidance of excess salt and moderate sun exposure are also recommended (LE 5; DR D; DA 100%).

A daily calcium intake of 1000 mg and serum 25-OH vitamin D levels of ≥30 ng/ml (75 nmol/l) is recommended (LE 5; DR D; DA 100%).

Sometimes, common diets do not provide these calcium requirements and therefore must be modified or supplemented with pharmacological calcium which, if taken isolated, has not shown a significant effect on the reduction of fractures in post-menopausal OP, but help reduce the loss of bone mass.71–73 In healthy women it has been suggested to increase cardiovascular risk74,75 and renal lithiasis,76 but this is a controversial and unclear subject.

Approximately 50% of the osteoporotic population presents low serum concentrations of vitamin D and it is advisable to supplement it with 800–1000 U in all patients. The efficacy of vitamin D supplements in the prevention of fractures is controversial.77–82 There is evidence that it reduces fractures in institutionalized elderly patients when administered with calcium.77–82 Additionally, some studies indicate that vitamin D supplements may reduce falls81 but other do not.82

In patients receiving anticatabolic treatment, we recommend an intake of 1000 mg of calcium and 800–1000 U of vitamin D is recommended (LE 1a; DR A; DA 95%).

In the elderly, measures directed at reducing the risk of falls, promoting the use of canes, avoiding psychopharmacologic agents, correcting visual disturbances and adapting living spaces are recommended. In high risk populations, hip protectors may be employed.83–85

For more information consult Table 3.

**How to Treat an Acute Vertebral Fracture?**

The goals of treatment of a vertebral fracture are acute pain control and functional recovery (LE 2b; DR B; DA 100%).

It is very important to inform patients that fractures may take up to 3 months to consolidate and that pain will gradually decrease and improve function.86

Oral analgesics, relative rest, orthoses and rehabilitation are the mainstays of treatment (LE 2b; DR B; DA 90%).

Oral analgesics are first-line drugs to reduce the pain of vertebral fractures. The choice should be appropriate to the magnitude of pain. In cases where the pain reaches a significant intensity and conventional painkillers failed, we recommend using opioids.87,88

If complete rest is indicated, return to sitting and walking should be accomplished in the shortest possible time. During the acute episode there may be a need for prescription orthotics and, once control of acute pain is achieved, rehabilitation may be useful (LE 5; DR B; DA 95%).

A back brace should be used with caution as excessive spinal immobility could increase OP,89 and rehabilitation should be directed by a specialist.90

In patients with acute vertebral fractures with pain that does not respond to the above measures, vertebroplasty or kyphoplasty may be indicated (LE 1c; DR B; DA 95%).

Several observational studies have shown rapid analgesic effect and reduced period of immobilization in a high percentage of patients, in the short to medium term, but this does not exempt these procedures from secondary.91–96 Recently, two controlled clinical trials have not shown that vertebroplasty was more effective than other conservative options.97,98 Another controlled trial has found benefit with the use of vertebroplasty in a subgroup of patients with persistent intense symptoms.99 Based on the above, patients who are going to undergo these interventions should be carefully selected.100

Currently, no generalization can be recommended for vertebroplasty or kyphoplasty to treat osteoporotic vertebral fractures (LE 5; DR D; DA 100%).

**What Drugs Should Be Recommended in Osteoporosis?**

The objective of pharmacologic treatment of OP is to reduce the risk of fracture (LE 1a; DR A; DA 100%).

Pharmacological intervention is performed with therapeutic agents capable of acting in both phases of bone remodeling. At present, there are three categories of anti-osteoporotic drugs, antiresorptive and anti-catabolic, which inhibit bone resorption by acting on osteoclasts and their precursors, decrease the rate of activation of bone remodeling, increase bone mineral density and preserve the microarchitecture of the bone; and anabolic drugs, which act on osteoblasts or their precursors resulting in increased bone remodeling, with bone formation increased to a greater extent than resorption, which in time increases mass and bone strength, as well as agents with a double mechanism of action where there is a combination of both.101,102

For more information regarding their indications, efficacy in relation to the prevention of fractures and adverse events, see Tables 4 and 5.

**Antiresorptive Drugs or Anti-catabolic.**

**Hormone Replacement Therapy.** Currently, HRT should not be recommended for the treatment of postmenopausal OP, except for women with early menopause, intense climacteric symptoms or in the case of not being able to administer other OP drugs due to adverse effects or ineffectiveness (LE 1c; DR B; DA 95%).

Estrogens may reduce the incidence of vertebral and peripheral fractures, although drugs such as alendronate are superior.103,104 There is evidence that hormone replacement therapy (HRT) increases the risk of breast cancer, heart disease, stroke and venous thromboembolism.105

<table>
<thead>
<tr>
<th>Interventions</th>
<th>DMO</th>
<th>Vertebral Fractures</th>
<th>Hip Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>A2</td>
<td>B–C</td>
<td>B–C</td>
</tr>
<tr>
<td>Dietary calcium</td>
<td>B</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Calcium supplements</td>
<td>A</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Vitamin D and calcium supplements</td>
<td>A</td>
<td>B2</td>
<td>B</td>
</tr>
<tr>
<td>Hip protectors</td>
<td>No studies</td>
<td>No studies</td>
<td>A in the elderly</td>
</tr>
</tbody>
</table>

BMD: Bone.

* Degree of recommendation according to CEMB: A: extremely recommended; B: favorable recommendation; C: favorable recommendation but non-conclusive; D: not recommended nor disproved.

* Except the elderly.

* Contradictory results.
Table 4
Characteristics of the Main Drugs Commercialized for Osteoporosis in Spain (According to the Data Sheet, Current to January 2010)*

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Dose and Administration</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogens</td>
<td>Dose: 1–2 tab Oral Freq: Daily</td>
<td>Prevention of OP in postmenopausal women and increased risk of fractures, who do not tolerate other drugs or have contraindications</td>
<td>Allergies to estrogens or contents. Personal history or suspicion of breast cancer. Malignant estrogen dependent tumors or suspicion of malignant tumors. Undiagnosed vaginal hemorrhage Untreated endometrial hyperplasia Idiopathic venous thromboembolism or history Known thrombophilia Active arterial or recent thromboembolic disease Pregnancy and lactation Acute liver disease or history of liver disease with altered liver function tests Porphyria</td>
<td>Frequent: vomiting, abdominal pain, anorexia, depression, vaginal hemorrhage, breast discharge, gynecomasia, breast pain, amenorrhea, dismenorrhea, cholestatic hepatitis, jaundice, endometrial hyperplasia, dizziness, alopecia, headache, ▼ weight Infrequent: changes in libido and humor, edema, alteration in menstrual fluid, vertigo, venous thromboembolism, migraines, breast cancer, vaginitis Rare: pancreatitis, stroke, ovarian cancer, allergic reactions, glucose intolerance, asthma exacerbation, hirsutism</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Dose: 100–200 UI Nasal Freq: daily</td>
<td>Postmenopausal OP and established to ▼ risk of vertebral fractures</td>
<td>Allergy to calcitonin/contents Hypocalcemia Pregnancy and lactation</td>
<td>Very frequent: rhinitis, nasal irritation Frequent: vertigo, headache, disgeusia, ulcerative rhinitis, epistaxis, sinusitis, pharyngitis, diarrhea, abdominal pain, musculoskeletal pain, flushing, fatigue Infrequent: alteration in vision, cough, HTA Rare: neutralizing antibodies to calcitonin, generalized rash</td>
</tr>
<tr>
<td>Alendronate</td>
<td>Dose: 70 mg Oral Freq: weekly At least 30 min before 1st meal or medication of the day, using only water</td>
<td>Postmenopausal OP</td>
<td>Allergy to alendronate/contents Esophageal abnormalities or other factors delaying esophageal emptying (stenosis, achalasia) Impossibility to remain seated or standing ≥ 30 min) Hypocalcemia Severe renal failure Pregnancy and lactation</td>
<td>Frequent: abdominal pain, dyspepsia, headache, constipation, diarrhea, flatulence, esophageal ulcer, dysphagia, musculoskeletal pain Infrequent: gastritis, esophagitis, esophageal ulcers, GI bleeding Rare: symptomatic hypocalcemia, uveitis, esophageal stenosis, PUH, ON jaw</td>
</tr>
<tr>
<td>Etidronateb</td>
<td>Dose: 400 mg Oral Freq: 2 week/3 months Empty stomach, at least 2 h before or after food or medication</td>
<td>Postmenopausal vertebral OP with no hormone replacement therapy</td>
<td>Allergy to alendronate/contents Severe renal failure Osteomalacia Pregnancy and lactation</td>
<td>Frequent: abdominal pain, constipation, diarrhea, flatulence, vomiting, muscle cramps in legs Rare: hypersensitivity reactions, pancytopenia, leukopenia, agranulocytosis</td>
</tr>
<tr>
<td>Active Ingredient</td>
<td>Dose and Administration</td>
<td>Indications</td>
<td>Contraindications</td>
<td>Adverse Events*</td>
</tr>
<tr>
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</tr>
<tr>
<td>Ibandronate</td>
<td>Dose: 150 mg Oral&lt;br&gt;Freq: monthly&lt;br&gt;After nocturnal fasting (minimum 6h) and 1 h before breakfast or 1st beverage (different from water) of the day or other drug or oral supplement (including calcium)</td>
<td>Postmenopausal OP and increased risk of fracture</td>
<td>Allergy toibandronate/contents&lt;br&gt;Esophageal abnormalities or other factors delaying esophageal emptying (stenosis, achalasia)&lt;br&gt;Impossibility to remain seated or standing ≥ 60 min&lt;br&gt;Hypocalcemia&lt;br&gt;Severe renal disease&lt;br&gt;Pregnancy and lactation&lt;br&gt;Special attention if esophageal abnormalities or other factors delaying esophageal emptying (stenosis, achalasia), upper gastrointestinal problems or active or recent esophageal bleeding</td>
<td>Frequent: headache, skin rash, esophagitis, gastritis, GERD, dyspepsia, diarrhea, abdominal pain, musculoskeletal pain, cold-like symptoms&lt;br&gt;Infrequent: esophagitis with ulcers or stenosis and dysphagia, vomiting, flatulence, fatigue&lt;br&gt;Rare: duodenitis, urticaria, angioedema</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Dose/frequency: 5 mg/d&lt;br&gt;35 mg/week&lt;br&gt;75 mg/2 d&lt;br&gt;followed/month&lt;br&gt;Oral&lt;br&gt;At least 30 min before the first food or liquid of the day except water</td>
<td>Postmenopausal OP, for a ↑ risk of vertebral and hip fractures&lt;br&gt;Prevention of OP in women with ↑ risk of osteoporosis&lt;br&gt;Maintain ↑ bone mass in postmenopausal women and prednisone use for ≥3 months and ≥7.5 mg/d OP in men with ↑ risk of fractures</td>
<td>Allergy to risedronate/contents&lt;br&gt;Hypocalcemia&lt;br&gt;Severe renal failure&lt;br&gt;Pregnancy and lactation&lt;br&gt;Special attention if: esophageal alterations or other factors delaying esophageal emptying (stenosis, achalasia), active or recent upper gastrointestinal problems, impossibility to remain seated or standing ≥ 30 min</td>
<td>Frequent: headache, constipation, dyspepsia, abdominal pain, diarrhea, musculoskeletal pain&lt;br&gt;Infrequent: iritis, gastritis, esophagitis, dysphagia, duodenitis, esophageal ulcer&lt;br&gt;Rare: glositis, esophageal stenosis, abnormal liver function tests</td>
</tr>
<tr>
<td>Raloxifen</td>
<td>Dose: 60 mg Oral&lt;br&gt;Freq: daily&lt;br&gt;It may be administered at any hour of the day, independent of meals</td>
<td>Treatment and prevention in postmenopausal women OP</td>
<td>Allergy to raloxifen/contents&lt;br&gt;Women who may become pregnant, pregnancy or lactation&lt;br&gt;History/current venous thromboembolic episode (DVT, pulmonary embolism, retinal thrombosis)&lt;br&gt;Liver failure, including cholestasis&lt;br&gt;Severe renal insufficiency&lt;br&gt;Unexplained uterine bleeding&lt;br&gt;Patients with signs or symptoms of endometrial cancer or in treatment for breast cancer</td>
<td>Very frequent: vasodilatation (hot flashes), cold like symptoms&lt;br&gt;Infrequent: leg cramps, peripheral edema&lt;br&gt;Infrequent: deep venous thromboembolism, pulmonary embolism, retinal thrombosis, superficial venous thrombosis&lt;br&gt;Rare: thrombocytopenia, nausea, vomiting, abdominal pain, dyspepsia, headache, rash, arterial thrombosis, ↑ blood pressure, breast pain</td>
</tr>
<tr>
<td>Bazedoxifen</td>
<td>Dose: 20 mg Oral&lt;br&gt;Freq: daily&lt;br&gt;May be administered at any hour of the day, independent of meals</td>
<td>OP in postmenopausal women with ↑ of risk of fracture</td>
<td>Allergy to bazedoxifen/contents&lt;br&gt;Presence or history of deep venous thromboembolism, lung embolism, and retinal vein thrombosis&lt;br&gt;Potentially fertile women&lt;br&gt;Unexplained uterine bleeding&lt;br&gt;Patients with signs or symptoms of endometrial cancer</td>
<td>Infrequent: hot flashes, muscle spasms&lt;br&gt;Frequent: hypersensitivity, fatigue, oral dryness, urticaria, peripheral edema, ↑ triglycerides, ALT, AST&lt;br&gt;Infrequent: DVT, lung embolism</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>Dose: 20 μg SC&lt;br&gt;Freq: daily</td>
<td>OP in postmenopausal women and men with ↑ risk of fracture&lt;br&gt;OP due to steroids in women and men with ↑ risk of fracture</td>
<td>Allergy to calcitonin/contents&lt;br&gt;Pregnancy and lactation&lt;br&gt;Preexisting hypercalcemia&lt;br&gt;Severe renal failure&lt;br&gt;Bone metabolic disease (hyperparathyroidism, Paget) different from primary or steroid associated OP&lt;br&gt;Unexplained elevation of alkaline phosphatase&lt;br&gt;History of external radiation or radiotherapy on the skeleton&lt;br&gt;Bone tumors or bone metastasis</td>
<td>Infrequent: limb pain&lt;br&gt;Frequent: palpitations, anemia, dizziness, muscle paresthesias, cystica, vertigo, dyspnea, GERD, ↑ sweating, fatigue, hypercholesterolemia, hypotension, thoracic pain, injection site reaction, headache, depression&lt;br&gt;Infrequent: tachycardia, ↑ weight, heart murmur, ↑ alkaline phosphatase, enphysema, hemorrhoids, muscle pain, joint pain, hypercalcemia ≥2.76 mmol/l, hyperuricemia&lt;br&gt;Rare: allergic reaction</td>
</tr>
<tr>
<td>Active Ingredient</td>
<td>Dose and Administration</td>
<td>Indications</td>
<td>Contraindications</td>
<td>Adverse Events</td>
</tr>
<tr>
<td>-------------------</td>
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<td>----------------</td>
</tr>
</tbody>
</table>
| Parathyroid hormone | Dose: 100 µg SC  
Freq: daily | OP in postmenopausal women with ↑ risk of fracture | Allergy to parathyroid hormone/contents  
Pregnancy and lactation  
Preeclampsia  
Hypocalcemia and other phosphorous calcium metabolic abnormalities  
Bone metabolic diseases (hyperparathyroidism, Paget) different from primary OP  
Unexplained elevation of alkaline phosphatase  
History of external radiation or radiotherapy on the skeleton  
Severe renal or liver failure  
Allergy to ranelate/contents | Infrequent: hypercalcemia, hypercalciuria, nausea  
Frequent: headache, dizziness, palpitations, injection site erythema, astenia, fatigue, vomiting, constipation, diarrhea, limb pain, paresthesias  
Infrequent: ↑ alkaline phosphatase, disgeusia, parosmia, abdominal pain, hyperuricemia, anorexia |
| Strontium ranelate | Dose: 2 g Oral  
Freq: daily  
Between meals preferably when going to sleep, minimum 2 h after dinner | Postmenopausal OP to ↓ risk of vertebral and hip fractures | Severe renal or liver failure  
Pregnancy and lactation  
Preeclampsia  
Hypocalcemia  
Severe renal insufficiency  
Special attention if: ↑ risk of venous thromboembolism | Frequent: Headache, cognition impairment, memory loss, diarrhea, dermatitis, venous thromboembolism, blood creatin-phosphokinase  
Infrequent: convulsions  
Unknown frequency: joint pain, fever, peripheral edema, ↑ transaminases, abdominal pain, vomiting, bronchial hyperreactivity |
| Zoledronic acid | Dose: 5 mg IV  
Freq: annual | OP in postmenopausal women and males with ↑ risk of fracture  
OP due to steroid use in postmenopausal women and men with ↑ risk of fracture | Allergy to the active ingredient, any bisphosphonate or any content  
Hypocalcemia  
Severe renal failure  
Pregnancy and lactation | Frequent: hypocalcaemia, headache, dizziness, hyperpermia ocular, atrial fibrillation, vomiitus, diarreha, joint pain  
Infrequent: infections, fatigue, insomnia, lethargy, paresthesia, anemia, tremors, syncope, vertigo, disgeusia, conjuntivitis, gastritis, esophagitis, dyspepsia, GERD, abdominal pain, constipation  
Rare: uveitis, episcleritis, iritis  
Unknown frequency: ON jaw |
| Denosumab (not marketed) | Dose: 60 mg SC  
Freq: 6 months | OP in postmenopausal women with ↑ risk of fractures  
Bone mass loss associated to hormone suppression in men with prostate cancer and ↑ risk of fractures | Allergy to denosumab/contents  
Hypocalcemia  
Pregnancy and lactation | Frequent: limb pain, respiratory and urinary tract infection, cystica, cataracts, constipation, skin rash  
Infrequent: diverticulitis, cellulitis, otitis, eczema, Rare: hypercalcemia |

Tab: tablets; Freq: frequency; HTA: arterial hypertension; iv: intravenous; mg: milligram; µg: microgram; w: weekly; ON: osteonecrosis; OP: osteoporosis; PUH: perforation, ulcers, hemorrhage; GER: gastroesophageal reflux; sc: subcutaneous; DVT: deep venous thrombosis.

a Data in this table is obtained from the Data Sheet of the Spanish Drug Agency.

b Information unavailable in data sheet. Obtained from Vademecum, Food and Drug Administration (FDA).

c Adverse events: very frequent (1 in 10 patients); frequent (1 in 100 patients); infrequent (1 in 1000 and less than 1 in 100); rare (1 in 10,000 and less than 1 in 1000 patients).

d Unknown frequency: postmarketing experience.
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>% FV PLC</th>
<th>% FV INT</th>
<th>RR (CI 95%)</th>
<th>RRR</th>
<th>RAR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphometric vertebral fracture</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black et al., 1996, CT double blind placebo controlled, 3 years</td>
<td>n = 2027 ♀ with ↓ BMD and ≥1 FV</td>
<td>Aln = 5 mg/day → 10 mg/day</td>
<td>15%</td>
<td>8%</td>
<td>0.53 (0.40–0.68)</td>
<td>47%</td>
<td>7%</td>
<td>14</td>
</tr>
<tr>
<td>Cummings et al., 1998, CT double blind placebo controlled, 4 years</td>
<td>n = 4432 ♀ with ↓ BMD no FV</td>
<td>Aln = 5 mg/day → 10 mg/d</td>
<td>14.1%</td>
<td>12.3%</td>
<td>0.86 (0.73–1.1)</td>
<td>14%</td>
<td>1.8%</td>
<td>55</td>
</tr>
<tr>
<td>Harris et al., 1999, CT double blind placebo control, 3 years</td>
<td>n = 2458 ♀ pam and ≥1 FV</td>
<td>Ris = 2.5 mg/d</td>
<td>16%</td>
<td>11%</td>
<td>0.36 (0.12–0.60)</td>
<td>64%</td>
<td>5%</td>
<td>20</td>
</tr>
<tr>
<td>Reginster et al., 2000, CT double blind, placebo controlled, 3 years</td>
<td>n = 1226 ♀ and OP pm and ≥2 FV</td>
<td>Ris = 5 mg/d</td>
<td>0.40 (0.17–0.65)</td>
<td>47%</td>
<td>4%</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chesnut et al., 2005, CT double blind placebo controlled</td>
<td>n = 2946 ♀ and OP pm and 1–4 FV</td>
<td>Ris = 5 mg/d</td>
<td>9.6%</td>
<td>4.7%</td>
<td>0.49 (0.22–0.76)</td>
<td>51%</td>
<td>4.9%</td>
<td>20</td>
</tr>
<tr>
<td>Black et al., 2007, CT double blind placebo controlled, 3 years</td>
<td>n = 7765 ♀ and OP pm (62% FV)</td>
<td>Iln = 20 mg/2 d 12, dose/3 months</td>
<td>10%</td>
<td>3.3%</td>
<td>0.47 (0.19–0.76)</td>
<td>53%</td>
<td>4.7%</td>
<td>21</td>
</tr>
<tr>
<td>Lyles et al., 2007, CT double blind placebo controlled, 1.9 years'</td>
<td>n = 2127 patients with FC</td>
<td>Zol = 1 annual infusion (5 mg)</td>
<td>3.8%</td>
<td>1.7%</td>
<td>0.54 (0.32–0.92)</td>
<td>46%</td>
<td>2.1%</td>
<td>48</td>
</tr>
<tr>
<td>Chesnut et al., 2000, CT randomized, 5 years</td>
<td>n = 1255 ♀ and OP pm and FV</td>
<td>Calciton = 100, 200, 300 U/d</td>
<td>3.8%</td>
<td>1.7%</td>
<td>0.54 (0.32–0.92)</td>
<td>46%</td>
<td>2.1%</td>
<td>48</td>
</tr>
<tr>
<td>Ertinger et al., 1998, CT blind placebo controlled, 3 years</td>
<td>n = 7705 ♀ and OP pm (30% FV)</td>
<td>Ral = 60 mg/d</td>
<td>4.5%</td>
<td>2.3%</td>
<td>0.45 (0.29–0.71)</td>
<td>55%</td>
<td>2.2%</td>
<td>45</td>
</tr>
<tr>
<td>Silverman et al., 2008, CT blind placebo/active controlled, 3 years</td>
<td>n = 7492 ♀ and OP pm (56% FV)</td>
<td>Ral = 120 mg/d</td>
<td>21.2%</td>
<td>14.7%</td>
<td>0.70 (0.56–0.86)</td>
<td>30%</td>
<td>6.5%</td>
<td>16</td>
</tr>
<tr>
<td>Cummings et al., 2010, CT blind placebo controlled, 5 years</td>
<td>n = 8556 ♀ and OP (28% FV)</td>
<td>Baz = 40 mg/d</td>
<td>21.2%</td>
<td>14.7%</td>
<td>0.70 (0.56–0.86)</td>
<td>30%</td>
<td>6.5%</td>
<td>16</td>
</tr>
<tr>
<td>Neer et al., 2001, CT randomized placebo controlled, 21 months</td>
<td>n = 1637 ♀ and pm FV</td>
<td>Las = 0.50 ng/d</td>
<td>14.3%</td>
<td>5%</td>
<td>0.35 (0.22–0.55)</td>
<td>65%</td>
<td>9.3%</td>
<td>11</td>
</tr>
<tr>
<td>Greenspan et al., 2007, EC double blind placebo controlled, 18 months</td>
<td>n = 2532 ♀ and OP pm (20% FV)</td>
<td>Trp = 40 μg/d</td>
<td>3.4%</td>
<td>1.4%</td>
<td>0.42 (0.24–0.72)</td>
<td>59%</td>
<td>2%</td>
<td>51</td>
</tr>
<tr>
<td>Meunier et al., 2004, CT phase III placebo controlled, 3 years</td>
<td>n = 1649 ♀ and OP pm and ≥1 FV</td>
<td>rSr = 2 g/s</td>
<td>32.8%</td>
<td>20.9%</td>
<td>0.41 (0.48–0.73)</td>
<td>59%</td>
<td>12%</td>
<td>8</td>
</tr>
<tr>
<td>Cummings et al., 2009, EC placebo controlled, 3 years</td>
<td>n = 7868 ♀ and OP pm (23% FV)</td>
<td>Den = 60 mg/6 months</td>
<td>7.2%</td>
<td>2.3%</td>
<td>0.32 (0.26–0.41)</td>
<td>68%</td>
<td>4.9%</td>
<td>20</td>
</tr>
<tr>
<td><strong>Hip fracture</strong></td>
<td></td>
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</tr>
<tr>
<td>Black et al., 1996, CT double blind placebo controlled, 3 years</td>
<td>n = 2027 ♀ with ↓ BMD and ≥1 FV</td>
<td>Aln = 5 mg/d → 10 mg/d</td>
<td>0.49 (0.23–0.99)</td>
<td>47%</td>
<td>1%</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>n (Sex/Age)</td>
<td>Intervention</td>
<td>RRR</td>
<td>NNT</td>
<td>years</td>
<td></td>
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</tr>
<tr>
<td>McClung et al. 2001</td>
<td>CT randomized placebo controlled, 3 years</td>
<td>n = 5445 ♀ (70–79 years) OP and 1 FR no hip fx</td>
<td>Ris = 2.5 mg/d</td>
<td>0.50 (0.30–0.90)</td>
<td>50%</td>
<td>1%</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Black et al. 2007</td>
<td>CT double blind placebo controlled, 3 years</td>
<td>n = 3886 ♀ ≥80 years and ≥1 FR no hip fx or ↓ BMD</td>
<td>Ris = 5 mg/d</td>
<td>0.80 (0.60–1.20)</td>
<td>NS</td>
<td>NS</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Lyles et al. 2007</td>
<td>CT double blind placebo controlled, 1.9 years</td>
<td>n = 2127 patients with FC</td>
<td>Zol = 1 annual infusion (5 mg)</td>
<td>0.59 (0.42–0.83)</td>
<td>41%</td>
<td>1.1%</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Reginster et al. 2005</td>
<td>CT double blind placebo controlled, 5 years</td>
<td>n = 5091 ♀ and OP pm (55% FV)</td>
<td>rSr = 2 g/d</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Cummings 2009</td>
<td>CT randomized placebo controlled, 3 years</td>
<td>n = 7858 ♀ and OP pm</td>
<td>Den = 60 mg/6 months</td>
<td>0.60 (0.37–0.97)</td>
<td>40%</td>
<td>0.5%</td>
<td>200</td>
<td></td>
</tr>
</tbody>
</table>

Ain: alendronate; Baz: bazadoxifene; Calciton: calcitonin; CT: Clinical trial; FC: fracture de cadera; FR: fracture de cadera; FV: vertebral fracture; CI: confidence interval; INT: intervention; mg: milligram; μg: microgram; ng: nanogram; Las: lasofoxifene; NA: not applicable; NNT: number needed to treat; NS: no statistical significance; OP: osteoporosis; PLC: placebo; pm: postmenopausal;Ral: raloxifen; Rr: risedronate; RR: relative risk; RR: relative risk reduction; RRR: relative reduction; rSr: strontium ranelate; Trp: teriparatide; Zol: zoledronate.

RRR: (1–RR)100; if an intervention reduces the risk of an event, the RRR expresses the percentage in which the intervention would contribute to the reduction of the risk of the event relative to that occurring in the control group. RAR: (incidence in non-exposed – incidence in exposed) × 100; refers to the percentage of events that could be avoided by intervention. If 0.40 (i.e. 40%), of every 100 persons treated with the intervention could lead to the avoidance of 40 events.

NNT: 1/RAR; necessary number of patients that should be treated to avoid an event.

1 Mean of follow up.

2 In a subgroup of 1,977 women with a very elevated risk of fracture (mean age 80) there was a reduction in risk of 36% (P = .046).


Table 6
Preventive Measures of Osteonecrosis of the Jaw of the Spanish Agency of Drugs and Health Products.

| BF: bisphosphonates | OJ: osteonecrosis of the jaw.
---|---|

**Calcitonin.** Calcitonin can be administered as a preventive measure and as a second line treatment of postmenopausal OP, after bisphosphonates, and may be indicated in the treatment of recent symptomatic vertebral fractures (LE 1c; DR B; DA 70%).

Calcitonin prevents loss of BMD in the spine,\textsuperscript{108} reduces the risk of new vertebral fractures in postmenopausal women with a history of vertebral fractures, but not the risk of peripheral fractures.\textsuperscript{107} It also has an analgesic effect in patients with vertebral fractures.\textsuperscript{108} Its effectiveness seems to be maintained in the long term.

**Raloxifene.** Raloxifene is recommended as second line treatment of postmenopausal OP (LE 1a; R A; DA 90%).

Raloxifene decreases the loss of BMD\textsuperscript{109} and reduces vertebral fracture risk in women with postmenopausal OP with and without fractures, but does not reduce the risk of non-vertebral fractures.\textsuperscript{110,111} In addition, it decreases serum cholesterol and low-density lipoprotein cholesterol, although it does not seem to reduce the risk of heart disease. It also decreases the incidence of estrogen receptor positive breast cancer,\textsuperscript{112} but is associated with increased thromboembolic events.\textsuperscript{113,114}

**Bazedoxifene.** Bazedoxifene is an alternative to raloxifene in the treatment of postmenopausal OP (LE 1c; DR B; DA 83%).

Bazedoxifene has demonstrated its protective action in BMD loss and reducing vertebral fractures in postmenopausal women with OP and, like raloxifene, has shown efficacy in reducing vertebral fractures, except in high-risk fracture population (post hoc). At a dose of 20 mg the most common side effects, cramps and hot flashes, were matched to raloxifene and deep vein thrombosis was observed in 0.4 and 0.2% of patients receiving bazedoxifene and placebo,\textsuperscript{115,116} respectively.

**Bisphosphonates.** The panel recommends bisphosphonates (BF) as first-line drugs in the treatment of OP (LE 1a; DR A; DA 100%).

BF are currently the most widely used drugs in the treatment of OP.\textsuperscript{117} Its anti-fracture effectiveness has been amply demonstrated\textsuperscript{118–121} and are generally well tolerated. On the other hand, the rate of adherence to treatment in the medium or long term (1 year) is low, between 47% in the monthly presentation and 30% in the weekly presentation. Therefore, measures aimed at improving patient compliance must be implemented.\textsuperscript{122}

We do not have enough evidence to recommend one drug over another, so the choice will be based on other factors such as dosage, characteristics, patient preferences and physician experience with the use of BF.

There is no general agreement on the optimal duration of treatment, although an average period of 5 years is advised, after which its continuation, suspension or discontinuation or replacement by another drug should be evaluated, taking into account the estimated residual risk of fracture at the time.\textsuperscript{123}

Before starting treatment, an adequate calcium and vitamin D supplementation should be ensured as well as basic guidelines to follow: BF should be taken in the morning (standing or seated with a glass of 200 ml of water), fasting since the previous day and waiting at least half an hour (1 h for monthly dose) before eating solid foods or drinking (except water).

The different BF approved for use in OP will now be discussed. For more information, see Tables 4 and 5.

**Etidronate.** Etidronate increases bone mass and moderately reduces the risk of vertebral fractures in women with OP, with a duration of 4 years,\textsuperscript{124,125} but does not significantly reduce the risk of hip and non-vertebral fractures. Its continued use can cause osteomalacia.\textsuperscript{126}

**Alendronate.** Alendronate significantly reduces the risk of vertebral and non-vertebral fractures, including the hip. Currently, the most common form of administration is a once weekly dosing of 70 mg. Although optimal duration of treatment\textsuperscript{127} was observed when the drug was discontinued after 5 years of treatment, 5 years later a decrease in lumbar and hip BMD was seen, 3.7 and 2.4% compared with when it was continued for 10 years and remodeling markers increased, with no differences in fracture incidence between groups (except clinical vertebral fractures), so treatment may be maintained for 10 years,\textsuperscript{128} but this also opens the possibility of a “therapeutic holiday” at 5 years due to the residual effect of the drug on the risk of fracture.

There is a presentation containing alendronate and vitamin D, and generic alendronate sodium with a similar bioequivalence with the brand product. Slight differences were observed in the in vitro decay\textsuperscript{129} and esophageal transit,\textsuperscript{130} raising doubts about some generic formulations, which may have lower bioavailability and potency, and greater ability to cause esophageal adverse effects.\textsuperscript{131} Because generic prescribing is a central objective of health systems, independent studies are needed for the clinician to prescribe generics without reserve.\textsuperscript{132}

**Risedronate.** Risedronate is effective in reducing the risk of vertebral and non-vertebral fractures, including hip and postmenopausal OP in women with and without previous fractures.\textsuperscript{133–137} The most commonly used dosage is 35 mg/week orally\textsuperscript{138} and there is also a presentation that allows its administration in doses of 75 mg monthly given in 2 consecutive days. There is also a generic preparation.

**Ibandronate.** Ibandronate is effective in preventing vertebral fractures at a dose of 2.5 mg/day orally in postmenopausal women with OP with and without prior fractures. Efficacy in non-vertebral fractures is significant only in the subgroup with higher risk. It has no efficacy in hip fracture. The bioequivalent single dose of 150 mg may be used monthly,\textsuperscript{130,139–144} It may also be administered as an intravenous injection of 3 mg every 3 or 4 months,\textsuperscript{145} which has an acceptable safety profile and may be performed as an outpatient procedure,\textsuperscript{146} as an option for patients with obvious risk of compliance failure.\textsuperscript{147}

**Zoledronate.** This BF is marketed for intravenous use only. Its standard dose is annually, 5 mg, day. It is effective in reducing
the incidence of clinical vertebral fractures, morphometric, non-vertebral and hip fractures over 3 years.\textsuperscript{148} It also reduces overall mortality in patients with hip fractures,\textsuperscript{149} without a clear explanation in this respect.\textsuperscript{150} It is an alternative for patients with OP and increased risk of fractures or those who do not tolerate or are contraindicated oral BF.

Adverse Events of Bisphosphonates. The overall safety profile of BF is acceptable (see Table 4). However, a number of adverse events potentially related to BF have been reported, which may be serious.\textsuperscript{151} Although it is not the purpose of this paper to perform a comprehensive review on the subject, we will discuss some relevant aspects.

The panel, on the basis of available evidence does not believe that there is a need to stop BF for dental procedures in relation to the risk of osteonecrosis (LE 2a; DR B; DA 95%).

There have been reports of osteonecrosis of the jaw (OJ), but its incidence in patients with OP is very low (1/10,000; 1:100,000), and it has been associated with prolonged use of BF.\textsuperscript{152,153} Among the recommendations issued in this regard, we point out those published by AEmyPS (Table 6), to which we refer the reader.\textsuperscript{154} These include a proper oral hygiene and review, and if invasive dental procedures are contemplated (tooth extraction or implant), it is better to complete the healing process before initiating BF. On the other hand, there is controversy about the approach to be followed in those patients already taking BF. The panel believes that discontinuation of 3–6 months should be assessed individually, weighing risks and benefits, since the benefit of this treatment has not been evaluated scientifically. It has also suggested the use of marker CTX, which above a certain threshold may be associated with increased risk of OJ,\textsuperscript{155} but there is no consistent evidence to support it.\textsuperscript{156}

Attention should be paid to the occurrence of thigh pain, especially in patients with prolonged treatment with BF, and X-rays used to rule out stress fractures (and try to prevent progress) or identify atypical fractures (LE 2a; DR B; DA 95%).

There have been reports of atypical fractures (subtrochanteric/femur shaft), with a very low incidence (although it could be underestimated). They are usually bilateral, often accompanied of pain of the thighs and/or groin, and are sometimes associated with some comorbidities and/or medications such as HRT, proton pump inhibitors or glucocorticoids.\textsuperscript{157–159}

There is an association between the development of atrial fibrillation and the use of intravenous zolendronic. There are isolated cases of esophageal cancer in patients taking oral BF, though this association has not been confirmed. Musculoskeletal pain, kidney damage and hepatotoxicity associated to BF are exceptional and rarely cause drug withdrawal.\textsuperscript{160}

If significant adverse events occur with the use of BF, the panel recommended suspending BF and evaluating the start of a drug with a different mechanism of action (LE 5; DR D; DA 95%).

If adverse events are significant, such as OJ, occur and although there is no scientific evidence indicating that the withdrawal of the drug improves the outcome of the process, it is prudent to suspend and evaluate the indication of drugs with different mechanisms of action from BF.

Denosumab. Denosumab may be recommended as first-line therapy for the treatment of postmenopausal OP with risk of fracture (LE 1b; DR A; DA 95%).

Denosumab is a monoclonal antibody that inhibits the formation, activation and survival of osteoclasts. It is therefore, an antiresorptive drug approved for the treatment of postmenopausal OP with a high risk of fracture, at a dose of 60 mg/6 months subcutaneously\textsuperscript{161,162} (Table 4).

Denosumab has been reported to reduce the risk of new vertebral fractures by 68% compared to placebo after 3 years of treatment (RR = 0.32, 95%, 0.26–0.41), the risk of hip fractures in 40% (RR = 0.60, 95% CI, 0.37–0.97), non-vertebral fractures by 20% (RR = 0.80, 95% CI, 0.67–0.95) and multiple fractures (≥2)\textsuperscript{163} (see Table 5). Its effect is reversible since the inhibition that occurs in bone resorption disappears rapidly as serum levels decline.\textsuperscript{164,165} It is effective in patients previously treated with alendronate, even without a rest interval,\textsuperscript{166} and reduced levels of biomarkers of bone turnover, particularly resorption markers, fall faster and more intensely than with alendronate.\textsuperscript{167,168} It also produces marked increases in BMD at the lumbar spine, total hip and femoral neck, distal radius and total body, from 12 months of treatment onward, with an effect greater than alendronate and far superior to placebo.\textsuperscript{163,164,167–171}

The overall incidence of adverse events was similar to placebo in terms of general infections, cancer, hypocalcemia and cardiovascular events,\textsuperscript{163,164,167–170} but described a slight increase in urinary tract and skin infections\textsuperscript{163,172} (see Table 4).

Anabolic Drugs.

Parathyroid Hormone Analogs. PTH analogs can be recommended as first-line drugs for the treatment of OP with a high risk of fracture (LE 1b; DR A; DA 95%).

PTH's osteoforming effects can prolong the life of osteoblasts, whether administered complete\textsuperscript{175} or as an amino fraction.\textsuperscript{176} There are two molecules on the market (see Table 4): teriparatide (Trp) or 1–34 rhPTH used at doses 20 mg/day subcutaneously, and the rhPTH 1–84 (PTH 1–84) at doses of 100 mg/day subcutaneously. They are, therefore, osteoforming drugs whose effect is primarily anabolic. The main difference is that Trp pharmacokinetics are found elevated within 3 h, while the PTH 1–84 lasts up to 9 h.\textsuperscript{177,178}

PTH 1–34 reduces the incidence of vertebral and nonvertebral fractures but not hip fractures, both as monotherapy and associated with HRT.\textsuperscript{179,180,181} PTH 1–84 shows effectiveness in reducing vertebral fractures in women with and without previous fracture.\textsuperscript{182} Both are superior to alendronate in increasing BMD\textsuperscript{183–186} (Table 5).

There is a limit of the duration of therapy to 2 years, both for Trp as for PTH 1–84, due to the occurrence of osteosarcomas in Fischer rats treated with Trp\textsuperscript{179,187} for 2 years, although in humans this association is not proven.\textsuperscript{188–190}

Adverse reactions generally are not serious with either drug. Mainly hypercalcemia and hypercalciuria\textsuperscript{177,179,182,191,192}, occur, so it is essential to monitor the levels of calcium in blood and urine in patients starting treatment. This monitoring of serum and urinary calcium during treatment is necessary only with PTH 1–84. For more information, see Table 4.

Mixed Action Drugs. Strontium Ranelate. Strontium ranelate (RSR) may be recommended as a first-line drug for the treatment of postmenopausal OP to reduce the risk of vertebral, non-vertebral and hip fractures in a subgroup at high risk (>70 years and femoral neck DXA T ≤3) (LE 1b; DR A; DA 90%).

RSR produces increased bone formation and decreased resorption in moderation, which translates into an actual increase in bone mass and strength.\textsuperscript{193–195} It is indicated for the treatment of OP in postmenopausal women (Table 4).

BMD increased from 12.7% to 14.4% in the lumbar spine, 5.7% to 8.2% in the femoral neck and 7.1% to 9.8% in the total hip.\textsuperscript{196,197} However, some of this increase is due to the deposition of strontium in bone, so the increase is 50% of what is referred. This effect is maintained for 5 years.\textsuperscript{198} RSR reduces vertebral fractures by 41% (effect detected in the first year), not 16% vertebral, non-vertebral fractures by 19% higher and hip fractures by 36% in a high-risk subgroup after 3 years of treatment (Table 5). This benefit remains up to 8 years afterward.\textsuperscript{199}

Although the possibility of an increased tendency for deep vein thrombosis and pulmonary embolism exists, it is not clearly
demonstrated. The data sheet recommends caution in patients at risk for these events. There have also been cases reported of DRESS syndrome and, although very rare, it is recommended that patients be informed to discontinue treatment if a rash appears and seek medical attention. The rest of the adverse events are generally mild and transient (see Table 4).

### Drugs in Development

Table 7 shows the drugs that can potentially increase the currently available arsenal against OP. Antiresorptive drug development is more advanced than that of anabolic drugs.

- Some seem to inhibit cathepsin K, whose main function is to degrade bone matrix, rapidly, selectively and reversibly.
- odanacatib and MK-0674.
- Also in development are drugs capable of inhibiting integrins or interfering with the acidification process (chloride channel, vacuolar ATPase).
- Developing anabolic drugs act on two regulatory elements of osteoblastic activity: the Wnt signaling pathway and activins.

### Combination and Sequential Therapy

We recommend antiresorptive therapy is instituted at the end of the 24 months cycle of anabolic drug administration and it is not recommended concomitantly with BF (LE 1b; DR A; DA 85%).

PTH analogs may be administered sequentially with bone resorption inhibitors or mixed-acting drugs. However, the use of raloxifene or estrogen does not seem to inhibit their action. The fact of having received prior treatment with antiresorptive does not appear to alter the anabolic effect of Trp.

Combined treatment with antiresorptives cannot be recommended across the board, although their use might be justified in highly selected cases (LE 5; DR D; DA 75%).

Multiple associations were tested: etidronate and estrogen, alendronate, risedronate or Trp, raloxifene plus alendronate, and PTH (1–84) with raloxifene and Trp. The combined administration of these drugs achieved, in most cases, a greater increase in BMD than monotherapy, but there is no clear evidence that it improves anti-fracture efficacy. Only the concomitant use of estrogen and Trp has shown a significant reduction of new vertebral fractures. However, combinations of these drugs are well-tolerated and no adverse effects could be seen on bone tissue.

### What Patients Should Undergo Drug Treatment?

Initiate pharmacological treatment (LE 5; DR D; DA 74%):

1. Postmenopausal women:
   - Low-trauma fracture intensity, regardless of the value of BMD.

   - OP (BMD below – 2.5 SD in the T-score of the spine and/or femur) with or without fractures, assessing risk factors.
   - The use of FRAX algorithm may help in decision making when considering the establishment of drug treatment.

   Evaluate pharmacologic treatment:

   - Early menopause (<45 years) by DXA and/or other risk factors.
   - Osteopenia (BMD between –1 and –2.5 SD on the T-score) Treatment is reserved for very specific cases, as would be intense osteopenias near the OP range in younger women with high risk factors for fracture.

   Table 1 shows the most important risk factors; some may be by themselves an indication for treatment, such as administration of glucocorticoids in doses higher than 5 mg/day for over 3 months.

### How Long Should Treatment Be Maintained and How Does One Assess its Effectiveness?

Treatment of OP, unless contraindicated, should be maintained for years (LE 5; DR D; DA 100%).

The two PTH analogs can be administered only for 24 months. The rest have maintained their efficacy and safety for varying periods: 10 years for alendronate, risedronate and etidronate up to 7 years ibandronate 3 years, raloxifene 8 years, zole-dreronate 6 years, calciotomin 5 years, denosumab 3 years, and rSr 8 years. We must remember that there have been reports of atypical fractures with prolonged treatment with BF.

Anti-osteoporotic drugs reduce but do not eliminate the risk of new fractures, so that treatment can be effective even though the patient has new fractures.

It is recommended to assess response to treatment by central DXA every 2–3 years regardless of the type of drug (LE 5; DR D; DA 75%).

At the beginning of treatment it may be desirable to repeat a central DXA at one year and, in situations of high risk for fracture such as transplanted patients, high dose steroids and multiple vertebral fractures, every 6 or 12 months (LE 5; DR D; DA 75%).

Bone turnover markers may be useful to assess the effectiveness of early treatment and to improve its persistence (LE 2c; DR C; DA 80%).

It is recommended to evaluate the therapeutic response to anti-osteoporotic drugs with central DXA, taking into account the characteristics of each patient. Bone turnover markers may be useful to assess its early efficacy.

The appearance of new fractures with a decrease in BMD values over 2%, which corresponds to the minimum significant change at least one year of treatment, may be seen as an inadequate therapeutic response. If there is only one of those two situations, the response is probably inadequate. By contrast, an appropriate response to treatment will be defined by the absence of these negative circumstances.

### What Is the Most Appropriate Anti-osteoporotic Drug?

The selection of a specific drug for a patient with OP should be based on: (a) evidence of efficacy in patients with the same characteristics, (b) absence of contraindications, (c) real possibility of compliance; (d) adverse events, and (e) efficiency of prescription.

Efficiency should be considered as a requirement in its entirety and not just by the price of the drug, given that factors such as costs associated with its administration or affect its anti-fracture effectiveness reflect on treatment costs. The prescription must be viable and take into account other associated treatments and empower the patient to achieve optimal compliance.

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Table 7

<table>
<thead>
<tr>
<th>Drugs in Development</th>
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<tbody>
<tr>
<td>Resorption inhibiting drugs</td>
<td>1. Cathepsin K inhibition</td>
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<td>MK-0674</td>
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<td>2. Integrin inhibition</td>
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<td>3. Src-kinase inhibition</td>
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<td>4. Acidification mechanism inhibition</td>
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<tr>
<td>Anabolic drugs</td>
<td>1. Wnt signaling pathway modulation</td>
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<td>Anti-sclerostin antibodies (AMG-785)</td>
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<td></td>
<td>sFRP inhibitors</td>
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<td>2. Activin inhibition (ACE-011)</td>
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[Note: The above text is a representation of the natural text of the document, converted into readable format.]
The patient must be informed to participate in decisions making regarding the selection of a particular drug (LE 5; DR D; DA 100%).

Male Osteoporosis

In the male, the densitometric diagnostic approach of OP is the same as in women (LE 5; DR D; DA 95%).

OP is a common male problem, and has a similar or higher morbidity than in women. The prevalence of densitometry OP in Spanish men >20 years of age is estimated between 2.5% and 4.2%3,23,27 that of radiographic vertebral fractures is 20% in men <65 years and in 25% >65 years,238 and the incidence of hip fracture is 73–115/100 000 inhabitants >50 years.239,240 However, its diagnostic suspicion is usually low, unless there are clear risk factors (steroids, chronic liver disease, chronic obstructive pulmonary disease, etc.).

In males, it is advisable to perform a basic study of the most common causes of secondary OP through a clinical history and the required laboratory tests (LE 5; DR D; DA 100%).

There are differences in etiopathogenesis241 and in risk factors between men and women. Secondary OP is more common in men.241–244 In Spain, the most common cause is hypogonadism (10%–20%),242 followed by chronic corticosteroid therapy and alcohol abuse, usually associated with liver disease.245,246

In the treatment of male OP the same general measures as in women, and the use of drugs approved for this purpose are recommended (LE 5; DR D; DA 75%).

Currently, drugs that have indications for male OP are risedronate,247 zoledronate248 and Trp,249 with the same dosage and schedule as in female OP.

It is recommended that monitoring, evaluation and duration of treatment be the same as in female OP (LE 5; DR D; DA 95%).

Premenopausal Osteoporosis

In premenopausal women, the diagnostic criteria differ according to DXA. Thus, the value of BMD should be applied using the Z scale and the diagnosis of “low bone mass” is set if Z scale <−2 SD. The presence of fragility fractures, particularly associated with low bone mass, allows the diagnosis of OP (LE 5; DR D; DA 87%).250,251

About 50% of cases are associated processes, and a comprehensive study is recommended to identify the underlying cause (LE 5; DR D; DA 91%).

The most common causes are glucocorticoid treatment or Cushing’s disease, pregnancy, osteogenesis imperfecta or estrogen deficiency, anorexia nervosa and/or intestinal malabsorptive diseases. In addition, it is known that idiopathic forms are frequent associated with hypercalciuria and a family history of OP.

The therapeutic approach includes an adequate intake of calcium and vitamin D, exercise, avoidance of tobacco and alcohol,252 and treating the underlying cause.

In patients who only show a decrease in BMD with no other risk factors, pharmacologic intervention is usually not required, although it is advisable to monitor these patients (LE 5; DR D; DA 96%).

Drug therapy is considered in specific cases such as in patients with fractures or in those with associated factors, especially treatment with glucocorticoids and hypogonadism. In these cases, BF, estrogen, calcitonin, PTH treatment or Trp may be indicated.

BF in women of childbearing potential should be used with caution, as there is few data on its safety (LE 5; DR D; DA 96%).

Therefore, contraceptive measures should be indicated in patients undergoing such treatment.7,253

Glucocorticoid-induced Osteoporosis

Glucocorticoids (GC) are the most common cause of secondary OP, representing up to 25% of all cases of OP.254 It is also estimated that fractures occur in one third of those treated after one year and 50% at some point in their evolution.255

The risk of fracture caused by GC depends on several factors: BMD at the beginning of treatment, daily and accumulated dose, and underlying disease. BMD loss is rapid, especially during the first year, even at low doses, and trabecular bone is most affected.256

There are individual characteristics that make these patients more vulnerable to lower doses of corticosteroids and develop osteoporosis more than others with higher doses.257 Due to the great changes that occur on the bone microarchitecture, fractures produced by GC appear with BMD values that are higher than in other types of OP, so that the threshold for intervention should be located above the T-score of postmenopausal OP.

The prevention and treatment of OP should begin as soon as possible. Preventive measures should be undertaken in patients using doses equivalent to >5 mg/day of prednisone for more than 3 months. If there is a history of fragility fractures or the patient is over 65, the start of drug treatment is recommended. In those that do not have fractures and are less than 65 years old, a DXA is indicated and if this presents a T <−1.5 SD, drug treatment is indicated.258

Preventive measures: in patients who are to take prolonged GC the following should be considered: (a) use the lowest GC dose possible and as suspend it as quickly as possible, (b) avoidance of the use of tobacco/alcohol, a balanced diet with adequate calcium intake, etc., (c) prevention of muscle loss and falls with a program of proper nutrition and exercise, (d) supplementation with calcium and vitamin D (LE 5; DR D; DA 90%).

Drug therapy: BF (alendronate, risedronate or zoledronate) and Trp have proven effective in the prevention and treatment of OP due to GC.258–267 All treatments should always be supplemented with adequate doses of calcium and vitamin D. In patients at a high risk of fracture, treatment may be started with osteoforming agents (Trp) followed by BF. Treatment with thiazides (25 mg/day) should be considered in patients with hypercalciuria.

According to technical data, drugs for corticosteroid associated OP are Trp, risedronate and zoledronic (see Table 4).

Discussion

As commented in the introduction, the objective of this document is to update on advances in the different clinical aspects of osteoporosis: diagnosis, evaluation, follow up and treatment. This has been a joint effort by members of the panel and the RU of SER and has entailed a large systematic review on different topics of interest and has provided the necessary scientific strength to emit recommendations with a degree of evidence but also of consensus, providing the reader a more objective evaluation of these recommendations.

This paper highlights a number of new contributions in the field and the inclusion of some tables that complement the various recommendations. On the one hand, we have expanded the areas of clinical interest with pre-menopausal osteoporosis, male osteoporosis and osteoporosis secondary to steroids. Furthermore, we have added two new antiresorptive drugs: bazedoxifen and denosumab. We have also included the results of systematic reviews aimed at answering the following questions: the relationship of bisphosphonates to osteonecrosis of the jaw and atypical fractures of the femur, the relationship between calcium supplementation and the occurrence of kidney stones, and the degree of evidence of different algorithms to calculate the risk of fracture. And finally, we
have joined the tables that summarize the effectiveness of different drugs in reducing fractures and current approved indications (data sheets), dosage, adverse events and interactions with other drugs.

It is also important to emphasize some observations in this document. The first is the fact that the evaluation of the risk for fracture was one of the topics that generated a greater debate among the panel members, because it had been intended that the same criteria as previous documents or the FRAX® algorithm were to be used. The panel’s solution was to expose both options so that the reader may have the largest information possible and so that it may help in identifying patients at risk for osteoporosis.

The degree of evidence of the different drugs is based on its “main studies” and in most of them the primary objective was the reduction in vertebral fractures, noting that the efficacy in the reduction of non-vertebral and hip fractures does not represent the same degree of evidence. Only rSr and risedronate have carried out studies in which the primary objective has been non-vertebral and hip fractures, respectively.

As stated in this document and, according to the European Drug Agency, indications for the use of bazedoxifene and denosumab are for women with high risk of fracture, contrasting with the analysis of their main studies which were based in populations with a majority of patients without previous fracture, making them moderate in risk. It is necessary to take this into account when choosing appropriate treatment.

In conclusion, the recommendations of this document constitute a background for management of OP. They are general norms that must be individualized in a role, as professionals, must assume.

Disclosures

The authors have no disclosures to make.

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