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Review article

Sequential management of postmenopausal health and osteoporosis: An update

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ABSTRACT

Increased life expectancy means that women are now in a hypoestrogenic state for approximately one-third of their lives. Overall health and specifically bone health during this period evolves in accordance with aging and successive exposure to various risk factors. In this review, we provide a summary of the approaches to the sequential management of osteoporosis within an integrative model of care to offer physicians a useful tool to facilitate therapeutic decision-making. Current evidence suggests that pharmacologic agents should be selected based on the risk of fractures, which does not always correlate with age. Due to their effect on bone turnover and on other hormone-regulated phenomena, such as hot flushes or breast cancer risk, we position hormone therapy and selective estrogen receptor modulators as an early postmenopause intervention for the management of postmenopausal osteoporosis. When the use of these agents is not possible, compelling evidence supports anti-resorptive agents as first-line treatment of postmenopausal osteoporosis in many clinical scenarios, with digestive conditions, kidney function, readiness for compliance, or patient preferences playing a role in choosing between bisphosphonates or denosumab during this period. For patients at high risk of osteoporotic fracture, the "anabolic first" approach reduces that risk. The effect on bone health with these bone-forming agents or with denosumab should be consolidated with the subsequent use of antiresorptive agents. Regardless of the strategy, follow-up and treatment should be maintained indefinitely to help prevent fractures.

Abbreviations: BMD, bone mineral density; BMI, body mass index; FRAX®, Fracture Risk Assessment tool; GSM, genitourinary syndrome of menopause; MHT, menopausal hormone therapy; OCEBM, Oxford Centre of Evidence-Based Medicine; PTHrP, PTH-related peptide; RANKL, receptor activator of nuclear factor kappa-B ligand; SERMs, selective estrogen receptor modulators.

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1. Introduction

Increased life expectancy implies that women remain in a hypoestrogenic state for approximately one-third of their lives. The overall health status and specifically bone health during this period evolves in accordance with aging and successive exposure to various risk factors.

The well-established relationship between estrogen deficiency and postmenopausal osteoporosis has led to the proposal of a sequential approach for the management of this disorder that is guided by the evolution of bone mineral density and the risk of fractures. However, this approach should also consider the impact of each therapeutic alternative on the quality of life and other medical disorders that may arise during this period, such as the occurrence of neurovegetative symptoms, cardiovascular risk factors, or hormone-related cancers. The overlap between the occurrence of postmenopausal osteoporosis and other threats to women's health and quality of life opens "windows of opportunity" to use sequential treatments designed to account for agonist and antagonist effects in relation to other health needs. Thus, in addition to their effect on bone mineral density, the efficacy of estrogens on vasomotor and genitourinary symptoms and the protective effect of selective estrogen receptor modulators (SERMs) on the breast have led to the proposal of the sequential use of "SERM-antiresorptive agents-bone anabolic agents". The need for long-term therapy, the evidence supporting the limitation of the duration of some treatments, and the availability of new therapeutic alternatives have introduced debate on the convenience of re-evaluating the classic sequence of treatment and/or the need for osteoporosis drug holidays.

Finally, integrative health care approaches to maintain the health of women after menopause with an adequate quality of life extends beyond the prevention and treatment of osteoporosis.

Health care providers involved in the care of women after menopause should consider all these variables when providing health counseling and should develop personalized long-term strategies that cover most of a woman's needs.

In this review, we provide a summary of the approaches to the sequential management of osteoporosis within this integrative model of care to ultimately offer clinical physicians a useful tool to facilitate the therapeutic decision-making process.

2. Methods

We conducted a literature review on the current approach to the sequential management of osteoporosis. The authors initially discussed the relevant topics in a panel and translated them into health care questions that were distributed among the panelists. Then, we conducted a search in MEDLINE and EMBASE in two steps. Initially, we mapped the evidence to identify guidelines and recommendations in the field and then focused on evidence reviews and primary research studies.

One reviewer selected the studies for each defined topic and assessed their internal validity using the Cochrane tool for trials [1] and the Newcastle Ottawa Scale for nonrandomized studies [2]. Each study was classified according to the Oxford Centre of Evidence-Based Medicine (OCEBM) levels of evidence [3]. The supplemental appendix 1 shows the search terms defined to conduct the search in the bibliographic databases and the supplementary appendix 2 the detailed assessment of the studies included.

The results of the literature search were distributed among all participant authors who prepared a draft of the assigned health care question. Each reviewer narratively synthesized the main findings from the selected studies according to their relevance for the different topics of interest. The first draft of each section was reviewed in a meeting with all participants, and with the input obtained, a second draft was produced. The later and subsequent drafts were circulated among all participants who approved the final draft. The entire process is summarized in Fig. 1.

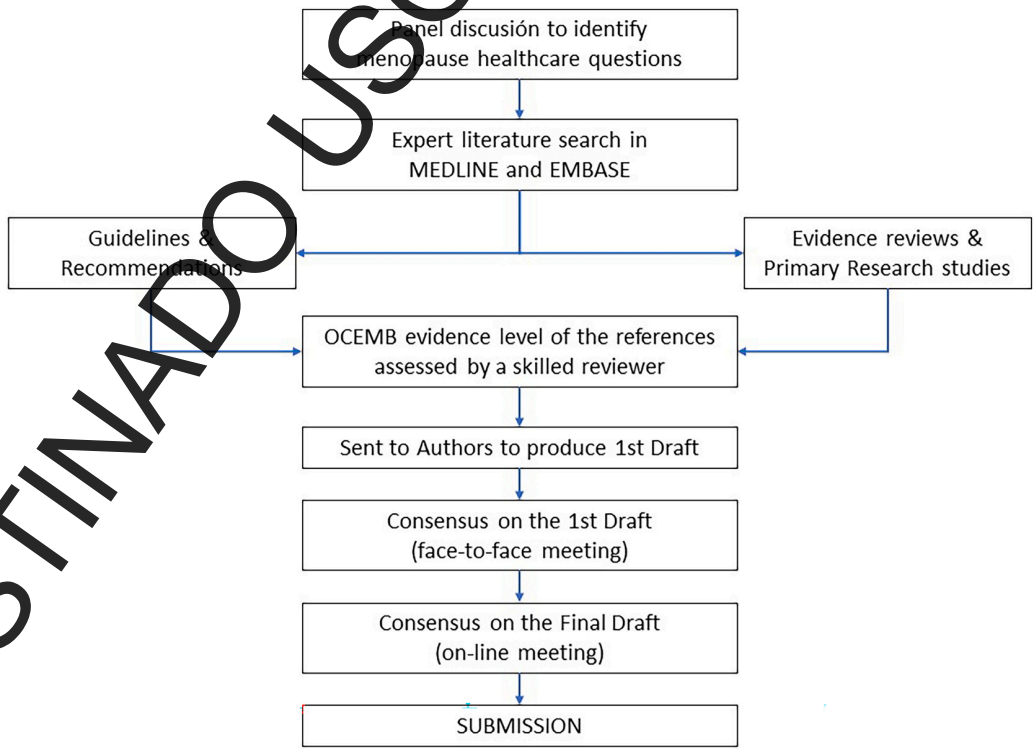

Fig. 1. Flow diagram of the elaboration process of this review.
OCEBM, Oxford Centre of Evidence-Based Medicine.

2.1. Healthy lifestyle, calcium and vitamin D

A healthy lifestyle is the basis for any pharmacological intervention. Such a lifestyle has been shown to improve vasomotor symptoms and prevent chronic diseases associated with aging and menopause [4,5]. Thus, healthy lifestyle counseling should be part of the health care provided to women at menopause.

Osteogenic exercise should involve at least 150 min of moderate-intensity physical activity or 75 min of vigorous-intensity aerobic activity per week. Performing 2 sessions of muscle-strengthening activity is also advisable [6].

A healthy diet, such as the Mediterranean diet, and a normal body mass index (BMI) can reduce the risk of vasomotor symptoms and cardiovascular events and should also be included in the counseling process for menopausal women [5,7].

The daily intake of calcium should be 1200 mg for women older than 50 years and 1000 mg if the patient is on hormone therapy. In addition, the daily intake of vitamin D is 600 IU for people up to 70 years of age and 800 IU for people over 70 years of to maintain target levels >20 ng/mL (50 nmol/L) [8].

Since all the pivotal trials of drugs for the management of osteoporosis included calcium and vitamin D supplements in the active and placebo groups, this treatment is not a sequential but a continuous concomitant strategy. Adequate levels of vitamin D play a key role in the musculoskeletal system and in general morbidity and mortality [9] and, although the mechanism has not been elucidated, may be important in fragility fracture healing. After a fragility fracture, levels of vitamin D > 75 nmol/L (30 ng/mL) should be maintained to ensure optimal musculoskeletal health [8–10].

Calcium plus vitamin D supplementation significantly reduces the risk of all fragility fractures and hip fractures in people with severe deficiency but not in the general population [11,12].

2.2. Menopausal hormone therapy

The Women's Health Initiative (WHI) trial demonstrated that menopausal hormone therapy (MHT) in postmenopausal healthy women reduces the risk of osteoporotic fractures at the spine by 35 %, at the hip by 33 %, and at the wrist/lower arm by 23 % [13]. Long-term data from this trial showed no evidence for increased fracture risk after stopping MHT [14].

The efficacy of MHT for the treatment of menopausal symptoms and osteoporosis is offset by an increased risk of cardiovascular disease, including coronary heart disease and stroke, and breast cancer [15]. The effect of MHT on osteoporosis or menopausal symptoms is highly dependent on treatment components, both estrogen and progestin, as well as on the timing of use in relation to age and years since menopause [16]. Thus, natural progesterone or dydrogesterone have been associated with a lower risk of breast cancer than medroxyprogesterone acetate, the progestogen used in the WHI trial [17–19], and MHT-associated cardiovascular risk is limited in younger women [20,21]. Therefore, the guidelines published immediately after the publication of the WHI trial recommended the use of MHT for the treatment of osteoporosis when no other drugs could be used. However, in light of new findings, this position has been nuanced in some guidelines as stated by Rozenberg et al. [22] and the North American Menopause Society currently considers MHT a first-choice option for the management of osteoporosis in symptomatic women younger than 60 years or within 10 years since menopause [23]. The rationale for this recommendation is reinforced by the evidence of a lower bone mineral density (BMD) in this subgroup [24]. The use of MHT for the prevention of chronic diseases in postmenopausal women, however, remains debatable [25,26].

If, as frequently is the case, anti-osteoporotic treatment should be maintained, protocols to facilitate the sequential transition from MHT to other anti-osteoporotic drugs have not yet been established. Although only based on expert opinion, a progressive reduction in MHT seems to be a practical approach in symptomatic women. The sequential use of SERMs has been suggested as a well-founded approach, given the more selective protection of SERMs against vertebral fractures, which are more prevalent at younger ages [27]. Other therapeutic alternatives, including the use of more potent antiresorptive drugs, may also be considered. The persistence of menopausal symptoms may be managed by specific approaches, such as local preparations, including vaginal estrogens, for genitourinary syndrome [23] or nonhormonal alternatives [28].

2.3. Selective estrogen receptor modulators (SERMs)

SERMs are compounds that act as agonists or antagonists for estrogen receptors depending on the target tissue (e.g., in bone, they act as agonists, while in the breast and uterus, they act as antagonists). Similar to natural estrogens, the net effect of SERMs in bone is a weak antiresorptive effect.

Despite the great effort to study and develop new SERMs at the beginning of the 2000s, after the publication of the raloxifene MORE trial [29], only bazedoxifene was added for the treatment of postmenopausal osteoporosis, and ospemifene was added to treat dyspareunia and vulvovaginal atrophy.

According to most clinical practice guidelines for the management of postmenopausal osteoporosis, the role of SERMs is limited to postmenopausal women with a low or intermediate risk of fracture, especially if they are at increased risk of breast cancer. This role is supported by data showing that raloxifene and bazedoxifene reduce the risk of vertebral fractures, although neither have been shown to reduce hip or nonvertebral fractures [29,30]. Moreover, results from pivotal trials showing that raloxifene is associated with a significant reduction in breast cancer were further confirmed in a larger comparative trial with tamoxifen, including women at high risk of breast cancer and low risk of fracture [31]; in addition, promising data on the effects of bazedoxifene on breast cancer have been published [32]. In contrast, raloxifene or bazedoxifene has been associated with a 3-fold increase in the risk of thromboembolism [33,34]. Based on these limited effects, SERMs could be considered the initial option for the management of osteoporosis in women under 65 years of age who have a reduced BMD in the spine but not in the hip, have no increased risk of venous thromboembolism and, especially, are at high risk of breast cancer. Bazedoxifene has been approved alone or in combination with conjugated estrogens on the basis that such a combination improves BMD and reduces hot flushes without the undesirable effects on the endometrium and breast associated with estrogen use in experimental settings [35]. SERMs alone have to be considered cautiously in previously symptomatic women who will probably benefit from switching to this combination.

Data on the efficacy and safety of SERMs are available for up to 8 years of use [36,37]. Therefore, withdrawal of SERM treatment should be considered after 8 years, after 3–5 years of treatment if the patient is considered at high risk of fracture [38] or if risk factors for thrombosis arise. After the discontinuation of SERMs, the use of another antiresorptive drug, such as bisphosphonates or denosumab, is recommended [39].

Other potential indications for the use of SERMs include sequential treatment after short-term treatment with denosumab or teriparatide. When the discontinuation of denosumab therapy is considered, sequential treatment with bisphosphonates or, in cases of bisphosphonate intolerance, with SERMs is mandatory [40]. However, the effect on bone after switching from denosumab to SERMs is controversial since some data suggest that they neither prevent bone loss nor vertebral fractures [41], whereas others found a positive effect when denosumab was discontinued after <2 years of treatment [42].

Treatment with teriparatide, a bone anabolic agent, should be followed by an antiresorptive agent [40], and raloxifene may play a role. Sequential raloxifene after teriparatide prevented rapid bone loss at the lumbar spine and increased hip BMD [43], and raloxifene combined

with teriparatide showed a similar increase in bone formation as teriparatide alone but with less increase in bone resorption [44].

2.4. Bisphosphonates

Bisphosphonates are pyrophosphate analogs that contain a P-C-P bond. They are antiresorptive agents due to their potent inhibitory effect on osteoclasts [45,46]. Bisphosphonates have been used for >30 years for the treatment of osteoporosis, as they have shown a 40–50 % reduction in the risk of radiographic vertebral fractures at 3–5 years compared to placebo and a 20–30 % reduction in the risk of nonvertebral and hip fractures [45–48].

According to the clinical practice guidelines, these therapies have demonstrated a positive risk-benefit balance for the management of osteoporosis in certain settings: as first-line treatment in patients with a 10-year Fracture Risk Assessment tool (FRAX®)-calculated high risk of fractures [49,50]; after an anabolic agent to maintain the induced gains in bone mass [49,50]; and when discontinuation of denosumab is considered to reduce the risk of rebound-associated fractures [50]. In this manuscript, we used the terms high or very high risk of fractures as they have been defined and used in those clinical practice guidelines [49,50] and described with greater detail elsewhere [49,50]. In brief, they are based on the presence of a fracture within past 12 months, multiple fractures, fracture while on treatment for osteoporosis or while on medication that may harm bone, very low T-score and FRAX probability >30 % (Major osteoporosis fracture) or >4.5 % (hip) for very high risk and age (postmenopausal), prior fracture (more than previous 12 months), T-score < −2.5 or T-score −1.0 to −2.5 and FRAX probability >20 % (Major osteoporosis fracture) or >3 % (hip) for high risk.

Treatment with bisphosphonates is usually maintained for 3–5 years, but for patients who still have a high risk for fractures, continuing therapy for up to 5 additional years should be considered [49].

Bisphosphonates are associated with common mild-to-moderate adverse effects, including gastroesophageal irritation, when administered orally. However, very rare but important adverse events associated with bisphosphonates may occur, such as osteonecrosis of the jaw [51,52], atypical femoral fractures [53], and arrhythmias [54]. These drugs are contraindicated or should be used with caution in patients with an estimated glomerular filtration rate of <30 mL/min/1.73 m^2 [55].

Compliance is a key issue when using oral bisphosphonates since the discontinuation rates are up to 50 % at 12 months and 85 % at 3 years [49,50], leading to suboptimal efficacy in terms of reduction of the risk of fractures and higher cost for the health system [56]. Intravenous formulations, in particular once-a-year zoledronate [48], for 3 or 6 years overcome this limitation and offer a potent and long-lasting effect. Among other strategies, novel formulations of oral bisphosphonates, such as effervescent alendronate [57] and gastro-resistant risedronate [58], seek to reduce gastrointestinal adverse reactions or the complexity of the administration and thus to improve treatment adherence.

2.5. Denosumab

Denosumab is a fully human monoclonal antibody that inhibits osteoclast formation by blocking the binding of receptor activator of nuclear factor kappa-B ligand (RANKL) to its receptor RANK. Denosumab has a reversible action that favors a rebound effect when it is discontinued and this effect should always be considered in the sequential treatment for osteoporosis [59].

In postmenopausal women with osteoporosis, denosumab has been shown to reduce the relative risk of fractures compared to placebo by 68 % for radiographic vertebral fractures, 40 % for nonvertebral fractures, and 20 % for hip fracture [60]. It is mainly indicated for patients with a high or very high risk of fracture. In patients with very high risk of fracture, denosumab could be indicated when there is a contraindication to administering an anabolic agent or as a continuation after completing treatment with these agents.

As sequential treatment, denosumab is appropriate after hormone treatment or treatment with a SERM when the risk of hip fracture remains high. In postmenopausal women with low BMD despite treatment with an oral bisphosphonate, switching to denosumab increased bone mass and reduced bone remodeling to a greater extent than the continuation of oral bisphosphonate [61]. In this setting, switching to denosumab was associated with greater BMD increases than switching to intravenous zoledronic acid [62]. Therefore, denosumab would be indicated after the failure of oral bisphosphonates or when adherence issues with these agents arise. In patients with a very high or imminent risk of fracture, the sequential administration of denosumab after an anabolic agent is a potent therapeutic option. After teriparatide treatment, the transition to denosumab increases BMD to a greater extent than the transition to bisphosphonates [63]. Likewise, treatment with romosozumab for 1 year followed by a transition to denosumab for up to 2 years is associated with a continuous and relevant increase in BMD and reduction in the risk of fracture [64]. Overall, denosumab has demonstrated efficacy and safety when transitioning from most anti-osteoporotic agents [65].

The reversible mechanism of action of denosumab and the risk of a rebound phenomenon after denosumab discontinuation mandates subsequent antiresorptive treatment that should be initiated within 6 months after the last dose of denosumab. The intravenous administration of zoledronate has been shown to mitigate the loss of bone mass that occurs with the rebound effect after discontinuing denosumab [66]. Oral bisphosphonates or SERMs do not seem efficacious for mitigating the rebound phenomenon with denosumab, although alendronate may mitigate BMD loss after discontinuation of short-term treatment with denosumab [67]. The transition from denosumab to teriparatide should also be avoided since there is a transient reduction in bone mass of the total hip [68]; in patients with a high risk of fracture, the combination of denosumab and teriparatide may be indicated due to their effect on BMD [69].

2.6. Anabolic agents

Anabolic agents stimulate osteoblast recruitment and activity to increase bone mass and reduce fracture risk. In postmenopausal women with a high or very high risk of fracture, regardless of age, starting treatment with an anabolic agent followed by an antiresorptive agent is widely recommended since emerging evidence supports the concept of “anabolic-first regimens” for this clinical setting [63,70].

Currently, three anabolic drugs have been approved in Europe for the treatment of osteoporosis: teriparatide, abaloparatide and romosozumab. Teriparatide is the recombinant human N-terminal fragment (1–34) of endogenous human parathyroid hormone, abaloparatide is the modified PTH-related peptide (PTHrP) 1–34, and romosozumab is a humanized monoclonal antibody that neutralizes sclerostin (inhibitor of the Wnt pathway and essential in osteoblastic activity) with a dual mechanism of action since it stimulates formation but also inhibits bone resorption via RANKL inhibition [70]. All three drugs are administered subcutaneously, teriparatide and abaloparatide daily for a period of time limited to two years and 18 months, respectively, and romosozumab monthly for up to one year; after this treatment period, an antiresorptive drug, either a bisphosphonate or denosumab, needs to be administered to maintain or enhance the effect of these drugs on bone mass and/or reduce fracture risk [63,70,71]. Thus, sequential treatment with alendronate after teriparatide or abaloparatide, and especially denosumab after teriparatide, is associated with a sustained increase in BMD in the lumbar spine and hip [71–73] and in bone strength measured by high-resolution peripheral quantitative computed tomography [74]. In addition, 18 months of abaloparatide followed by 24 months of alendronate reduces the risk of vertebral, nonvertebral, clinical, and major osteoporotic fractures [73]. After discontinuing romosozumab, treatment with denosumab for one or two years significantly increases

BMD and maintains the reduction in the risk of vertebral, clinical, and nonvertebral fractures [64,75]. The administration of romosozumab followed by alendronate is more effective in increasing BMD and reducing the risk of vertebral fracture and clinical, nonvertebral, and hip fractures than alendronate alone for the same period of time [76]. Teriparatide and abaloparatide are contraindicated in the following situations: preexisting hypercalcemia, severe renal impairment, unexplained elevations of alkaline phosphatase, prior external beam or implant radiation therapy to the skeleton, and skeletal malignancies or bone metastases; teriparatide is also contraindicated metabolic bone diseases other than primary osteoporosis or glucocorticoid-induced osteoporosis. Romosozumab is contraindicated in patients with hypocalcemia or a history of myocardial infarction or stroke.

In clinical practice, the use of anabolic agents is common after failed treatment with antiresorptive agents, especially oral bisphosphonates, since they are a first-line treatment. However, the use of teriparatide or romosozumab after treatment with a potent bisphosphonate, such as alendronate, reportedly attenuates BMD gains [77,78]. This effect is more marked in the hip at the start of treatment with teriparatide, but it does not appear to affect its efficacy in reducing the risk of clinical fractures [79]. As stated above, the transition from denosumab to teriparatide is not recommended since a transient reduction in total hip BMD with this sequence has been reported [71].

2.7. Fragility fracture, imminent fracture, and sequential therapy

The occurrence of a fragility fracture is associated with a significantly increased risk of a subsequent fracture, especially in the first months after its occurrence [80]. In people aged 65 or older, these fractures are associated with a mortality rate at 1 year that is twofold higher than expected for almost any location [81]. This excess mortality persists for 5 years regardless of the fracture location and extends up to 10 years for hip fractures [82]. This higher and imminent risk of new fractures and the associated mortality explain why patients with osteoporosis who have a fragility fracture are considered at very high risk of fractures and require immediate and long-term and possible lifetime treatment of osteoporosis [68], emphasizing the need for sequential therapy. In addition to their effect on bone health, supplementation with calcium and vitamin D, could prevent the occurrence of hypocalcemia in certain settings, such as treatment with zoledronic acid or denosumab, due to a phenomenon similar to that of hungry bone syndrome after parathyroidectomy [83].

Fragility fractures commonly require surgical treatment, and the type of treatment may condition the selection of osteoporosis therapy. In patients who undergo joint replacement, treatment is selected and initiated as usual. However, if osteosynthesis is needed, none of the anabolic agents interfere with callus formation and can be initiated at any time. The use of antiresorptive agents, in contrast, is debated since they may interfere with callus formation by osteoclastic inhibition; however, this effect has not been observed in clinical practice [48]. When treatment with zoledronic acid is selected, delaying its administration for three weeks after the fracture is advisable to avoid drug-sequestration at the fracture site and to normalize the serum levels of calcium and vitamin D.

2.8. Genitourinary syndrome of menopause

Genitourinary syndrome of menopause (GSM) is a chronic condition caused by estrogen deficiency [84]. Although its management is not part of the sequential treatment of osteoporosis, as is the case for healthy lifestyle, calcium and vitamin D, it should be considered an important component of the continuous concomitant strategy for the integral management of postmenopausal women. The clinical presentation varies from woman to woman [85], but it worsens with age [86] and impairs sexual functioning and overall quality of life [87]. Without treatment, structural and functional changes occur in the involved tissues.

Vaginal moisturizers and lubricants relieve GSM symptoms, although they do not modify structural tissue changes [88]. They are recommended in women who do not want to use estrogens or with contraindications to their use [89]. They can be used concomitantly with any of the treatments for osteoporosis.

Vaginal estrogens (estradiol, estriol and promestriene) or prasterone are the treatment of choice in moderate-severe GSM [90]. They have shown greater efficacy than placebo in alleviating the symptoms of GSM [91,92] without relevant safety issues [93] and do not interfere with the use of therapies for osteoporosis.

Ospemifene, an oral SERM, has demonstrated efficacy [94] with an adequate safety profile [95] for the management of some GSM symptoms and can be used in women with a history of breast cancer after completion of adjuvant treatment [96,97]. It should not be combined with other SERMs, such as raloxifene. Evidence on the concomitant use of ospemifene with antiresorptive or bone-forming drugs is not available, although we foresee no major issues with these combinations based on their mechanisms of action.

The treatment of GSM must be initiated early and maintained over time because the symptoms and histological changes will return if it is discontinued.

3. Discussion

We have comprehensively reviewed the available treatments for postmenopausal osteoporosis with an emphasis on sequential strategies. Fig. 2 summarizes the potential distribution of the different treatment alternatives. The overlap between the different curves displays opportunities for their sequential use. Current evidence supports that the selection of the pharmacologic agent should be based on the risk of fractures, which does not always correlate with age. Like many chronic illnesses, postmenopausal osteoporosis is a lifelong process. Therefore, we propose subsequent interventions that cover an indefinite time, largely beyond the duration of the clinical trials. In addition, we have considered other important aspects in the management of women's health after menopause, such as diet and lifestyle interventions and the management of climacteric symptoms.

We have also considered potential synergies between bone turnover modulation and effects on other hormone-regulated phenomena, such as hot flushes or breast cancer risk, to position hormone therapy and SERMs as an early postmenopause alternative for the management of postmenopausal osteoporosis.

When it is not the case, compelling evidence supports antiresorptive agents as first-line treatment of postmenopausal osteoporosis in many clinical scenarios. Digestive conditions, kidney function, readiness for compliance, or patient preferences play a role in choosing between bisphosphonates or denosumab during this period. However, their use should be re-evaluated at 3–5 years due to safety issues. In patients at high/very high osteoporotic fracture risk, the “anabolic first” approach more effectively reduces the risk of fractures. Thus, although there are no head-to-head comparisons, a recent network metanalysis has shown that denosumab was less effective in reducing clinical fractures than parathyroid hormone receptor agonists and romosozumab [98]. The effect on bone health with these bone-forming agents or with denosumab should be consolidated with the subsequent use of antiresorptive agents. Regardless of the strategy, follow-up and treatment should be maintained indefinitely to maintain adequate prevention of fractures.

Our work has strengths, such as a practical approach to diseases after menopause based on the best available evidence. A methodologist expert on conducting systematic reviews has evaluated the quality of the pieces of evidence used to formulate therapeutic strategies. We also proposed therapeutic interventions for the different stages of menopausal transition and levels of fracture risk. However, the major limitation is that, despite our proposals, high-quality evidence is lacking for many clinical scenarios.

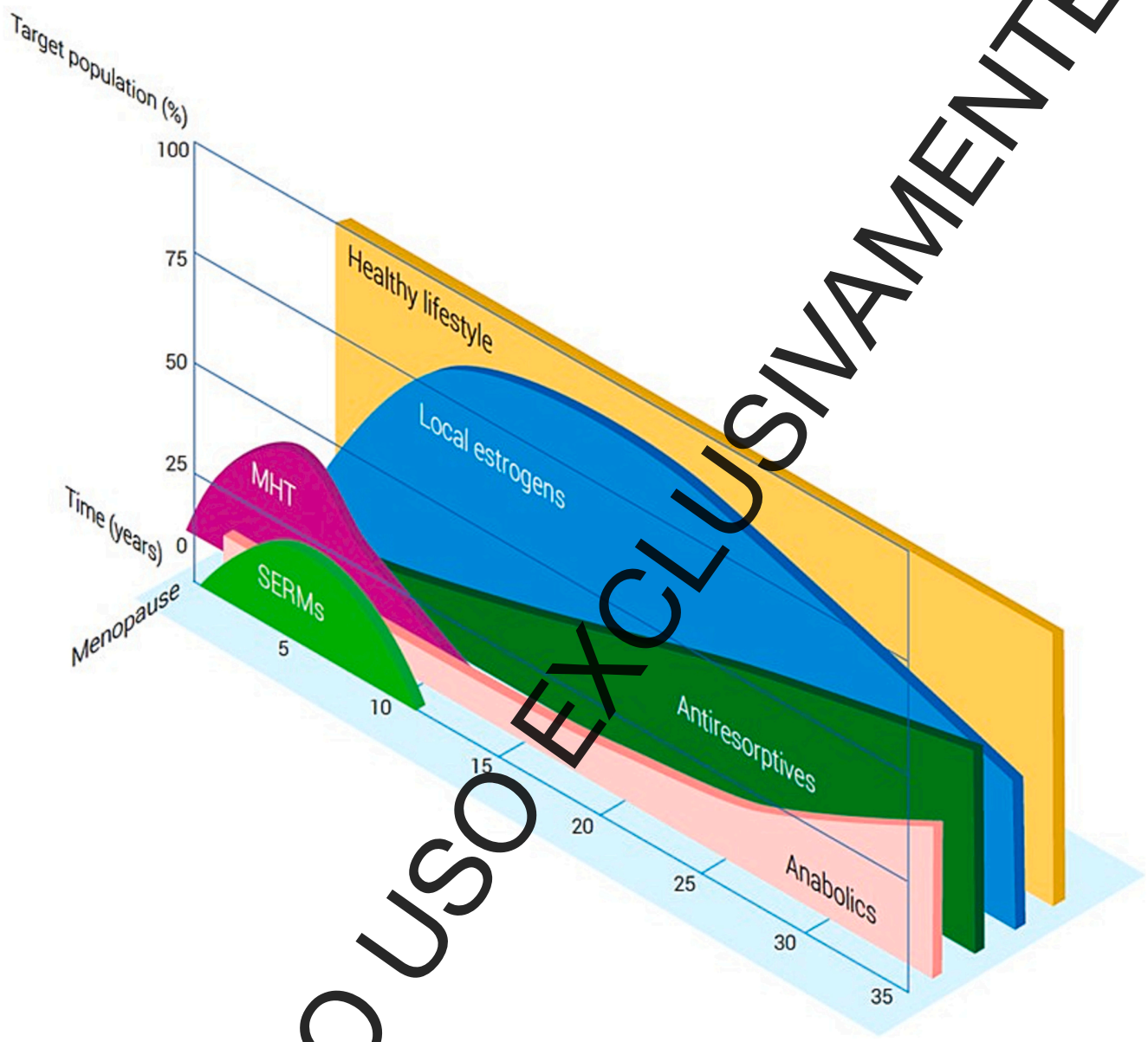

Fig. 2. Distribution of the different therapeutic options in the *peri* and postmenopausal period.
MHT, menopausal hormone therapy; SERMs, selective estrogen receptor modulators.
In the Y axis is represented the approximate percentage of women theoretically candidates to each treatment In the X axis is represented the postmenopausal age starting at 0 (at the menopause, i.e., approximately 50 years) until 35 years later, around the age of 85. The height of the curves is an estimate of the target population to be covered by the drugs in ideal conditions. For healthy lifestyle (including adequate calcium and vitamin D supply) 100 % of the population is considered candidate.

In summary, postmenopausal osteoporosis is a long-lasting process that requires treatment adapted to the fracture risk profile. Because this condition spans several decades in a woman's life, sequential treatment strategies are needed to maintain adequate disease control. New evidence needs to be generated to answer clinical questions that lack robust evidence. However, we already have sufficient treatment options to minimize the risk of fractures in patients with postmenopausal osteoporosis.

Contributors

Joaquin Calaf-Alsina was responsible for the conceptualization and coordination of the project and writing the introduction and discussion of the manuscript, and contributed to the design of the project, and writing and revision of the whole manuscript.

Antonio Cano contributed to the design of the project, writing the manuscript, and critical revision of the manuscript.

Núria Guañabens contributed to the design of the project, writing the manuscript, and critical revision of the manuscript.

Santiago Palacios contributed to the design of the project, writing the manuscript, and critical revision of the manuscript.

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Xavier Nogues contributed to the design of the project, writing the manuscript, and critical revision of the manuscript.

Adolfo Diez-Perez was responsible for the conceptualization and coordination of the project and writing the introduction and discussion of the manuscript, and contributed to the design of the project, and writing and revision of the whole manuscript.

All authors approved the final version of the manuscript.

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Provenance and peer review

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Declaration of competing interest

JC-A has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Bayer, Gedeon Richter, Organon, and Theramex; payment for expert testimony from Gedeon Richter; support for attending meetings and/or travel from Theramex; and has participated on a Data Safety Monitoring Board or Advisory Board with Organon.

AC has been advisory board member for Astellas, Viatris, Theramex; has received speaker honorarium from Astellas, Viatris, Theramex, Abbott; and has received consulting honorarium from Astellas, Viatris, Theramex.

NG, has been advisory board member for Amgen, UCB; has received speaker honorarium from Amgen, UCB, Lilly, Gedeon-Richter, Theramex; and has received travel grants from Lilly, UCB.

SP has been advisory board member for Theramex; has received grants or contracts from Bayer, Gedeon Richter, Procare Lacer; has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Servier, Procare, Theramex, Shionogi, Procaps, Exeltis, UCB, NovoNordisk; has received support for attending meetings and/or travel from Shionogi, NovoNordisk; has participated in a Data Safety Monitoring Board or Advisory Board for Theramex, Shionogi, Procare, NovoNordisk.

MJC, has received speaker honorarium from Theramex, Shionogui.

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Appendix A. Supplementary data

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