Treatment of Osteoporosis

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Guidelines for pharmacologic intervention in postmenopausal women and men ≥50 years of age

History of hip or vertebral fracture.
T-score ≤-2.5 (DXA) at the femoral neck or spine, after appropriate evaluation to exclude secondary causes.
T-score between -1 and -2.5 at the femoral neck or spine, and a 10-year probability of hip fracture ≥3 percent or a 10-year probability of any major osteoporosis-related fracture ≥20 percent based upon the United States-adapted WHO algorithm.

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

References:

1. *Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 2014; 25:2359.*
2. *Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012; 97:1802.*

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The treatment of osteoporosis

- **Lifestyle measures**
- **Pharmacologic therapy**

lifestyle measures

- Adequate **calcium and vitamin D**,
- Exercise,
- **Smoking** cessation,
- Counseling on **fall prevention**, and
- Avoidance of heavy **alcohol** use.
- In addition, affected patients **should avoid**, if possible, **drugs that increase bone loss**, such as **glucocorticoids**.

Foods and drinks with calcium

Food	Calcium, milligrams
Milk (skim, 2 percent, 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 (1/2 cup [113 g])	435
Cheese (1 oz [28 g])	195 to 335 (hard cheese = higher calcium)
Cottage cheese (1/2 cup [113 g])	130
Ice cream or frozen yogurt (1/2 cup [113 g])	100
Soy milk (8 oz [240 mL])	300
Beans (1/2 cup cooked [113 g])	60 to 80
Dark, leafy green vegetables (1/2 cup cooked [113 g])	50 to 135
Almonds (24 whole)	70
Orange (1 medium)	60

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PHARMACOLOGIC THERAPY

Candidates for therapy

- **(NOF) recommendations:**
- We recommend pharmacologic therapy for postmenopausal women with a history of **fragility fracture** or with **osteoporosis** based upon BMD measurement (T-score ≤-2.5).
- We also suggest pharmacologic therapy for the treatment of **high-risk postmenopausal women with T-scores between -1.0 and -2.5**. We calculate fracture risk using the WHO Fracture Risk Assessment Tool **(FRAX)** (FRAX website).
- A reasonable cut point that may be cost effective in some settings is a 10-year probability of hip fracture or combined major osteoporotic fracture of **≥3.0 or ≥20** percent, respectively.

- In 2008, a World Health Organization (WHO) task force introduced FRAX, which estimates the 10-year probability of hip fracture or major osteoporotic fractures combined (**hip, spine, shoulder, or wrist**) for an untreated patient using **femoral neck BMD** and easily obtainable **clinical risk factors** for fracture.

Choice of drug :

- Efficacy,
- Safety,
- Cost,
- Convenience, and
- Other patient-related factors
- Should have normal serum calcium and 25-hydroxyvitamin D levels prior to starting therapy, and they should receive supplemental calcium and vitamin D if dietary intake is inadequate.

- **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 [33].**

- **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.**

Initial therapy

- For most postmenopausal women with osteoporosis, we suggest **oral bisphosphonates as first-line therapy**.
- We **prefer** oral bisphosphonates as initial therapy because of their efficacy, favorable cost, and the availability of long-term safety data.
- We suggest alendronate or risedronate as our choice of bisphosphonate due to efficacy in reducing vertebral and hip fracture. We most commonly use **alendronate**.

- For postmenopausal women at very high risk of fracture (eg, T-score of ≤-3.5 in the absence of fragility fracture, T-score of ≤-2.5 plus a fragility fracture, severe or multiple vertebral fractures), we suggest an anabolic agent (teriparatide, abaloparatide, romosozumab).
- Teriparatide and abaloparatide must be injected subcutaneously daily, whereas romosozumab is injected once monthly.

- **For patients at high risk for fracture (eg, osteoporosis by BMD in the absence of fragility fracture, T-score > -2.5 with a fragility fracture, single vertebral fracture), denosumab is a reasonable option, particularly in patients with impaired renal function.**

Contraindications/intolerance to oral bisphosphonates

- Oral bisphosphonates should not be used as initial therapy in patients with **esophageal disorders**, an **inability** to follow the dosing requirements (eg, stay upright for at least 30 to 60 minutes), or chronic kidney disease (**CKD**) (estimated glomerular filtration rate [eGFR] **<30** mL/min).

Contraindications/intolerance to oral bisphosphonates

- **Alternatives** for initial therapy in patients with contraindications or intolerance to oral bisphosphonates include **intravenous (IV) bisphosphonates** (except if the contraindication is CKD), **denosumab , teriparatide** (except in CKD), and selective estrogen receptor modulators (**SERMs**).
- The choice of initial agent depends upon the nature of the contraindication/intolerance, the severity of the osteoporosis, and subsequent risk for fracture.

Gastrointestinal disease or difficulty with dosing requirements

- For patients with esophageal disorders, gastrointestinal intolerance, or an inability to follow the dosing requirements of oral bisphosphonates, including an inability to sit upright for 30 to 60 minutes and/or to swallow a pill, we suggest **IV bisphosphonates**.
- We prefer IV **zoledronic acid (Aclasta) ,** which has been demonstrated to reduce vertebral and hip fractures.

- **Denosumab** is an **alternative** to IV zoledronic acid for women at high risk for fracture (such as **older patients**) who have **difficulty with the dosing requirements** of oral bisphosphonates, who prefer to avoid IV bisphosphonates due to **side effects** (eg, acute phase reaction), or who have **impaired renal function**.

- **However, emerging data have raised concern about increased risk of vertebral fracture after discontinuation of denosumab.**
- **Thus, the need for indefinite treatment should be addressed with patients before denosumab is initiated.**

CKD

- **Oral and IV bisphosphonates** should not be used routinely in patients with CKD and an eGFR <30 to 35 mL/min.
- Use of any bisphosphonate in patients with an eGFR <30 mL/minute should only be considered by **specialists in metabolic bone disease** and after biochemical testing and/or bone biopsy.

Contraindications/intolerance to any bisphosphonates

- Options include **teriparatide**, **denosumab**, or SERMs.
- For postmenopausal women with **severe osteoporosis** (T-score of -3.5 or below even in the absence of fractures, or T-score of -2.5 or below plus a fragility fracture), we prefer teriparatide. **Teriparatide** must be injected subcutaneously daily, whereas **denosumab** is injected once every six months.

- For **some patients with severe osteoporosis**, it may be beneficial to treat with **teriparatide first** (maximum of two years), **followed by denosumab**, to preserve the gains in BMD achieved with teriparatide.
- For patients who do not meet criteria for severe osteoporosis but have had **fragility fractures**, **denosumab** rather than teriparatide is a reasonable option, particularly in patients with impaired renal function.

- Since the anti resorptive effects of **raloxifene** are less than those of bisphosphonates, we reserve the use of this drug for **postmenopausal women** with osteoporosis and **no history of fragility fractures** who **cannot tolerate** any bisphosphonates or who have an increased risk of **invasive breast cancer**.

Severe osteoporosis

- **Teriparatide** is generally **not used as a first-line drug** for treatment or prevention of osteoporosis. However, for some patients with severe osteoporosis, it may be beneficial to treat with **teriparatide first (maximum of two years), followed by an anti resorptive drug, preferably a bisphosphonate**, to preserve the gains in BMD achieved with teriparatide.
- For women who are unable to tolerate oral or IV bisphosphonates, **denosumab** or raloxifene are post-teriparatide alternatives.

Response to therapy (Monitoring)

- **DXA** – For patients starting on therapy, we suggest a follow-up DXA of hip and spine after **two years**, and if BMD is stable or improved, less frequent monitoring thereafter.
- **Bone turnover markers** - Routine monitoring of patients on anti resorptive therapy with bone turnover markers is not necessary.

Guidelines for monitoring response to therapy

- **ISCD** – The ISCD recommends follow-up BMD testing (DXA spine and hip) when the expected change in BMD equals or exceeds the **least significant change (LSC)**, which is typically **one to two years** after initiation or change of therapy, with longer intervals once therapeutic effect is established.**(International Society for Clinical Densitometry)**

- **NAMS** – The North American Menopause Society (NAMS) recommends repeat DXA **one to two years** after initiating therapy, and less frequently thereafter if BMD is stable.

- A **more conservative approach** to monitoring takes the position that monitoring for efficacy of anti resorptive therapy is **unnecessary**, as only a minority of patients continue to lose bone on therapy. This approach is used **infrequently** by clinicians but may be applicable to patients from **remote areas** without access to medical facilities.

Bone mineral density stable or increased

- In order for **a change in BMD** to be considered **significant**, it should be **greater than the LSC** for the densitometer in question.

Bone mineral density decreased or fracture during therapy

- Should trigger **additional evaluation** for contributing factors, which may include **poor adherence to therapy**, **inadequate gastrointestinal absorption**, **inadequate intake of calcium and vitamin D**, or the development of a **disease** or disorder with adverse skeletal effects.

Decline in BMD

- When the change in BMD is **<5 percent** and the patient is taking the drug correctly and has no discernible contributing factors, we suggest continuing the same therapy and **repeating the BMD two years later**.
- When the decline in BMD is **≥5 percent**, we usually **switch** from an oral bisphosphonate to an IV bisphosphonate, typically zoledronic acid. If the lack of response is related to poor absorption, switching to an IV preparation should result in a more favorable response. Other alternatives include switching to denosumab or teriparatide.

Fracture while taking bisphosphonates

- **Switching to teriparatide** is a good option for patients with severe osteoporosis who continue to fracture after one year of bisphosphonates.
- **Denosumab is an alternative** for patients who are unresponsive to other therapies and in those with **impaired renal function**.
- However, if there are no contraindications, it may be beneficial to treat with **teriparatide first (maximum of two years), followed by denosumab**, to preserve the gains in BMD achieved with teriparatide.

Bisphosphonates

Contraindications/intolerance

- Oral bisphosphonates should not be used as initial therapy in patients with **esophageal disorders** (eg, achalasia, esophageal stricture, esophageal varices, Barrett's esophagus) or with **an inability to follow the dosing requirements** (eg, stay upright for at least 30 minutes).
- Oral and IV bisphosphonates should not be used routinely in patients with **chronic kidney disease** and an estimated GFR <30 to 35 mL/min.

Practical management issues

- **Pretreatment evaluation** — Before starting bisphosphonates, patients should be evaluated to detect potentially remediable causes of or other contributing factors to osteoporosis.
- Calcium
- 25-hydroxyvitamin D (25[OH]D)
- Creatinine

- For both oral and IV bisphosphonates, we also inquire about imminent plans for invasive **dental procedures** (extractions, implants) and discuss risk factors for developing osteonecrosis of the jaw (ONJ), a rare complication of IV or oral therapy.

- If a **dental implant or extraction** is already planned, we frequently **delay bisphosphonate** therapy for a **few months** until healing of the jaw is complete.
- If a patient is already taking bisphosphonates, the approach is uncertain, and there are few data to guide management. Some clinicians ask patients to discontinue bisphosphonates and resume again when healing is complete, while others suggest not stopping bisphosphonates.

- Guidelines from the **American Association of Oral and Maxillofacial Surgeons** suggest performing dentoalveolar surgery, such as extractions and implants, as usual in patients who have been treated with oral bisphosphonates for **less than four years** and have no clinical risk factors. They suggest discontinuing bisphosphonates if a patient has been treated for **more than four years** or has taken concomitant glucocorticoids.

Oral regimen

- Bisphosphonates are **poorly absorbed orally (<1 %**)
- Should not be given in **active upper GI disease**.
- Should be discontinued in patients who develop any symptoms of **esophagitis**.
- Should be taken alone on an **empty stomach** first thing in the **morning** with at least **240 mL of plain water**. After administration, the patient **should not have food**, drink, medications, or supplements for at least **one-half hour.**
- Patients should remain **upright** (sitting or standing) for at least **30 minutes.**

IV regimen

- **Zoledronic acid** is administered **yearly** and must be **infused** over a period of **at least 15 minutes**.
- **Hypocalcemia** may occur in patients treated with IV bisphosphonates.
- Individuals with **vitamin D deficiency** should be treated prior to the infusion.
- Some clinicians also advise patients to increase **calcium** supplementation (**doubling of usual dose**) for 5 to 7 days.
- Prior to each zoledronic acid infusion, clinicians should measure serum **creatinine** and make sure that patients are adequately **hydrated**.

- Zoledronic acid is not recommended for use in patients with **creatinine clearance ≤35** mL/min
- IV bisphosphonates may be associated with **flu-like symptoms.**
- Acetaminophen or ibuprofen can be administered to prevent or treat flu-like symptoms.

Duration of therapy

For patients taking **alendronate** or **risedronate** for **five years** or who received **zoledronic acid** once yearly for **three years**, have a stable BMD, have no previous vertebral fractures, and are at low risk for fracture in the near future, we suggest discontinuing the drug, as there appears to be residual BMD and fracture benefit.

- However, for women **at highest risk for fracture** (history of osteoporotic fracture before or during therapy, T-score below -3.5 in the absence of fractures) who are taking alendronate or risedronate, we suggest continuing therapy for **up to 10 years**, as clinical trial data show maintenance of BMD and fracture benefits with no increased risk of adverse events. For similar women treated with zoledronic acid, we would continue therapy **up to six years**.

Length of holiday

- The decision to resume the drug is often based on **a combination of factors**, including duration of the holiday, decrease in BMD, clinical risk factors for fracture, and increase in markers of bone turnover.
- We typically restart bisphosphonates when there is **persistent bone loss (approximately 5 percent) at the femoral neck on at least two dual-energy x-ray absorptiometry (DXA) measurements taken at least two years apart**, using the same make and model DXA scanner.

- As an **alternative**, bisphosphonates can be restarted **after a three to five-year holiday** in women who showed improvement during their initial course of bisphosphonates and did not have a previous fracture.

Combination therapy

- We suggest not using combination therapy, as the additional BMD benefits are small and there is no proven additional fracture benefit.

Parathyroid hormone therapy for osteoporosis

- PTH is an **84-amino** acid polypeptide secreted by the parathyroid glands in response to relatively small changes in serum calcium. PTH is one of the two major hormones modulating calcium and phosphate homeostasis; the other is calcitriol.
- **Intermittent administration** of recombinant human PTH (both full-length 1-**84** or fragment 1-**34**) has been shown to stimulate bone formation more than resorption.

Candidates

- **Not used as a first-line drug** for treatment or prevention of osteoporosis.
- **Severe osteoporosis** (T-score of -3.5 or below even in the absence of fractures; T-score of -2.5 or below plus a fragility fracture)
- Who are **unable to tolerate bisphosphonates**
- Who **fail** other osteoporosis therapies
- Selected men and women with **glucocorticoid-induced osteoporosis.**

Contraindications/precautions

- Primary or secondary **hyperparathyroidism**
- Other **hypercalcemic** disorders
- Patients who are at increased baseline risk for **osteosarcoma**, such as those with **Paget disease of bone, history of prior radiation therapy, or unexplained elevation of alkaline phosphatase, or pediatric/young adult patients with open epiphyses**.
- Pre-existing **malignancies, renal stones, or renal insufficiency**

Pretreatment evaluation

- Dual-energy x-ray absorptiometry (**DXA**) (if not performed in the past two years)
- Serum **calcium**, **phosphorus**, **creatinine**, **alkaline phosphatase**, **albumin**, 25-hydroxyvitamin D (**25[OH]D**)
- **24-hour urine calcium**, creatinine to evaluate for baseline hypercalciuria

- If hypercalcemia develops, the first step should be a **reduction in calcium** supplementation (no more than 500 mg calcium daily) and/or **temporary cessation of vitamin D** with repeat measurement of the serum **calcium 24 hours after** the last dose of PTH.
- If hypercalcemia persists, PTH dosing is adjusted to **alternate-day** therapy.
- If hypercalcemia does not resolve, PTH should be **discontinued**.

Standard daily dosing

- The dose of Teriparatide is **20 mcg/day**.
- A multi-dose prefilled **pen** (containing 28 doses) is available.
- It is administered via **subcutaneous** injection into the **thigh or abdominal wall**.
- The **initial dose** should be administered in a setting where the patient can **sit or lay flat**, if symptoms of orthostatic hypotension occur.
- Due to the potential risk of carcinogenicity, PTH treatment should be given for a maximum of **two years**.

Combination therapy

- We suggest not using PTH in combination with other osteoporosis agents.

Monitoring

- Pulse and **blood pressure** should be monitored carefully following the first PTH injection.
- There are no guidelines for when to measure **calcium**, although in the clinical trials, it is usually assessed at several time points including at **baseline, 1, 6, and 12 months.**
- Frequency of **BMD measurements** is subjective, but most investigators would not consider a follow-up BMD for at least **one to two years**.

Duration of therapy

- PTH treatment should be limited to those most severely affected and for a maximum of **two years**.

After PTH

- We typically prescribe an anti resorptive, preferably a **bisphosphonate**, after PTH treatment is discontinued.
- The goal is to preserve or increase gains in BMD acquired with PTH alone. Denosumab (women or men) or raloxifene (women) are **alternatives** for individuals who are unable to tolerate oral or intravenous bisphosphonates.

- Postmenopausal women (n = 27) who received teriparatide for 24 months followed by denosumab for 24 months had increases in BMD at the lumbar spine, femoral neck, and total hip of 8.6, 5.6, and 4.7 percent, respectively, during the 24 months of denosumab therapy .

Retreatment with PTH

- We **do not recommend retreatment** with teriparatide, particularly in patients who have already received a two-year course, owing to the lack of fracture efficacy and safety data with longer-term therapy and to cost.

Adverse events

- **Hypercalcemia and hypercalciuria** are the two most common side effects of both types of PTH treatment.
- Occasional **hypotension** or **tachycardia** can occur with the first few doses. **Nausea** and **headache** are reported among individuals treated with teriparatide

- Serum uric acid increases with teriparatide and 1-84 PTH, and in some subjects may precipitate an attack of **gout** .
- The most theoretically worrisome adverse event is the development of **osteosarcoma**. Although outside groups have studied the potential risk for osteosarcoma in humans and concluded there was minimal risk, the US Food and Drug Administration (FDA) contends that PTH therapy be **limited to two years**.

- Of more than **one million patients** worldwide treated with teriparatide, there have been **three** reported case of osteosarcoma.
- Causality between teriparatide and osteosarcoma could not be clearly established in these cases.

EFFICACY

- Teriparatide is an anabolic therapy that results in significant increases in BMD.
- As an example, in the **Fracture Prevention Trial** of teriparatide, **1637 postmenopausal women** with previous **vertebral fractures** were assigned to receive PTH 20 mcg/day subcutaneously or placebo.
- After 18 months of treatment, the following results were seen:
- When compared with placebo, BMD increased by **9** and **3** more percentage points in the lumbar spine and femoral neck, respectively.

PTH effect on fracture

- In addition to improvements in BMD, PTH treatment for at least 18 months **markedly reduces the risk of spine fractures** in postmenopausal women with osteoporosis.
- The risk reduction becomes apparent **after six months** of treatment, and the effect is not dose dependent nor does it depend upon the type of PTH. However, **non-vertebral fracture** efficacy has only been established for teriparatide (PTH 1-34).

Denosumab for osteoporosis

- **Denosumab** is a fully human **monoclonal antibody** to the receptor activator of nuclear factor kappa B ligand (RANKL), an osteoclast differentiating factor.
- It **inhibits osteoclast formation**, decreases bone resorption, increases bone mineral density (BMD), and reduces the risk of fracture.

Candidates for therapy

- **Denosumab** is not considered initial therapy for most patients with osteoporosis.
- Denosumab could 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 or who have markedly impaired renal function.**

- **Denosumab** is an option for patients who are **intolerant** of or **unresponsive** to other therapies (including intravenous bisphosphonates) and in those with **impaired renal function.**
- Denosumab may have a role in **men** who are intolerant of or unresponsive to other therapies and in those with impaired renal function**.**

- Given the absence of long-term safety data and the availability of other agents, denosumab is **not** recommended for osteoporosis **prevention**.
- Denosumab is **not** intended for use in **premenopausal women or children**.

- The **reduction in vertebral fracture** noted with denosumab is **similar** to the reductions reported for subcutaneous teriparatide and intravenous zoledronic acid, and greater than that reported for oral alendronate.

Pretreatment evaluation

- The evaluation of patients who may receive denosumab is the **same as** the evaluation recommended for all patients with osteoporosis.

Dosing

- Denosumab (60 mg) is administered by **subcutaneous injection once every six months**.
- It may be administered in the **upper arm, thigh, or the abdomen**. It is available in a single-use prefilled syringe or a single-use vial. The vial requires a 27 gauge needle with syringe to withdraw and inject the 1 mL dose. Denosumab should be stored in the refrigerator and brought to room temperature by removing from the refrigerator 15 to 30 minutes before administration.

- **Serious infections and skin reactions** were reported more frequently in the denosumab than in the placebo group.
- **Monitoring the bone density** response to denosumab therapy is similar to the monitoring of other osteoporosis therapies.

Monitoring

- Patients with **chronic kidney disease** (creatinine clearance **<30** mL/min, including patients receiving **dialysis**) and/or other conditions that predispose to **hypocalcemia** (eg, malabsorption syndromes) are at higher risk for hypocalcemia following denosumab administration than patients without these conditions. **Calcium should be measured** in such patients approximately **10 days** after denosumab administration.

Duration of therapy

- We do not generally discontinue **denosumab** after a given treatment period. However, some clinicians may choose to stop denosumab after long-term use (due to concerns about cost or potential adverse effects) if the BMD rise is substantial and T-scores show **osteopenia**, following the discontinuation with one dose of intravenous **zoledronic acid** to protect against bone loss in the ensuing year.

- Continuous denosumab treatment (**four years**) increased BMD at the **LS** (**9.4 to 11.8 percent**) and total **hip** (**4.0 to 6.1 percent**).

Emerging therapies

- Sclerostin inhibitors (romosozumab 210 mg monthly)
- PTH1 receptor ligands (Abaloparatide)
- Integrin antagonists
- Cathepsin K inhibitors