



# Overview of the management of low bone mass and osteoporosis in postmenopausal women

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Literature review current through: **Apr 2024**.

This topic last updated: **Mar 26, 2024**.

## INTRODUCTION

The treatment of osteoporosis consists of lifestyle measures and pharmacologic therapy [1]. An overview of the approach to the prevention and treatment of osteoporosis in postmenopausal women will be presented here. The diagnosis and evaluation of osteoporosis in postmenopausal women and the management of osteoporosis in other patient groups are discussed separately.

- (See "[Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women](#)".)
- (See "[Treatment of osteoporosis in men](#)".)
- (See "[Evaluation and treatment of premenopausal osteoporosis](#)".)
- (See "[Osteoporosis in patients with chronic kidney disease: Management](#)".)
- (See "[Prevention and treatment of glucocorticoid-induced osteoporosis](#)".)

## DEFINITIONS

**Low bone mass** — Low bone mass (osteopenia) based on bone mineral density (BMD) criteria is defined as a T-score between -1.0 and -2.5.

**Osteoporosis** — Osteoporosis may be diagnosed based on history of fragility fracture, BMD, or calculated 10-year fracture risk ([algorithm 1](#)).

- **Fragility fracture** – A clinical diagnosis of osteoporosis may be made in the presence of a fragility fracture, particularly at the spine, hip, wrist, humerus, and pelvis, without measurement of BMD. Fragility fractures are those occurring from a fall from a standing height or less, without major trauma such as a motor vehicle accident. Fractures at some skeletal sites (including the skull, cervical spine, hands, and feet) are not considered fragility fractures. Stress fractures are also not considered fragility fractures as they are due to repetitive injury, often in individuals with otherwise healthy bones. Rib fractures may present as fragility fractures but more commonly result from trauma. (See "[Overview of stress fractures](#)" and "[Osteoporotic fracture risk assessment](#)", section on '[Personal history of fracture as an adult](#)'.)

A history of a fragility fracture is an important risk factor for subsequent fracture and warrants pharmacotherapy. Patients should be informed of this increased risk and the diagnosis of osteoporosis [2]. Although BMD measurement is not necessary for initiating treatment, baseline measurement is helpful to assess osteoporosis severity and to monitor treatment response. In the United States and Europe, most patients who sustain fragility fractures do not receive osteoporosis therapy [3-6], despite data demonstrating that pharmacotherapy reduces the risk of a second fracture. (See '[Patient selection](#)' below and '[Choice of initial therapy](#)' below.)

In most patients, a recent fracture should not preclude use of bisphosphonates, which can be initiated two weeks postfracture if the patient is able to sit upright for at least 30 minutes (for oral bisphosphonates). Bisphosphonate use in this setting is reviewed elsewhere. (See "[Bisphosphonate therapy for the treatment of osteoporosis](#)", section on '[Use immediately after fracture](#)'.)

- **Bone mineral density** – In the absence of a fragility fracture, BMD assessment by dual-energy x-ray absorptiometry (DXA) is the gold standard to diagnose osteoporosis, according to the classification of the World Health Organization (WHO) [7]. BMD that is 2.5 standard deviations (SDs) or more below the mean BMD of a young adult reference population (ie, T-score  $\leq -2.5$ ) qualifies for a diagnosis of osteoporosis, provided that other causes of low BMD have been excluded. (See "[Overview of dual-energy x-ray absorptiometry](#)", section on '[Clinical applications of DXA](#)'.)

Individuals with T-scores of  $\leq -2.5$  have a high risk of fracture. However, more fractures occur in patients with a T-score between -1.0 and -2.5 because so many more patients are in this category [8]. (See "[Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women](#)" and "[Clinical manifestations, diagnosis, and evaluation of osteoporosis in men](#)" and "[Osteoporotic fracture risk assessment](#)", section on '[Assessment of fracture risk](#)'.)

- **Elevated fracture risk** – The National Bone Health Alliance recommends that, in the United States, a clinical diagnosis of osteoporosis may be made when the Fracture Risk Assessment Tool (FRAX) 10-year probability of major osteoporotic fracture is  $\geq 20$  percent or the 10-year probability of hip fracture is  $\geq 3$  percent [9,10]. For clinicians practicing outside the United States, intervention thresholds may be accessed directly from the [FRAX website](#) (click on "Calculation Tool" and select country of practice). Although fracture prediction algorithms and national recommendations provide general clinical guidance, osteoporosis treatment should remain individualized through shared decision-making between patient and clinician. (See '[Patient selection](#)' below and "[Osteoporotic fracture risk assessment](#)", section on '[Assessment of fracture risk](#)'.)

The FRAX algorithm uses femoral neck BMD ( $\text{g}/\text{cm}^2$ ) and clinical risk factors for calculation of fracture probability ( [table 1](#)). BMD from non-hip sites has not been validated and is, therefore, not recommended for use. The technical aspects of FRAX are reviewed in detail separately. (See "[Osteoporotic fracture risk assessment](#)", section on '[Fracture risk assessment tool](#)'.)

**Very high fracture risk** — Some individuals are at very high risk of fracture, which may influence the choice of initial pharmacotherapy [11]. No consensus exists on the definition of very high fracture risk. Examples may include a T-score of  $\leq -2.5$  plus a fragility fracture, T-score of  $\leq -3.0$  in the absence of fragility fracture(s), or history of severe or multiple fractures. Specific criteria for very high fracture risk vary across clinical trials and society and national guidelines, reflecting regional differences in fracture incidence and cost analyses of pharmacotherapy [12-14]. (See '[Choice of initial therapy](#)' below.)

## LIFESTYLE MEASURES TO REDUCE BONE LOSS

All postmenopausal women should continue or adopt general lifestyle measures to reduce bone loss. Lifestyle measures include adequate intake of calcium and vitamin D, exercise, smoking cessation, and avoidance of heavy alcohol use. Women also should receive counseling on fall prevention and, if possible, avoid drugs that increase bone loss (eg, glucocorticoids). (See "[Falls: Prevention in community-dwelling older persons](#)" and "[Clinical features and evaluation of glucocorticoid-induced osteoporosis](#)" and "[Prevention and treatment of glucocorticoid-induced osteoporosis](#)" and "[Drugs that affect bone metabolism](#)".)

**Calcium/vitamin D** — All postmenopausal women should ingest adequate calcium and vitamin D. Women with adequate calcium intake from diet alone (approximately 1200 mg daily) ( [table 2](#) and [table 3](#)) do not need to take calcium supplements. Women with inadequate dietary intake should take supplemental elemental calcium (generally 500 to 1000 mg/day, in divided doses at mealtime) to reach a total (diet plus supplement) of approximately 1200 mg/day ( [table 4](#)) [15]. The impact of calcium supplements on cardiovascular disease risk is controversial and discussed in detail separately. (See "[Calcium and vitamin D supplementation in osteoporosis](#)", section on '[Side effects](#)'.)

Women also should ingest 800 international units of vitamin D daily. In some settings, higher doses are required (eg, gastrointestinal malabsorption, accelerated vitamin D metabolism due to concomitant antiseizure medication therapy). Most postmenopausal women with osteoporosis require vitamin D supplementation as the target intake is difficult to achieve with diet alone ( [table 5](#)). (See "[Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment](#)", section on '[Defining vitamin D sufficiency](#)'.)

Data on skeletal health outcomes with calcium and vitamin D supplementation are discussed in detail elsewhere. (See "[Calcium and vitamin D supplementation in osteoporosis](#)", section on '[Skeletal health outcomes](#)'.)

**Diet** — An optimal diet for skeletal health includes adequate caloric intake to avoid malnutrition. We do not recommend modifying protein intake as a strategy for preventing bone loss; however, adequate dietary protein intake should be achieved (eg, approximately 0.8 g per kg body weight per day). Data are conflicting on the impact of supplemental protein intake on bone density [16]. Whereas some

studies suggest that higher protein intake may be associated with a lower risk of hip fractures [17] and bone loss [18-21], others suggest that high protein intake may increase bone resorption and calcium excretion [22].

In adults with bone loss due to celiac disease, a gluten-free diet may improve bone mineral density (BMD) [23]. (See "[Management of celiac disease in adults](#)".)

**Exercise** — Postmenopausal women should engage in weightbearing exercise for at least 30 minutes on most days of the week and incorporate muscle-strengthening and posture exercises two to three days a week [24]. Exercises that increase muscular strength and improve balance may confer the most benefit for fracture reduction by decreasing risk of falls [25-27]. For patients with frailty or history of vertebral fracture, brisk walking is sufficient and safe weightbearing exercise. (See "[Physical activity and exercise in older adults](#)", section on '[Overview of physical activity components](#)'.)

- **Fracture prevention** – In prospective cohort studies, exercise was associated with a reduced risk of hip fracture in older women [25,28]. In a meta-analysis of 10 trials, exercise reduced the occurrence of overall fractures in older adults (4.8 versus 10.9 percent in the control group; relative risk [RR] 0.49, 95% CI 0.31-0.76) [29]. The reduction in vertebral fractures was not statistically significant (three trials, 18 versus 30 percent; RR 0.56, 95% CI 0.30-1.04) [29], possibly due to the small number of patients included in the vertebral fracture trials. A subsequent meta-analysis of 20 trials similarly demonstrated that exercise interventions reduced the number of overall and major osteoporotic fractures, though supervised regimens reduced fractures to a greater extent than unsupervised regimens [30].
- **Increased bone mineral density** – Exercise also has beneficial effects on BMD in postmenopausal women [31,32]. In a meta-analysis of 43 randomized trials (4320 postmenopausal women), exercise increased BMD at the lumbar spine (mean difference 0.85 percent, 95% CI 0.62-1.07) and trochanter (mean difference 1.03 percent, 95% CI 0.56-1.49) compared with controls [31]. A variety of exercise types, including resistance training, jogging, jumping, and walking, were effective. The most effective type of exercise for BMD of the femoral neck was non-weightbearing, high-force exercise (eg, progressive resistance strength training), whereas a combined program (mixture of more than one exercise type) was most effective for lumbar spine BMD [31]. The meta-analysis was limited by loss to follow-up and the poor quality of allocation concealment and blinding. Overall, the beneficial effect of exercise on BMD is small. However, these changes reflect areal BMD measurements. It is still uncertain how long-term exercise affects other measures of bone architecture.
- **Intensity of exercise** – No convincing evidence demonstrates greater benefit from high-intensity exercise (eg, running) than from lower-intensity exercise (eg, walking). The benefits of exercise are quickly lost after the woman stops exercising [33], so we advise women to pick a regular weightbearing exercise regimen that they enjoy to facilitate long-term compliance.

**Smoking cessation** — We strongly recommend smoking cessation because cigarette smoking accelerates bone loss. Meta-analyses have shown that cigarette smoking is associated with reduced BMD [34] and increased risk of fracture [35]. As an example, in a study that evaluated female twins who were discordant for smoking, smoking one pack per day throughout adult life was associated with a 5 to 10 percent reduction in bone density [36]. In postmenopausal women, smoking may also negate the beneficial skeletal effects of estrogen therapy [37,38], possibly due in part to acceleration of estradiol metabolism.

**Avoid heavy alcohol use** — Excess alcohol intake is detrimental to skeletal health for many reasons [39]. The effects of moderate alcohol intake (for females,  $\leq 1$  United States drink per day and  $< 7$  drinks per week) on BMD and fracture risk are uncertain. (See "[Overview of the risks and benefits of alcohol consumption](#)", section on '[Osteoporosis](#)'.)

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## LOW BONE MASS

**Our approach** — In postmenopausal women with low bone mass who have not experienced a fragility fracture, we calculate absolute fracture risk using the Fracture Risk Assessment Tool (FRAX). (See '[Patient selection](#)' below and "[Osteoporotic fracture risk assessment](#)", section on '[Assessment of fracture risk](#)'.)

- **High estimated fracture risk** – Patients with prior fragility fracture or high estimated fracture risk (eg, 10-year probability of major osteoporotic fracture  $\geq 20$  percent or 10-year probability of hip fracture  $\geq 3$  percent) are considered to have osteoporosis. Treatment of osteoporosis is reviewed below. (See '[Definitions](#)' above and '[Patient selection](#)' below and '[Choice of initial therapy](#)' below.)
- **Low to moderate estimated fracture risk** – For most patients with low to moderate fracture risk (eg, 10-year probability of major osteoporotic fracture  $< 20$  percent and 10-year probability of hip fracture  $< 3$  percent), we suggest **not** using pharmacologic therapy

to prevent bone loss or fracture [10]. Management decisions should be individualized based on patient preferences and the expected benefits and potential risks of drug therapy.

**Options for pharmacotherapy (usually deferred)** — If a decision is made to initiate pharmacologic therapy, we suggest an oral bisphosphonate or [raloxifene](#) ( [table 6](#)).

- **Choice of oral bisphosphonate** – We prefer weekly [alendronate](#) or [risedronate](#) to other bisphosphonates because of their efficacy, favorable cost, and the availability of long-term safety data. Limitations of oral bisphosphonates include the complex dosing regimen and poor long-term adherence to therapy. (See "[Bisphosphonate therapy for the treatment of osteoporosis](#)".)

In postmenopausal women **without** osteoporosis, [alendronate](#) [40-44], [risedronate](#) [45-47], and [ibandronate](#) [48] prevent bone loss, but trial data have not established a reduction in fracture risk.

- **Raloxifene** – We prefer [raloxifene](#) to other selective estrogen receptor modulators (SERMs) because it has eight-year safety and efficacy data and reduces the risk of breast cancer. Raloxifene inhibits bone resorption and reduces the risk of vertebral fracture. Raloxifene also increases thromboembolic events and hot flashes and has no apparent effect on heart disease or the endometrium. (See "[Selective estrogen receptor modulators for prevention and treatment of osteoporosis](#)", section on 'Raloxifene'.)

Bazedoxifene, another SERM, is available in Europe and Japan for the treatment of postmenopausal osteoporosis. In the United States, it is available in combination with [conjugated estrogen](#) for **prevention** of osteoporosis [49]. SERMs are discussed in more detail elsewhere. (See "[Selective estrogen receptor modulators for prevention and treatment of osteoporosis](#)" and "[Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention](#)".)

- **Alternative therapies**

- **Zoledronic acid** – For women unable to take oral bisphosphonate therapy due to intolerance or a contraindication, intravenous (IV) [zoledronic acid](#) is a reasonable alternative. In a two-year trial of zoledronic acid (5 mg IV once at baseline or yearly for two years) versus placebo in 581 postmenopausal women with low bone mass, patients randomly assigned to zoledronic acid had significant increases in lumbar spine and total hip BMD (approximately 3 percent) [50]. The study was not powered to assess fracture prevention.
- **Menopausal hormone therapy** – Although we do not consider estrogen a first-line option for fracture prevention, women who initiate hormone therapy for menopausal symptoms will have reduced risk of bone loss and fracture [51-54]. We typically start women on a transdermal estradiol preparation, which imparts beneficial skeletal effects at doses as low as 0.014 mg/day [55-57]. Treatment options and the relative benefits and risks of menopausal hormone therapy are reviewed elsewhere. (See "[Menopausal hormone therapy in the prevention and treatment of osteoporosis](#)", section on 'Efficacy of estrogen therapy' and "[Menopausal hormone therapy: Benefits and risks](#)".)

## OSTEOPOROSIS

**Patient selection** — Our approach to initial osteoporosis pharmacotherapy is largely in agreement with the Bone Health and Osteoporosis Foundation (BHOFF, formerly the National Osteoporosis Foundation [NOF]) recommendations, which apply to postmenopausal women and men aged  $\geq 50$  years ( [table 7](#)) [10]. These recommendations are widely accepted and supported by clinical trial data on fracture prevention. (See "[Bisphosphonate therapy for the treatment of osteoporosis](#)".)

- We recommend pharmacologic therapy for postmenopausal women with a history of fragility fracture or with osteoporosis based upon bone mineral density (BMD) measurement (T-score  $\leq -2.5$ ). Particular attention should be paid to treating women with a recent fracture, including hip fracture, because they are at high risk for a second fracture [2,58]. (See '[Osteoporosis](#)' above and "[Osteoporotic fracture risk assessment](#)", section on 'Personal history of fracture as an adult'.)
- We also suggest pharmacologic therapy for high-risk postmenopausal women with T-scores between -1.0 and -2.5. We calculate fracture risk using the Fracture Risk Assessment Tool ( [FRAX](#)). In the United States, a reasonable threshold to define high risk is a 10-year probability of hip fracture or combined major osteoporotic fracture of  $\geq 3$  or  $\geq 20$  percent, respectively. (See '[Osteoporosis](#)' above and "[Osteoporotic fracture risk assessment](#)", section on 'Assessment of fracture risk'.)

### Choice of initial therapy

**Most women with osteoporosis** — For most postmenopausal women with osteoporosis, we suggest oral bisphosphonates as first-line therapy ( [algorithm 2](#)). We prefer oral bisphosphonates as initial therapy because of their efficacy, favorable cost, and the availability of long-term safety data. (See "[Bisphosphonate therapy for the treatment of osteoporosis](#)", section on '[Choice of bisphosphonate](#)' and "[Risks of bisphosphonate therapy in patients with osteoporosis](#)".)

Choice of therapy should be based upon efficacy, safety, cost, convenience, and the individual's fracture risk [[13,59-64](#)]. Systematic reviews have confirmed that many drugs prevent fractures compared with placebo [[60,65-67](#)]. In a 2019 meta-analysis of 107 trials evaluating pharmacologic therapies in postmenopausal women with osteoporosis, [alendronate](#), [zoledronic acid](#), [risedronate](#), [denosumab](#), [romosozumab](#), and estrogen with [progesterone](#) reduced the risk of hip fracture [[62](#)]. Alendronate, zoledronic acid, risedronate, [ibandronate](#), denosumab, [abaloparatide](#), [teriparatide](#), parathyroid hormone (1-84), romosozumab, [raloxifene](#), bazedoxifene, lasofoxifene, estrogen with progesterone, [tibolone](#), and [calcitonin](#) reduced the risk of vertebral fractures. The anabolic agents (teriparatide, abaloparatide, romosozumab) and denosumab had the highest relative efficacy, although few trials directly compared the drugs for fracture prevention.

**Very high fracture risk** — For patients with very high fracture risk (eg, T-score of  $\leq -2.5$  plus a fragility fracture, T-score of  $\leq -3.0$  in the absence of fragility fracture[s], history of severe or multiple fractures), we suggest initial treatment with an anabolic agent ([teriparatide](#), [abaloparatide](#), [romosozumab](#)). Patients most likely to benefit from anabolic therapy are those with the highest risk of fracture (eg, T-score  $\leq -3.5$  with fragility fracture[s], T-score  $\leq -4.0$ , recent major osteoporotic fracture, or multiple recent fractures). For patients with very high fracture risk who cannot be treated with an anabolic agent due to cost, inconvenience, contraindications, or personal preference, a bisphosphonate or [denosumab](#) may be appropriate ( [algorithm 2](#)). Patients should be under the care of a provider with expertise in treating osteoporosis to facilitate shared decision-making. (See '[Very high fracture risk](#)' above and '[Selection of anabolic agent](#)' below and '[Selection of oral bisphosphonate \(usually preferred\)](#)' below.)

In contrast to antiresorptive agents, the anabolic agents [teriparatide](#) and [abaloparatide](#) stimulate bone formation and activate bone remodeling. The anabolic agent [romosozumab](#) uniquely stimulates bone formation and inhibits bone resorption. In postmenopausal women with very high fracture risk, trial data demonstrate greater fracture prevention with anabolic therapies compared with oral bisphosphonates [[68,69](#)]. For example, in a trial comparing teriparatide with [risedronate](#) in 680 postmenopausal women (mean age 72.1 years) with severe osteoporosis (mean number of prevalent fractures 2.7), the teriparatide group exhibited fewer new radiographic vertebral fractures (5.4 versus 12 percent) and fewer clinical fractures at all sites (4.8 versus 9.8 percent) [[68](#)]. The incidence of nonvertebral fractures did not differ between groups. Most women had received at least one previous osteoporosis medication (median duration of previous bisphosphonate use 3.6 years).

**Selection of oral bisphosphonate (usually preferred)** — We typically prefer [alendronate](#) as our choice of oral bisphosphonate due to efficacy in reducing vertebral and hip fracture and evidence showing residual fracture benefit after a five-year course of therapy is completed [[70](#)]. [Risedronate](#) is a reasonable alternative. Generic alendronate and risedronate are available in many countries, including the United States. Most patients prefer the convenience of the once-weekly regimen. (See "[Bisphosphonate therapy for the treatment of osteoporosis](#)", section on '[Choice of bisphosphonate](#)'.)

General principles of bisphosphonate administration, adverse effects, duration of use, and drug holidays are discussed in detail elsewhere. (See "[Bisphosphonate therapy for the treatment of osteoporosis](#)" and "[Risks of bisphosphonate therapy in patients with osteoporosis](#)".)

**Contraindications and precautions** — Oral bisphosphonates should **not** be used as initial therapy in patients with esophageal disorders (achalasia, scleroderma involving the esophagus, esophageal strictures), an inability to follow the dosing requirements (eg, stay upright for at least 30 to 60 minutes), or advanced chronic kidney disease (CKD; estimated glomerular filtration [eGFR] rate  $<30$  mL/min/1.73 m<sup>2</sup>) ( [algorithm 2](#)). Oral bisphosphonates also should be avoided after certain types of bariatric surgery in which surgical anastomoses are present in the gastrointestinal tract (eg, Roux-en-Y gastric bypass). (See '[Gastrointestinal malabsorption or difficulty with dosing requirements](#)' below and '[Chronic kidney disease](#)' below and "[Bisphosphonate therapy for the treatment of osteoporosis](#)", section on '[Contraindications to bisphosphonates](#)'.)

All patients should have normal serum calcium and 25-hydroxyvitamin D levels prior to starting pharmacotherapy, and they should receive supplemental calcium and vitamin D if dietary intake is inadequate ( [algorithm 2](#)). (See '[Calcium/vitamin D](#)' above and "[Bisphosphonate therapy for the treatment of osteoporosis](#)", section on '[Pretreatment evaluation](#)'.)

**Gastrointestinal malabsorption or difficulty with dosing requirements** — For patients with esophageal disorders, gastrointestinal intolerance, history of Roux-en-Y gastric bypass, or an inability to follow the dosing requirements of oral bisphosphonates,



we suggest intravenous (IV) bisphosphonates. (See "[Risks of bisphosphonate therapy in patients with osteoporosis](#)", section on '[Gastrointestinal](#)').)

- **Zoledronic acid** – For patients unable to take oral bisphosphonates, we prefer IV [zoledronic acid](#), which reduces vertebral and hip fractures. IV [ibandronate](#) is also available; however, no direct fracture prevention data exist for IV ibandronate. (See "[Bisphosphonate therapy for the treatment of osteoporosis](#)", section on '[IV regimen](#)').)
- **Denosumab** – [Denosumab](#) is an alternative to IV [zoledronic acid](#) for women at high risk for fracture who have difficulty with the dosing requirements of oral bisphosphonates or who prefer to avoid IV bisphosphonates due to side effects (eg, acute phase reaction). It may be used as initial therapy in certain patients at high risk for fracture, such as older patients who have difficulty with the dosing requirements of oral bisphosphonates. However, increased risk of vertebral fracture is evident after discontinuation of denosumab, so the need for indefinite treatment should be addressed with patients before denosumab initiation. (See "[Denosumab for osteoporosis](#)", section on '[Patient counseling](#)' and "[Denosumab for osteoporosis](#)", section on '[Duration of therapy](#)').)

In several trials in postmenopausal women, [denosumab](#) improved BMD and reduced the incidence of new vertebral, hip, and nonvertebral fractures. If denosumab is discontinued, administering an alternative therapy (typically a bisphosphonate) is advised to prevent rapid bone loss and vertebral fracture. (See "[Denosumab for osteoporosis](#)", section on '[Increased vertebral fractures](#)' and "[Denosumab for osteoporosis](#)", section on '[Sequential osteoporosis therapy](#)').)

**Contraindications or intolerance to any bisphosphonates** — Patients who are allergic to bisphosphonates or who develop severe bone pain with them require an alternative treatment. For patients who cannot take oral or IV bisphosphonates, the choice of agent depends on risk of fracture (eg, history of prior fragility fractures, T-score, comorbidities), drug efficacy and adverse effect profile, and patient preferences.

For postmenopausal women **with** very high fracture risk (eg, T-score of  $\leq -2.5$  plus a fragility fracture, T-score of  $\leq -3.0$  in the absence of fragility fracture(s), history of severe or multiple fractures) who were not treated initially with anabolic therapy, we suggest switching to an anabolic agent ([teriparatide](#), [abaloparatide](#), [romosozumab](#)). [Denosumab](#) is an alternative. (See "[Selection of anabolic agent](#)" below and "[Denosumab for osteoporosis](#)".)

After initial therapy with an anabolic agent is discontinued, patients should be treated with an antiresorptive agent (typically a bisphosphonate) to preserve the gains in BMD from anabolic therapy. For individuals who are unable to tolerate oral or intravenous bisphosphonates, alternatives may include [denosumab](#) or [raloxifene](#). (See "[Parathyroid hormone/parathyroid hormone-related protein analog therapy for osteoporosis](#)", section on '[Management after teriparatide](#)' and "[Parathyroid hormone/parathyroid hormone-related protein analog therapy for osteoporosis](#)", section on '[Management after abaloparatide](#)').)

For women **without** very high fracture risk, treatment options include the following:

- **Denosumab** – [Denosumab](#) is not considered initial therapy for most patients with osteoporosis but is an option for patients who are intolerant of or unresponsive to any bisphosphonate, those with impaired kidney function, or those in whom desired increases in BMD exceed typical gains achieved with oral bisphosphonate therapy. As discussed above, because of concerns about an increased risk of vertebral fracture after discontinuation of denosumab, the need for indefinite administration of denosumab should be discussed with patients prior to its initiation. (See "[Denosumab for osteoporosis](#)", section on '[Duration of therapy](#)').)
- **Raloxifene** – We reserve the use of the selective estrogen receptor modulator (SERM) [raloxifene](#) for postmenopausal women with osteoporosis and without history of fragility fractures who are not candidates for any bisphosphonate or [denosumab](#). Raloxifene is also a reasonable choice in women with increased risk of invasive breast cancer. Among SERMs, we prefer raloxifene because it has eight-year safety and efficacy data and also reduces the risk of breast cancer. Raloxifene inhibits bone resorption and reduces the risk of vertebral fracture. However, the antiresorptive effects of SERMs are less potent than those of bisphosphonates. Raloxifene increases thromboembolic events and possibly hot flashes and has no apparent effect on heart disease or the endometrium. (See "[Selective estrogen receptor modulators for prevention and treatment of osteoporosis](#)" and "[Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention](#)", section on '[Raloxifene](#)').)

[Tamoxifen](#) is another SERM used primarily for the prevention and management of breast cancer. In postmenopausal women, tamoxifen therapy used to prevent or treat breast cancer likely confers protective effects on bone. (See "[Selective estrogen receptor modulators for prevention and treatment of osteoporosis](#)", section on '[Tamoxifen](#)').)

Bazedoxifene, another SERM, is available in Europe and Japan for the treatment of postmenopausal osteoporosis. Although it has similar efficacy as [raloxifene](#) in preventing and treating postmenopausal osteoporosis, bazedoxifene has few long-term safety data,

and it has not been adequately studied for breast cancer prevention. It is not available as a standalone drug in the United States. SERMs are discussed in more detail elsewhere. (See ["Selective estrogen receptor modulators for prevention and treatment of osteoporosis"](#) and ["Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention"](#).)

- **Estrogen/progestogen therapy** — Combined therapy with an estrogen and progestogen (either natural or synthetic [ie, progestin]) is **not** a first-line approach for the treatment of osteoporosis in postmenopausal women due to potential risks of therapy [52]. (See ["Menopausal hormone therapy: Benefits and risks"](#).)

In postmenopausal women with osteoporosis, estrogen-progestogen therapy (or estrogen-only therapy for those with prior hysterectomy) may be used if also indicated to treat persistent menopausal symptoms. Menopausal hormone therapy is also an option for women who are unable to tolerate any other antiresorptive therapy. In the Women's Health Initiative (WHI), both combined estrogen-progestin and estrogen-only treatment reduced hip and vertebral fracture risk ( [figure 1](#)). The use of estrogen therapy for osteoporosis management is reviewed in detail elsewhere. (See ["Menopausal hormone therapy in the prevention and treatment of osteoporosis"](#).)

- **Anabolic therapy** – While use of anabolic agents is generally reserved for individuals with very high risk of fracture, these agents may be used in patients with less severe osteoporosis (eg, T-score  $\leq$ -2.5 without a fragility fracture) who are unable to tolerate oral or IV bisphosphonates. (See ["Selection of anabolic agent"](#) below and ["Parathyroid hormone/parathyroid hormone-related protein analog therapy for osteoporosis"](#), section on ["Patient selection"](#).)

After initial therapy with an anabolic agent is discontinued, patients should be treated with an antiresorptive agent (typically a bisphosphonate) to preserve the gains in BMD from anabolic therapy. For individuals who are unable to tolerate oral or intravenous bisphosphonates, alternatives may include [denosumab](#) or [raloxifene](#). (See ["Parathyroid hormone/parathyroid hormone-related protein analog therapy for osteoporosis"](#), section on ["Management after teriparatide"](#) and ["Parathyroid hormone/parathyroid hormone-related protein analog therapy for osteoporosis"](#), section on ["Management after abaloparatide"](#).)

**Selection of anabolic agent** — Anabolic agents are not considered initial therapy for most patients. Possible candidates for anabolic agents include postmenopausal women with any of the following:

- Very high risk of fracture. (See ["Very high fracture risk"](#) above.)
- Prior fragility fracture **and** contraindications or intolerance to any bisphosphonates. (See ["Contraindications or intolerance to any bisphosphonates"](#) above.)
- Fragility fracture and/or decline in BMD on other osteoporosis agent(s) despite treatment adherence.

If the decision is made to treat with an anabolic agent, options include [teriparatide](#), [abaloparatide](#), or [romosozumab](#) [64]. Teriparatide has a long track record of safety, whereas fewer data exist for long-term use of abaloparatide. Romosozumab induces a greater BMD response than either abaloparatide or teriparatide, but clinical experience is limited and long-term side effects are uncertain. Teriparatide and abaloparatide are administered as a daily subcutaneous injection. Romosozumab is administered by a health care professional once monthly as two subcutaneous injections. (See ["Parathyroid hormone/parathyroid hormone-related protein analog therapy for osteoporosis"](#), section on ["Patient selection"](#) and ["Parathyroid hormone/parathyroid hormone-related protein analog therapy for osteoporosis"](#), section on ["Choice of therapy"](#).)

Treatment with [teriparatide/abaloparatide](#) is generally limited to 18 to 24 months and with [romosozumab](#) to 12 monthly doses. However, treatment with teriparatide (brand name only) may be continued past 24 months in selected individuals if fracture risk remains high. (See ["Parathyroid hormone/parathyroid hormone-related protein analog therapy for osteoporosis"](#), section on ["Duration of therapy"](#).)

After initial therapy with an anabolic agent is discontinued, patients should be treated with an antiresorptive agent (preferably a bisphosphonate) to preserve the gains in BMD from anabolic therapy. For women who are unable to tolerate oral or IV bisphosphonates, [denosumab](#) or [raloxifene](#) are alternatives. Increased risk of vertebral fracture develops soon after discontinuation of denosumab, so the need for indefinite administration should be discussed with patients prior to its initiation. (See ["Denosumab for osteoporosis"](#), section on ["Patient counseling"](#) and ["Denosumab for osteoporosis"](#), section on ["Duration of therapy"](#).)

Clinical data have not firmly established a persistent reduction in fracture risk with the use of antiresorptive therapy after anabolic therapy is discontinued. (See ["Parathyroid hormone/parathyroid hormone-related protein analog therapy for osteoporosis"](#), section on ["Management after teriparatide"](#).)

**Parathyroid hormone/parathyroid hormone-related protein analog** — The use of the anabolic agents [teriparatide](#) and [abaloparatide](#) for osteoporosis therapy is reviewed in detail elsewhere. (See "[Parathyroid hormone/parathyroid hormone-related protein analog therapy for osteoporosis](#)".)

**Romosozumab** — [Romosozumab](#) is an anabolic agent approved by the US Food and Drug Administration (FDA) in 2019 based on trials showing a reduction in vertebral and nonvertebral fractures with romosozumab compared with placebo or with [alendronate](#) [71].

[Romosozumab](#) is a monoclonal anti-sclerostin antibody. Sclerostin is produced by osteocytes and inhibits bone formation. Sclerostin knockout mice have increased bone formation and high bone mass [72], and sclerostin inhibition with romosozumab enhances osteoblast function, improves bone mass, and reduces fractures.

- **Bone mineral density** – [Romosozumab](#) increases BMD when administered as initial therapy or after prior treatment with [alendronate](#).
  - In a phase II trial in postmenopausal women, all doses of a monoclonal anti-sclerostin antibody ([romosozumab](#)) increased bone density at the lumbar spine, total hip, and femoral neck [73,74]. In this one-year trial, 419 postmenopausal women with low bone mass (T-score between -2.0 and -3.5 at the lumbar spine, total hip, or femoral neck) were randomly assigned to subcutaneous romosozumab (variable dosing once monthly or once every three months), an active comparator (oral [alendronate](#) [70 mg weekly] or subcutaneous [teriparatide](#) [20 mcg daily]), or placebo injections (monthly or every three months). The greatest increase in lumbar spine BMD occurred in the group receiving romosozumab 210 mg monthly (11.3 percent compared with 4.1 and 7.1 percent in the alendronate and teriparatide groups, respectively). Romosozumab treatment caused a transient increase in bone formation markers and a more sustained decrease in bone resorption markers, a unique pattern among available osteoporosis therapies.
  - In a phase III, open-label trial, 436 postmenopausal women with osteoporosis and a history of fracture who had taken an oral bisphosphonate for at least three years (mean 6.2 years) and had low BMD (T-score  $\leq$ -2.5 at the hip or spine) were randomly assigned to [romosozumab](#) (210 mg subcutaneously once monthly) or [teriparatide](#) (20 mcg subcutaneously once daily) [75]. After 12 months, the mean change from baseline in total hip (+2.6 versus -0.6 percent) and lumbar spine (+9.8 versus +5.4 percent) BMD was better with romosozumab. Fracture data were collected as adverse events and occurred in a similar proportion of patients (3 to 4 percent).
- **Fracture reduction** – In two subsequent trials specifically designed to assess fracture outcomes, treatment with [romosozumab](#) reduced the incidence of radiographic vertebral [69,76] and, in one study, nonvertebral [69] fractures.
  - In one trial, 7180 postmenopausal women with osteoporosis (mean T scores at the lumbar spine, total hip, and femoral neck of -2.72, -2.47, and -2.75, respectively) were randomly assigned to [romosozumab](#) (210 mg subcutaneously once monthly) or placebo for 12 months [76]. Thereafter, all women received [denosumab](#) (60 mg subcutaneously every six months) for an additional 12 months. The incidence of radiographic vertebral fracture was lower in the romosozumab group than in the placebo group after 12 months (0.5 versus 1.8 percent; risk ratio 0.27, 95% CI 0.16-0.47) and 24 months (0.6 versus 2.5 percent). The reduction in the incidence of nonvertebral fracture, a secondary endpoint, was not significant (1.6 versus 2.1 percent, hazard ratio [HR] 0.75, 95% CI 0.53-1.05).
  - In another trial, 4093 postmenopausal women with osteoporosis and prior fragility fracture (mean T-scores at the lumbar spine, total hip, and femoral neck of -2.96, -2.80, and -2.90, respectively) were randomly assigned to monthly subcutaneous [romosozumab](#) (210 mg) or weekly oral [alendronate](#) (70 mg) for 12 months [69]. All patients subsequently received weekly oral alendronate. After 24 months, fewer radiographic vertebral fractures occurred in the romosozumab-to-alendronate group than the alendronate-to-alendronate group (6.2 versus 11.9 percent, RR 0.52, 95% CI 0.40-0.66). At the time of the primary analysis, the risk of clinical fractures (9.7 versus 13 percent), nonvertebral fractures (8.7 versus 10.6 percent), or hip fractures (2.0 versus 3.2 percent) was also lower in the romosozumab group. Romosozumab followed by alendronate appears more effective than alendronate alone in postmenopausal women with established osteoporosis [77].
- **Adverse effects/contraindications** – In the [romosozumab](#) trials, romosozumab-treated groups had an increased frequency of injection site reactions [69,75,76]. No cases of atypical femoral fractures or osteonecrosis of the jaw occurred in two trials [69,75], whereas two cases of osteonecrosis of the jaw and one atypical femoral fracture occurred in the other (all in the romosozumab group) [76].



In one trial, more patients in the [romosozumab](#) group had serious cardiovascular events (cardiac ischemic events and cerebrovascular accidents [0.8 versus 0.3 percent]) [69]. Further evaluation is needed to determine the etiology of the cardiovascular events. In the interim, romosozumab should not be offered to women with prior history or at increased risk of myocardial infarction or stroke.

- **Duration of therapy** – Treatment with [romosozumab](#) (210 mg monthly by subcutaneous injection) is limited to 12 monthly doses, although this can be repeated in the future if indicated. After discontinuation of romosozumab, patients are typically treated with an antiresorptive agent (preferably a bisphosphonate) to preserve the gains in BMD from anabolic therapy [64,69].

**Therapies not recommended** — Numerous therapies have been evaluated for the treatment of osteoporosis with disappointing or conflicting results. We typically do not recommend the following therapies:

**Combination therapy** — We suggest **not** using combination therapy. Combination therapy has not been shown to provide additional benefit for fracture prevention compared with monotherapy. Combination osteoporosis therapies are discussed separately. (See "[Parathyroid hormone/parathyroid hormone-related protein analog therapy for osteoporosis](#)", section on 'Combination therapy not recommended' and "[Menopausal hormone therapy in the prevention and treatment of osteoporosis](#)", section on 'Estrogen versus bisphosphonate therapy' and "[Bisphosphonate therapy for the treatment of osteoporosis](#)", section on 'Choice of bisphosphonate'.)

**Calcitonin** — We prefer other drugs to [calcitonin](#) because of its relatively weak effect on BMD and poor antifracture efficacy compared with bisphosphonates and parathyroid hormone/parathyroid hormone-related protein analogs [78]. Concern exists about the long-term use of calcitonin for osteoporosis due its association with an increase in cancer rates. This is reviewed separately. (See "[Calcitonin in the prevention and treatment of osteoporosis](#)", section on 'Concerns about the use of calcitonin'.)

**Other** — In postmenopausal women with osteoporosis or low BMD with high fracture risk, we do **not** routinely use any of the pharmacologic or nonpharmacologic therapies below.

### Pharmacologic therapies

- **Calcitriol** – In postmenopausal women, [calcitriol](#) use is limited by potential adverse effects and a lack of consistent, demonstrated benefit. Patients treated with calcitriol should follow a low-calcium diet and must be monitored for hypercalcemia, hypercalciuria, and impaired kidney function. Clinical trials of calcitriol in postmenopausal women have shown mixed results and are reviewed elsewhere. (See "[Calcium and vitamin D supplementation in osteoporosis](#)".)

In contrast, [calcitriol](#) appears effective for preventing glucocorticoid-induced and post-transplant-related bone loss. (See "[Prevention and treatment of glucocorticoid-induced osteoporosis](#)", section on 'Calcium and vitamin D' and "[Prevention and treatment of osteoporosis after solid organ or stem cell transplantation](#)", section on 'Contraindications/intolerance to bisphosphonates'.)

- **Strontium ranelate** – In postmenopausal women with osteoporosis, we do not use strontium ranelate. It is a weak antiresorptive agent [79], and more effective osteoporosis agents are available in most regions. Strontium ranelate is an orally active drug comprising two atoms of stable strontium and an organic moiety (ranelic acid). Although strontium robustly increases measured BMD, some of this effect represents artifact from the accumulation of strontium in bone [80,81]. The manufacturer discontinued marketing and distribution in 2017 [82-84].

In 2014, the European Medicines Agency recommended restriction in the use of strontium based upon an analysis of pooled data showing an increased risk of myocardial infarction with use of strontium ranelate and other, previously identified serious risks (severe skin reactions, thromboembolic disease) [79,85-90]. However, in subsequent observational studies (United Kingdom Clinical Practice Research Datalink and a nationwide Danish study), the risk of myocardial infarction was not increased with use of strontium ranelate [91,92].

- **Tibolone** – [Tibolone](#) is used for osteoporosis management in some countries but is not available in the United States. It is a synthetic steroid with metabolites that have estrogenic, androgenic, and progestogenic properties [93].

[Tibolone](#) improves BMD in older postmenopausal women with established osteoporosis and prevents bone loss in early postmenopausal women without osteoporosis [94-97]. It also reduces vertebral fracture risk. The Long-Term Intervention on Fractures with Tibolone (LIFT) trial was designed to examine the effect of tibolone on vertebral fracture risk in postmenopausal women. Compared with placebo, tibolone reduced the absolute risk of vertebral and nonvertebral fracture (relative hazards of 0.55, 95% CI 0.41-0.74 and 0.74, 95% CI 0.58-0.93, respectively) [98]. However, this trial was discontinued early due to an excess risk of

stroke. Nonskeletal effects of tibolone are discussed separately. (See "[Preparations for menopausal hormone therapy](#)", section on '[Tibolone](#)'.)

- **Androgens** – We do not advise androgen therapy for osteoporosis management in women. Combined androgen and estrogen therapy does not appear to increase BMD more than estrogen therapy alone, and androgen therapy confers adverse virilizing effects [99]. In men, the beneficial effects of testosterone on bone mass may require aromatase-mediated conversion of testosterone to estradiol [100,101]. (See "[Overview of androgen deficiency and therapy in females](#)" and "[Etiology of osteoporosis in men](#)", section on '[Hypogonadism](#)'.)

### Supplemental therapies and vibration platforms

- **Vitamin K** – We do not recommend routine [vitamin K](#) supplementation for the maintenance of skeletal health or fracture prevention in high-risk individuals. Exogenous vitamin K is required for the carboxylation of osteocalcin, which allows osteocalcin to bind to hydroxyapatite mineral. A vitamin K2 preparation (menatetrenone) is widely used for the treatment of osteoporosis in Japan, based on clinical trial data showing improvement in BMD and a reduction in fracture risk in postmenopausal Japanese women [102-104]. However, aggregate data are conflicting, and no benefit has been demonstrated in other populations [105-107].
- **Folate/vitamin B12** – We do not recommend supplemental [folic acid](#) or [vitamin B12](#) for the treatment of osteoporosis or primary prevention of fracture. In adults with high cardiovascular disease risk and normal baseline homocysteine concentrations, folate and B12 supplementation did not reduce the incidence of vertebral or nonvertebral fractures [108].
- **Isoflavones** – We do **not** recommend isoflavone supplements to prevent or treat osteoporosis. Isoflavones (a type of phytoestrogen) are micronutrient substances that have estrogenic properties. Two types of isoflavones, genistein and daidzein, are found in soybeans, chickpeas, and lentils and are thought to be the most potent phytoestrogens. Ipriflavone is a synthetic isoflavone derivative and is widely available as an over-the-counter product in many countries.

Some studies have found a beneficial effect of phytoestrogens on markers of bone resorption, BMD, and fracture risk in animal models [109] and in postmenopausal women [110-113], while others have not [114-117]. Inconsistent findings may be due, in part, to the composition of the isoflavones studied. No randomized trials have assessed the effect of isoflavones on fracture as a primary outcome.

- **Fluoride** – We do **not** recommend [fluoride](#) for the treatment of patients with osteoporosis, given the availability of other anabolic therapies that unequivocally reduce fracture risk. Although fluoride increases BMD substantially, trial data have not consistently demonstrated fracture reduction [118-122]. While some studies demonstrated a decrease in the incidence of new vertebral fracture with fluoride [119,120,122], others reported no change [121] or even an increase in nonvertebral fractures [118,123]. Fluoride impairs bone mineralization, even at a dose as low as 20 mg daily [123].
- **Vibration platforms** — Although whole-body vibration platforms have been proposed as a nonpharmacologic therapy for postmenopausal osteoporosis [124,125], trial data show minimal to no improvement in BMD with the use of whole-body vibration platforms when compared with sham vibration, walking, or no treatment [126-128]. Thus, data are insufficient to recommend this therapy in postmenopausal women.

## MONITORING RESPONSE TO INITIAL PHARMACOTHERAPY

**Our approach** — Monitoring the response to therapy is important for identifying patients who may require a change in therapy, as up to one-sixth of women taking [alendronate](#) continue to lose bone [129]. Various approaches are used to monitor therapy, and no consensus exists on the optimal approach [130-133]. Serial dual-energy x-ray absorptiometry (DXA) measurements are typically used to assess the bone mineral density (BMD) response, although most of the efficacy of bisphosphonates for fracture reduction is not captured by DXA.

Several published guidelines address monitoring the response to osteoporosis therapy [10,66,134-136]; all recommend follow-up BMD (DXA) testing. However, guidance differs for the optimal frequency of monitoring and preferred site(s) to monitor. The use of biochemical markers of bone turnover for monitoring response to therapy has not been addressed in current guidelines, and no prospective trials have defined the optimal approach for incorporating markers into monitoring strategies [137]. Nonetheless, bone turnover markers may be useful for assessing treatment response, particularly when access to DXA is limited. (See '[Society guideline links](#)' below and "[Bone physiology and biochemical markers of bone turnover](#)" and "[Use of biochemical markers of bone turnover in osteoporosis](#)".)

Our approach to monitoring oral bisphosphonate therapy is presented below, as most women with osteoporosis are initially treated with these agents. For women treated with another agent as initial therapy, monitoring strategies may differ and are reviewed separately. (See ["Parathyroid hormone/parathyroid hormone-related protein analog therapy for osteoporosis"](#), section on 'Monitoring' and ["Denosumab for osteoporosis"](#), section on 'Monitoring'.)

**Repeat DXA** — For patients who initiate osteoporosis pharmacotherapy, we obtain a follow-up DXA of the hip and spine after one to two years, on the same instrument when possible ( [algorithm 3](#)).

A change in BMD is considered statistically significant only if it exceeds the least significant change (LSC) for the specific densitometer used. If LSC is not available, a threshold change of  $\geq 5$  percent has been suggested as an alternative, although evidence to support this is lacking [138]. This threshold approximates average LSC across facilities and may not be valid for an individual facility and instrument. (See ["Overview of dual-energy x-ray absorptiometry"](#), section on 'Precision assessment' and ["Overview of dual-energy x-ray absorptiometry"](#), section on 'Repeat BMD testing'.)

**BMD stable or increased** — BMD that is stable or improving is evidence of a therapeutic response. In such cases, we typically continue therapy and remeasure BMD in two to five years based on the individual's estimated fracture risk and initial treatment response. However, BMD stability or improvement does **not** uniformly indicate that fracture risk has been adequately mitigated. A patient may respond to therapy yet still have very low BMD and remain at high risk of fracture, potentially warranting more aggressive therapy (eg, an anabolic agent). (See ["Interim fragility fracture or T-score  \$\leq -2.5\$ "](#) below.)

Some [139-143], but not all [144], studies suggest that changes in BMD during therapy correlate with reduction in fracture risk. In one study, the greatest fracture reduction occurred in those who gained BMD, although those with stable BMD still had fewer fractures than those who lost BMD [139]. A meta-analysis of 12 clinical trials concluded that improvement in spine BMD accounts for a consistent but small part of the reduction in fracture risk [145].

**BMD decreased or fracture during therapy** — In a patient treated for at least one year, a BMD decrease equal to or greater than the LSC or new fragility fracture should trigger additional evaluation. Management in this setting is controversial and expert approaches may vary. Whenever possible, patients should be under the care of a clinician with expertise in osteoporosis management. We ask patients about adherence to osteoporosis pharmacotherapy and assess their calcium and vitamin D intake. We also evaluate for possible gastrointestinal malabsorption or the interim development of a disease or disorder with adverse skeletal effects (eg, primary hyperparathyroidism, celiac disease) [146,147]. Evaluation for secondary causes of bone loss should be performed and is reviewed in detail separately ( [table 8](#)). (See ["Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women"](#), section on 'Evaluation'.)

If a secondary cause of bone loss is identified, it should be addressed if possible. Once the secondary cause is mitigated, we remeasure BMD in one to two years. If the secondary cause of bone loss cannot be mitigated, or no secondary cause is identified, management depends on BMD and whether an interim fragility fracture occurred.

**Interim fragility fracture or T-score  $\leq -2.5$**  — For postmenopausal women who experience a fragility fracture or have a BMD T-score  $\leq -2.5$  on bisphosphonate therapy, we suggest discontinuing the bisphosphonate and switching to anabolic therapy. [Teriparatide](#) and [romosozumab](#) are effective in increasing BMD after previous bisphosphonate treatment, although the improvement may be less than in women not previously exposed to bisphosphonates [148]. No data suggest that initiation of teriparatide (or likely other anabolic therapy) requires a waiting interval after discontinuing long-term bisphosphonate treatment [149,150]. After switching to anabolic therapy, we remeasure BMD in one to two years. (See ["Selection of anabolic agent"](#) above.)

**BMD decreased but no interim fracture and T-score  $> -2.5$**  — In the absence of interim fragility fracture or T-score in the osteoporotic range, we perform the following assessments:

- **Measure bone turnover markers** – If such patients are on antiresorptive therapy, we typically measure fasting serum C-telopeptide (CTX) and/or serum procollagen type 1 N-terminal propeptide (P1NP). P1NP does not need to be measured in a fasted state. Urinary N-telopeptide (NTX) is a reasonable alternative marker though less precise than CTX or P1NP. If these markers are suppressed during antiresorptive therapy (eg, at or below the mean of the reference range for premenopausal women), treatment nonadherence or malabsorption is less likely [151]. (See ["Use of biochemical markers of bone turnover in osteoporosis"](#), section on 'Osteoporosis therapy'.)
- **Number of skeletal sites with decreased bone mineral density** – Apparent decline in BMD that is limited to one skeletal site, particularly in the presence of suppressed bone turnover markers, may reflect measurement error rather than true bone loss

[152,153].

- **Clinical assessment** – We also assess patients for any treatment side effects, treatment adherence, and possible challenges with oral bisphosphonate dosing requirements.
  - **Therapy likely ineffective** – If bone turnover markers are unsuppressed (eg, at or above the mean of the reference range for premenopausal women), BMD loss is evident at >1 site, and/or treatment side effects, nonadherence, or malabsorption are apparent, we stop the oral bisphosphonate and switch to intravenous (IV) [zoledronic acid](#). We remeasure BMD with DXA in one to two years. If nonadherence or malabsorption underlies the lack of treatment effectiveness, switching to IV bisphosphonate therapy should lead to gains in BMD. Switching to [denosumab](#) is a reasonable alternative.
  - **Therapy likely effective** – If bone turnover markers are suppressed, BMD loss is evident only at a single site, and no evidence of treatment side effects, nonadherence, or malabsorption is apparent, oral bisphosphonate therapy is likely effective. In such cases, we typically continue oral bisphosphonate therapy and remeasure BMD with DXA in one to two years.

**Duration of therapy** — The ideal duration of osteoporosis therapies depends on the specific agent, therapeutic response, and reassessment of fracture risk. This is reviewed for [romosozumab](#) above and for other agents separately. (See '[Romosozumab](#)' above and '[Bisphosphonate therapy for the treatment of osteoporosis](#)', section on '[Duration of therapy](#)' and '[Denosumab for osteoporosis](#)', section on '[Duration of therapy](#)' and '[Parathyroid hormone/parathyroid hormone-related protein analog therapy for osteoporosis](#)', section on '[Duration of therapy](#)' and '[Selective estrogen receptor modulators for prevention and treatment of osteoporosis](#)', section on '[Duration of therapy](#)'.)

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## SPECIAL POPULATIONS

**Glucocorticoid-induced osteoporosis** — Glucocorticoid therapy leads to high risk of bone loss that is most pronounced during the first few months of use. Glucocorticoids also increase fracture risk, and fractures occur at higher BMD values in glucocorticoid-induced osteoporosis than in postmenopausal osteoporosis. The evaluation, prevention, and treatment of glucocorticoid-induced osteoporosis is reviewed separately. (See "[Clinical features and evaluation of glucocorticoid-induced osteoporosis](#)" and "[Prevention and treatment of glucocorticoid-induced osteoporosis](#)".)

**Chronic kidney disease** — Patients with osteoporosis and chronic kidney disease (CKD) present unique management challenges. Oral and intravenous (IV) bisphosphonates should **not** be used routinely in patients with CKD and an estimated glomerular filtration rate (eGFR) <30 to 35 mL/min/1.73 m<sup>2</sup>. In patients with CKD, data are limited for fracture prevention efficacy and long-term adverse effects of osteoporosis pharmacotherapies. Both oral bisphosphonates and [denosumab](#) have been studied in this population. However, use of any bisphosphonate in patients with an eGFR<30 mL/min/1.73 m<sup>2</sup> should only be considered by specialists in metabolic bone disease and after biochemical testing and/or bone biopsy exclude renal osteodystrophy. The diagnosis, evaluation, and management of osteoporosis in patients with CKD is reviewed separately. (See "[Osteoporosis in patients with chronic kidney disease: Diagnosis and evaluation](#)".)

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## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "[Society guideline links: Osteoporosis](#)".)

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## INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5<sup>th</sup> to 6<sup>th</sup> grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10<sup>th</sup> to 12<sup>th</sup> grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "[Patient education: Osteoporosis and osteopenia \(low bone mass\) \(The Basics\)](#)" and "[Patient education: Calcium and vitamin D for bone health \(The Basics\)](#)" and "[Patient education: Medicines for osteoporosis \(The Basics\)](#)")
- Beyond the Basics topics (see "[Patient education: Osteoporosis prevention and treatment \(Beyond the Basics\)](#)" and "[Patient education: Calcium and vitamin D for bone health \(Beyond the Basics\)](#)")

## SUMMARY AND RECOMMENDATIONS

- **Lifestyle measures** – Lifestyle measures to reduce bone loss include adequate calcium and vitamin D intake, exercise, smoking cessation, fall prevention, and avoidance of heavy alcohol use. In general, women should achieve 1200 mg of elemental calcium daily (total diet plus supplement) and 800 international units of vitamin D daily ( [table 5](#)). If dietary calcium intake is inadequate ( [table 2](#)), we suggest calcium supplementation (**Grade 2C**). (See "[Calcium and vitamin D supplementation in osteoporosis](#)".)
- **Low bone mass (osteopenia)** – In postmenopausal women with low bone mass and **without** fragility fracture, we calculate absolute fracture risk using the Fracture Risk Assessment Tool (FRAX) ( [algorithm 1](#)). For most patients with low to moderate fracture risk, we suggest **not** using pharmacologic therapy to prevent bone loss or fracture (**Grade 2C**). (See '[Our approach](#)' above.)
- **Patient selection for osteoporosis pharmacologic therapy**
  - For postmenopausal women with a diagnosis of osteoporosis based on bone mineral density (BMD; T-score  $\leq -2.5$ ) or fragility fracture, we recommend treatment with pharmacotherapy ( [algorithm 1](#)) (**Grade 1A**). (See '[Patient selection](#)' above.)
  - For postmenopausal women with low BMD (T-score between -1.0 and -2.5) and high fracture risk, we also suggest pharmacologic therapy (**Grade 2B**). In the United States, a 10-year probability of hip fracture or combined major osteoporotic fracture of  $\geq 3$  or  $\geq 20$  percent, respectively, is a reasonable threshold for pharmacotherapy. (See '[Patient selection](#)' above.)
- **Choice of initial therapy**

- **Most women with osteoporosis** – For the initial treatment of osteoporosis in most postmenopausal women, we suggest oral bisphosphonates ( [algorithm 2](#)) (**Grade 2B**). We prefer these agents based on efficacy, cost, and long-term safety data. Oral bisphosphonates are contraindicated in those with esophageal disorders (eg, esophageal stricture) or known malabsorption (eg, Roux-en-Y gastric bypass) ( [algorithm 2](#)).

We typically prefer [alendronate](#) as our choice of oral bisphosphonate due to efficacy in reducing vertebral and hip fracture and evidence showing residual fracture benefit after a five-year course of therapy is completed. [Risedronate](#) is a reasonable alternative. (See '[Selection of oral bisphosphonate \(usually preferred\)](#)' above and "[Bisphosphonate therapy for the treatment of osteoporosis](#)", section on '[Choice of bisphosphonate](#)'.)

- **Very high fracture risk** – For postmenopausal women with very high fracture risk (eg, T-score of  $\leq -2.5$  plus a fragility fracture, T-score of  $\leq -3.0$  in the absence of fragility fracture[s], history of severe or multiple fractures) ( [algorithm 1](#)), we suggest initial treatment with an anabolic agent (**Grade 2B**). Patients most likely to benefit from anabolic therapy are those with the highest risk of fracture (eg, T-score  $\leq -3.5$  with fragility fracture[s], T-score  $\leq -4.0$ , recent major osteoporotic fracture, or multiple recent fractures). Options for anabolic therapy include [teriparatide](#), [abaloparatide](#), or [romosozumab](#). For patients with very high fracture risk who cannot be treated with an anabolic agent due to cost, inconvenience, contraindications, or personal preference, a bisphosphonate or [denosumab](#) may be appropriate ( [algorithm 2](#)). Patients should be under the care of a provider with expertise in treating osteoporosis to facilitate shared decision-making. (See '[Very high fracture risk](#)' above.)
- **Contraindications to bisphosphonates**
  - **Oral bisphosphonates contraindicated** – Patients who cannot take oral bisphosphonates can be treated with an intravenous (IV) bisphosphonate instead ( [algorithm 2](#)). [Zoledronic acid](#) is our agent of choice, as it is the only IV bisphosphonate with demonstrated efficacy for fracture prevention. [Denosumab](#) is a reasonable alternative. (See '[Gastrointestinal malabsorption or difficulty with dosing requirements](#)' above.)
- **Oral and IV bisphosphonates contraindicated**
  - **Most women with osteoporosis** – For most patients who cannot tolerate **any** bisphosphonate, we suggest [denosumab](#) rather than an anabolic agent (**Grade 2C**). Increased risk of vertebral fracture develops after discontinuation of denosumab, so the need



for indefinite administration should be discussed with patients prior to denosumab initiation.

Anabolic agents may be used in patients with less severe osteoporosis when bisphosphonates are contraindicated. For patients with **no** history of fragility fracture(s), particularly those at high risk for breast cancer, [raloxifene](#) is a reasonable alternative.

- **Very high fracture risk** – For patients at very high risk of fracture (eg, T-score of  $\leq -2.5$  plus a fragility fracture, T-score of  $\leq -3.0$  in the absence of fragility fracture(s), history of severe or multiple fractures) who were not treated initially with anabolic therapy, we suggest switching to an anabolic agent (**Grade 2C**). [Denosumab](#) is an alternative. (See '[Contraindications or intolerance to any bisphosphonates](#)' above and '[Parathyroid hormone/parathyroid hormone-related protein analog therapy for osteoporosis](#)', section on '[Overview of approach](#)'.)

After initial therapy with an anabolic agent is discontinued, patients should be treated with an antiresorptive agent (typically a bisphosphonate) to preserve the gains in BMD from anabolic therapy. For individuals who are unable to tolerate oral or intravenous bisphosphonates, alternatives may include [denosumab](#) or [raloxifene](#). (See '[Parathyroid hormone/parathyroid hormone-related protein analog therapy for osteoporosis](#)', section on '[Management after teriparatide](#)' and '[Parathyroid hormone/parathyroid hormone-related protein analog therapy for osteoporosis](#)', section on '[Management after abaloparatide](#)'.)

- **Monitoring** – For patients who initiate osteoporosis pharmacotherapy, we obtain a follow-up dual-energy x-ray absorptiometry (DXA) of the hip and spine after one to two years ( [algorithm 3](#)). A change in BMD is considered significant only if it exceeds the least significant change (LSC) for the specific densitometer used. If LSC is not available, a threshold change of  $\geq 5$  percent has been suggested as an alternative. (See '[Our approach](#)' above.)
- **Bone mineral density stable or increased** – If BMD is stable or improved, we continue therapy and remeasure BMD less frequently (eg, two to five years based on the clinical setting).
- **Bone mineral density decreased or fracture during therapy** – After at least one year of osteoporosis pharmacotherapy, a BMD decrease greater than the LSC or new fragility fracture should trigger additional evaluation, including assessment for treatment nonadherence or interim development of a secondary cause of bone loss ( [table 8](#)). Whenever possible, patients should be under the care of a clinician with expertise in osteoporosis management.

If a remediable secondary cause of bone loss is identified, it should be treated. If the secondary cause of bone loss cannot be mitigated, or no secondary cause is identified, management depends on BMD and whether an interim fragility fracture occurred.

- **Interim fragility fracture or T-score  $\leq -2.5$**  – For postmenopausal women who experience a fragility fracture or have a T-score  $\leq -2.5$  on bisphosphonate therapy, we suggest discontinuing the bisphosphonate and switching to anabolic therapy (**Grade 2C**). [Teriparatide](#) and [romosozumab](#) increase BMD after previous bisphosphonate treatment. (See '[Interim fragility fracture or T-score  \$\leq -2.5\$](#) ' above and '[Selection of anabolic agent](#)' above.)
- **BMD decreased but no interim fracture and T-score  $> -2.5$**  – In the absence of interim fragility fracture or T-score  $\leq -2.5$ , we use bone turnover markers and clinical assessments to evaluate the likelihood of treatment effectiveness. If treatment is unlikely effective, we stop the oral bisphosphonate and switch to IV [zoledronic acid](#). If treatment is likely effective, we typically continue oral bisphosphonate therapy and remeasure BMD with DXA in one to two years. (See '[BMD decreased but no interim fracture and T-score  \$> -2.5\$](#) ' above.)

## ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Marc K Drezner, MD, who contributed to an earlier version of this topic review.

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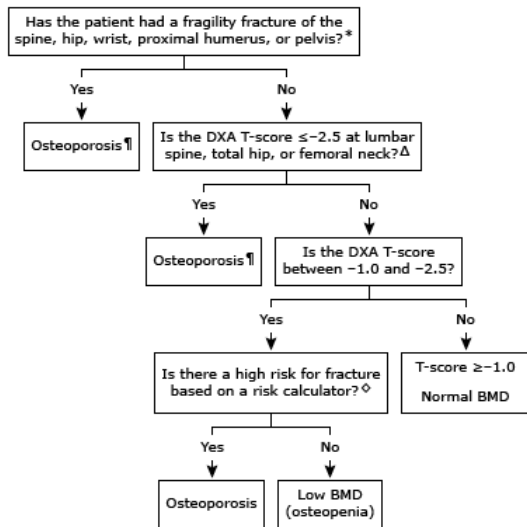
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Topic 2064 Version 87.0

## GRAPHICS

### Diagnosis of osteoporosis in postmenopausal women



BMD: bone mineral density; DXA: dual-energy x-ray absorptiometry; FRAX: Fracture Risk Assessment Tool.

\* Fragility fractures are those occurring spontaneously or from minor trauma (eg, a fall from a standing height or less). The most common sites of fragility fracture are the spine (vertebral compression fractures), hip, and wrist. Fragility fractures also occur at the humerus, rib, and pelvis.

¶ Some individuals with osteoporosis are at very high risk of fracture. No consensus exists on the definition of very high fracture risk. Examples may include:

- Severe or multiple fractures
- T-score  $\leq -2.5$  plus a fragility fracture
- T-score  $\leq -3.0$

Δ When the hip or lumbar spine cannot be measured due to structural abnormalities (eg, osteoarthritis), the 33% (one-third) radius can be measured and considered for diagnostic classification.

◇ We use FRAX to calculate absolute risk of fracture. In the United States, high risk is defined as a 10-year probability of:

- Hip fracture  $\geq 3\%$
- or**
- Combined major osteoporotic fracture (ie, clinical vertebral, hip, forearm, or proximal humerus)  $\geq 20\%$

FRAX risk thresholds are country specific. For clinicians practicing outside of the United States, intervention thresholds may be accessed directly from the FRAX website.

**Clinical risk factors for fracture independent of bone mineral density**

Advancing age
Previous fracture
Glucocorticoid therapy
Parental history of hip fracture
Low body weight
Current cigarette smoking
Excessive alcohol consumption
Rheumatoid arthritis
Secondary osteoporosis (eg, hypogonadism or premature menopause, malabsorption, chronic liver disease, inflammatory bowel disease)

Data from: Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. *Osteoporos Int* 2005; 16:581.

Graphic 76445 Version 4.0

**Foods and drinks with calcium**

<b>Food</b>	<b>Calcium in milligrams</b>
Milk (skim, 2%, or whole; 8 oz [240 mL])	300
Yogurt (6 oz [168 g])	250
Orange juice (with calcium; 8 oz [240 mL])	300
Tofu with calcium (0.5 cup [113 g])	435
Cheese (1 oz [28 g])	195 to 335 (hard cheese = higher calcium)
Cottage cheese (0.5 cup [113 g])	130
Ice cream or frozen yogurt (0.5 cup [113 g])	100
Fortified non-dairy milks (soy, oat, almond; 8 oz [240 mL])	300 to 450
Beans (0.5 cup cooked [113 g])	60 to 80
Dark, leafy green vegetables (0.5 cup cooked [113 g])	50 to 135
Almonds (24 whole)	70
Orange (1 medium)	60

Graphic 67824 Version 8.0



## Dietary Reference Intakes for calcium and vitamin D

Life stage group	Calcium			Vitamin D		
	Estimated average requirement (mg/day)	Recommended dietary allowance (mg/day)	Upper level intake (mg/day)	Estimated average requirement (international units/day)	Recommended dietary allowance (international units/day)	Upper level intake (international units/day)
Infants 0 to 6 months	*	*	1000	¶	¶	1000
Infants 6 to 12 months	*	*	1500	¶	¶	1500
1 to 3 years old	500	700	2500	400	600	2500
4 to 8 years old	800	1000	2500	400	600	3000
9 to 13 years old	1100	1300	3000	400	600	4000
14 to 18 years old	1100	1300	3000	400	600	4000
19 to 30 years old	800	1000	2500	400	600	4000
31 to 50 years old	800	1000	2500	400	600	4000
51 to 70 year old males	800	1000	2000	400	600	4000
51 to 70 year old females	1000	1200	2000	400	600	4000
>70 years old	1000	1200	2000	400	800	4000
14 to 18 years old, pregnant/lactating	1100	1300	3000	400	600	4000
19 to 50 years old, pregnant/lactating	800	1000	2500	400	600	4000

\* For infants, adequate intake is 200 mg/day for 0 to 6 months of age and 260 mg/day for 6 to 12 months of age.

¶ For infants, adequate intake is 400 international units/day for 0 to 6 months of age and 400 international units/day for 6 to 12 months of age.

*Dietary Reference Intakes: The Essential Guide to Nutrient Requirements.* Otten JJ, Hellwig JP, Meyers LD (Eds), The National Academies Press, Washington, DC 2006. pp.530-541. Modified with permission from the National Academies Press, Copyright © 2006, National Academy of Sciences.

Sources: *Dietary reference intakes for Thiamin, Riboflavin, Niacin, Vitamin B<sub>6</sub>, Folate, Vitamin B<sub>12</sub>, Panthothenic acid, Biotin, and Choline (1998)*; *Dietary reference intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000)*; *Dietary Reference Intake reports of the Food and Nutrition Board, Institute of Medicine (2010)*. These reports may be accessed via [www.nap.edu](http://www.nap.edu).

Graphic 71669 Version 18.0

**Elemental calcium content per pill of different calcium supplements**

	<b>Elemental Ca/tablet</b>	<b>Ca compound</b>	<b>Vitamin D</b>
<b>Caltrate 600 + D3</b>	600 mg	Carbonate	800 units (20 mcg)
<b>Caltrate 600 + D3 Soft Chews</b>	600 mg	Carbonate	800 units (20 mcg)
<b>Caltrate Gummy Bites</b>	250 mg	Tribasic calcium phosphate	400 units (10 mcg)
<b>Caltrate 600 + D3 Plus Minerals Chewables</b>	600 mg	Carbonate	800 units (20 mcg)
<b>Caltrate 600 + D3 Plus Minerals Minis</b>	300 mg	Carbonate	800 units (20 mcg)
<b>Citracal Petites</b>	200 mg	Citrate	250 units (6.25 mcg)
<b>Citracal Maximum</b>	315 mg	Citrate	250 units (6.25 mcg)
<b>Citracal Plus Magnesium &amp; Minerals</b>	250 mg	Citrate	125 units (3.12 mcg)
<b>Citracal + D Slow Release</b>	600 mg	Citrate + carbonate blend	500 units (12.5 mcg)
<b>Citracal Calcium Gummies</b>	250 mg	Tricalcium phosphate	500 units (12.5 mcg)
<b>Citracal Calcium Pearls</b>	200 mg	Carbonate	500 units (12.5 mcg)
<b>Os-Cal Calcium + D3</b>	500 mg	Carbonate	200 units (5 mcg)
<b>Os-Cal Extra + D3</b>	500 mg	Carbonate	600 units (15 mcg)
<b>Os-Cal Ultra</b>	600 mg	Carbonate	500 units (12.5 mcg)
<b>Os-Cal Chewable</b>	500 mg	Carbonate	600 units (15 mcg)
<b>Tums</b>	200 mg	Carbonate	-
<b>Tums Extra Strength</b>	300 mg	Carbonate	-
<b>Tums Ultra Strength</b>	400 mg	Carbonate	-
<b>Tums Chewy Delights</b>	400 mg	Carbonate	-
<b>Viactiv Calcium plus D + K</b>	650 mg	Carbonate	500 units (12.5 mcg)

Ca: calcium; units: international units.

Graphic 78814 Version 8.0

**Selected food sources of vitamin D<sup>[1]</sup>**

Food	Amount per serving	
	In international units (IU)	In micrograms (mcg)
Cod liver oil, 1 tablespoon (15 mL)	1360	34
Salmon (sockeye), cooked, 3 ounces (85 g)	380 to 570*	9.5 to 14*
Mushrooms that have been exposed to ultraviolet light to increase vitamin D, 3 ounces (85 g) (not yet commonly available)	889	22.3
Mackerel, cooked, 3 ounces (85 g)	388	9.7
Tuna fish, canned in water, drained, 3 ounces (85 g)	40 to 68	1 to 2
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 8 ounces (240 mL)	100	2.5
Orange juice fortified with vitamin D, 8 ounces (240 mL) (check product labels, as amount of added vitamin D varies)	100	2.5
Yogurt, fortified with vitamin D, 6 ounces (180 mL) (more heavily fortified yogurts provide more of the DV)	80	2
Margarine, fortified, 1 tablespoon (15 g)	60	1.5
Sardines, canned in oil, drained, 2 sardines	46	1

Liver, beef, cooked, 3.5 ounces (100 g)	46	1
Ready-to-eat cereal, fortified with vitamin D, 6 to 8 ounces (227 g) (more heavily fortified cereals might provide more of the DV)	40	1
Egg, 1 whole (vitamin D is found in yolk)	25	0.6
Cheese, Swiss, 1 ounce (29 g)	6	0

In the United States, reference values are listed on food labels as a percentage of DVs (%DV), based on a 2000 calorie daily energy intake.

#: percent; DV: daily value.

\* Vitamin D content of fish varies substantially even within species. Wild salmon tends to have higher vitamin D content than farmed salmon.

*Reference:*

1. US Department of Agriculture, Agricultural Research Service. *USDA Nutrient Database for Standard Reference, Release 28, 2017.*

Graphic 77982 Version 8.0

**Available FDA-approved medications for the prevention of osteoporosis in postmenopausal women\***

<b>Drug class</b>	<b>Medication</b>	<b>Dose</b>
Estrogens	Many	Variable
Bisphosphonates	Alendronate	35 mg/week or 5 mg/day
	Risedronate	35 mg/week, 5 mg/day, or 150 mg/month
	Ibandronate	150 mg/month
	Zoledronic acid	5 mg IV once every two years
Selective estrogen receptor modulators (SERMs)	Raloxifene	60 mg/day
	Bazedoxifene - conjugated equine estrogen	20 mg/0.45 mg daily

FDA: US Food and Drug Administration; IV: intravenous.

\* There are no FDA-approved medications for prevention of osteoporosis in men.

Graphic 64685 Version 8.0

## Guidelines for pharmacologic intervention in postmenopausal females and males $\geq 50$ years of age

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History of fracture of vertebrae (clinical or subclinical), hip, wrist, pelvis, or humerus.

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T-score  $\leq -2.5$  (DXA) at the lumbar spine, femoral neck, or total hip.\*

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T-score between  $-1$  and  $-2.5$  at the femoral neck or spine, and a 10-year probability of hip fracture  $\geq 3\%$  or a 10-year probability of any major osteoporosis-related fracture  $\geq 20\%$  based upon the United States-adapted WHO algorithm.

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DXA: dual-energy x-ray absorptiometry; WHO: World Health Organization.

\* Predictive value of isolated measurement of 1/3 radius varies with clinical context.

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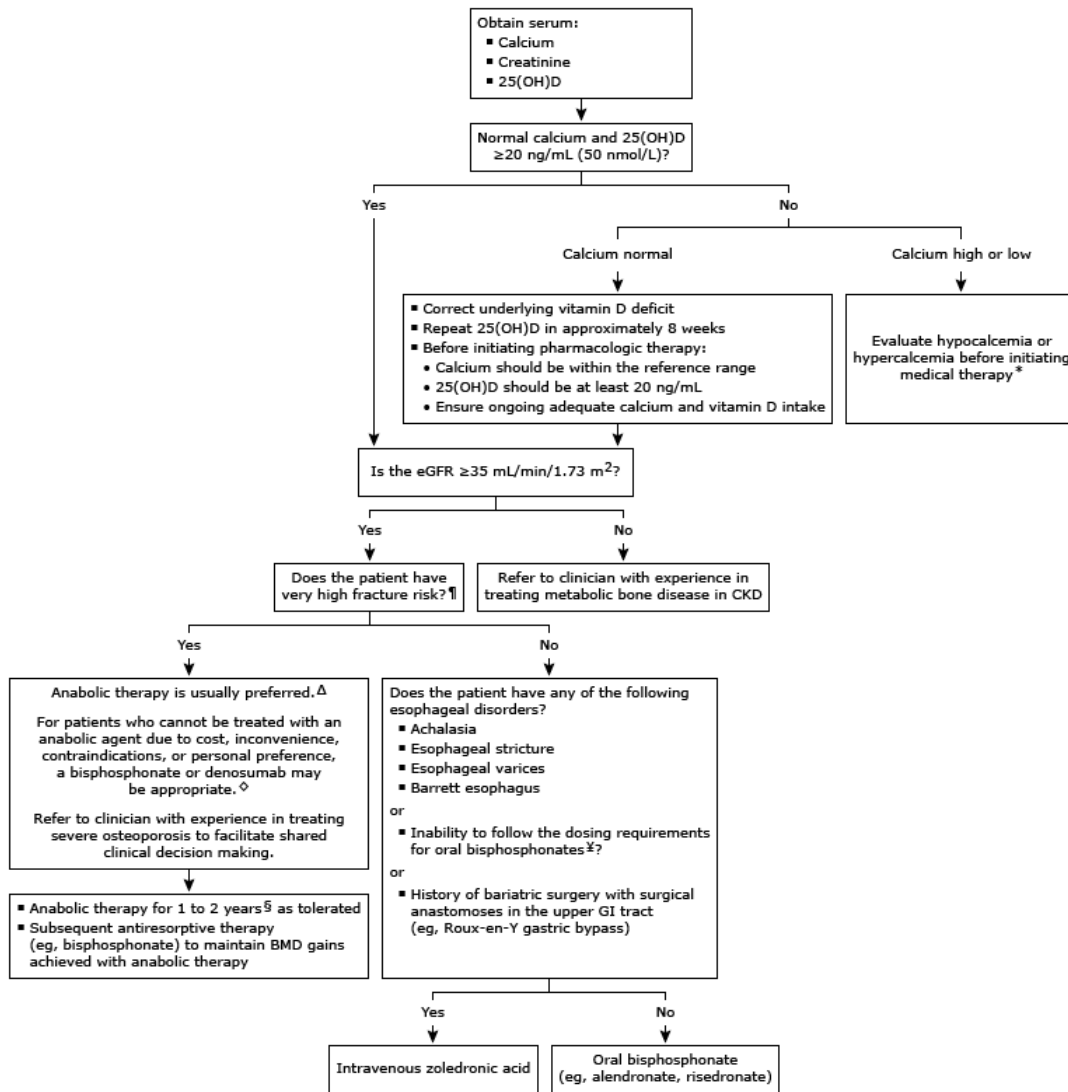
### References:

1. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012; 97:1802.
  2. LeBoff MS, Greenspan SL, Insogna KL, et al. *The clinician's guide to prevention and treatment of osteoporosis*. Osteoporos Int 2022.
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Graphic 52512 Version 9.0



## Medical therapy to prevent fractures in people with osteoporosis



25(OH)D: 25-hydroxyvitamin D; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; GI: gastrointestinal.

\* Refer to additional UpToDate content on evaluation of hypercalcemia and hypocalcemia.

¶ Very high risk of fracture: No consensus exists on the definition of very high fracture risk. Examples may include: T-score of  $\leq -3.0$  even in the absence of fractures, T-score of  $\leq -2.5$  plus a fragility fracture, severe or multiple vertebral fractures.

Δ Patients most likely to benefit from anabolic therapy are those with the highest risk of fracture (eg, T-score  $\leq -3.5$  with fragility fracture[s], T-score  $\leq -4.0$ , recent major osteoporotic fracture, or multiple recent fractures).

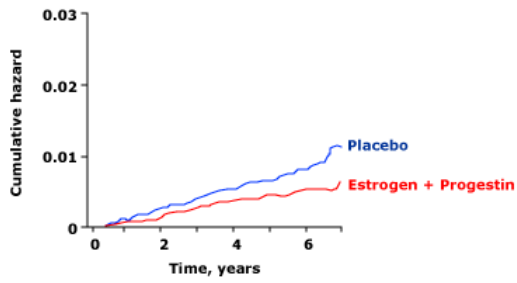
◇ Increased risk of vertebral fracture is evident after discontinuation of denosumab; the need for indefinite administration of denosumab should be discussed with patients prior to its initiation.

§ Anabolic agents include teriparatide, abaloparatide, romosozumab.

¥ Oral bisphosphonates are poorly absorbed and must be taken on an empty stomach first thing in the morning with at least 240 mL (8 oz) of water. After administration, the patient should not have food, drink, medications, or supplements and should remain upright for at least 1 half-hour.

Graphic 131952 Version 4.0

## Estrogen-progestin therapy reduces hip fracture



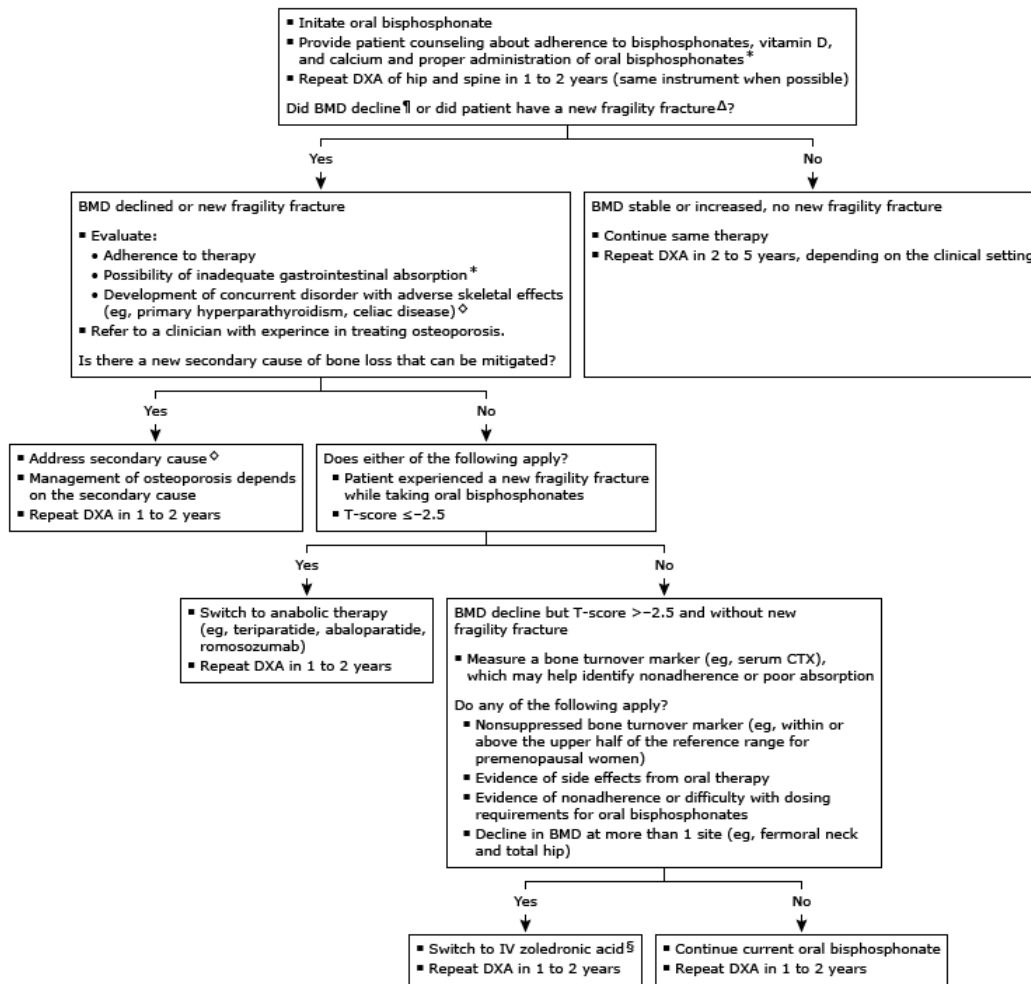
In the Women's Health Initiative, combined estrogen-progestin replacement therapy was associated with significant reduction in hip fracture (five fewer hip fractures per 10,000 person-years; HR 0.7, unadjusted 95% CI 0.4-1.0).

HR: hazard ratio.

Data from: Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen and progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288:321.

Graphic 55425 Version 4.0

## Osteoporosis in postmenopausal women: Monitoring initial therapy with oral bisphosphonates



Oral bisphosphonates (eg, alendronate, risedronate) are selected as initial therapy for most postmenopausal women with osteoporosis. This algorithm presents our general approach to monitoring bisphosphonate therapy. Monitoring treatment with other osteoporosis agents may differ. The algorithm is intended for use with additional UpToDate content on postmenopausal osteoporosis.

BMD: bone mineral density; CTX: C-telopeptide; DXA: dual-energy x-ray absorptiometry; IV: intravenous; LSC: least significant change.

\* Inadequate absorption is often related to insufficient time interval between drug intake and food or calcium ingestion.

¶ A change in BMD is considered significant if it exceeds the LSC for the specific densitometer used. If LSC is not reported, a simplified approximation for exceeding LSC is  $\geq 5\%$ .

Δ Fragility fractures are those occurring spontaneously or from minor trauma (eg, a fall from a standing height or less). The most common sites of fragility fracture are the spine (vertebral compression fractures), hip, and wrist. Fragility fractures also occur at the humerus, rib, and pelvis.

◇ There are many disorders/drugs with adverse skeletal effects. Clinical findings guide the evaluation for a specific concurrent disorder (eg, incident hypercalcemia may indicate primary hyperparathyroidism).

§ If lack of response is related to poor absorption, switching to an IV bisphosphonate should result in an improvement in BMD. Denosumab is a reasonable alternative. There is an increased risk of vertebral fracture after discontinuation of denosumab; the need for indefinite administration of denosumab should be discussed with patients prior to its initiation.

Graphic 142817 Version 1.0

## Causes of osteoporosis

<b>Drugs</b>	<b>Marrow-related disorders</b>
Glucocorticoids	Amyloidosis
Immunosuppressants (cyclosporine)	Hemochromatosis
Antiseizure medications (particularly phenobarbital and phenytoin)	Hemophilia
Aromatase inhibitors	Leukemia
GnRH agonists and antagonists	Lymphoma
Heparin	Mastocytosis
Cancer chemotherapy	Multiple myeloma
<b>Endocrine disorders</b>	Pernicious anemia
Acromegaly	Sarcoidosis
Adrenal insufficiency	Sickle cell anemia
Cushing's syndrome	Thalassemia
Eating disorders	<b>Organ transplantation</b>
Endometriosis	Bone marrow
Hyperparathyroidism	Heart
Hyperprolactinemia	Kidney
Hyperthyroidism	Liver
Hypogonadism (primary or secondary)	Lung
Diabetes mellitus	<b>Miscellaneous causes</b>
<b>Gastrointestinal disease/nutritional disorders</b>	Ankylosing spondylitis
Alcohol-related liver disease	Chronic obstructive pulmonary disease
Celiac disease	Epidermolysis bullosa
Chronic active hepatitis	Idiopathic hypercalciuria
Chronic cholestatic disease	Multiple sclerosis
Gastrectomy	Rheumatoid arthritis
Inflammatory bowel disease	<b>Genetic disorders</b>
Jejunioileal bypass	Hypophosphatasia
Malabsorption syndromes	Osteogenesis imperfecta
Pancreatic insufficiency	Homocystinuria due to cystathionine deficiency
Parenteral nutrition	
Primary biliary cholangitis	
Severe liver disease	
Vitamin D and/or calcium deficiency	

GnRH: gonadotropin-releasing hormone.

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Graphic 54926 Version 9.0

## Contributor Disclosures

**Harold N Rosen, MD** No relevant financial relationship(s) with ineligible companies to disclose. **E Michael Lewiecki, MD** Other Financial Interest: International Society for Clinical Densitometry [Osteoporosis]; Osteoporosis Foundation of New Mexico [Osteoporosis]. All of the relevant financial relationships listed have been mitigated. **Clifford J Rosen, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Kenneth E Schmader, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Katya Rubinow, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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