Recommendations for Treatment Initiation in Osteoporosis

Author: Rachelle Davis, PharmD

Key Changes from 2021 Osteoporosis Pearl

- Current guidelines recommend using cholecalciferol 5,000 IU PO daily for vitamin D repletion
  - This recommendation change was made due to 25(OH)D assays not all measuring 25(OH)D_2, and high levels of 25(OH)D_2 inaccurately skewing overall 25(OH)D results on many assays
- A maintenance dose is also now recommended to be in the range of 1,000 – 2,000 IU daily

Executive Summary

Prior to initiation of pharmacotherapy, ensure five fundamental steps are taken to promote bone health, including completing baseline lab work (at bare minimum a CMP and vitamin D level), treating vitamin D insufficiency or deficiency, proper calcium intake, implementing lifestyle modifications and employing fall prevention strategies. Alendronate is the recommended first-line treatment in most patients unless contraindications are present or in certain severe situations.

Acronyms	
BMD	Bone mineral density
CMP	Comprehensive metabolic panel
FIT	Fracture Intervention Trial
GFR	Glomerular filtration rate
GI	Gastrointestinal
PPI	Proton pump inhibitors
RR	Relative risk

Lab Monitoring

Once a patient is diagnosed with osteoporosis (refer to Osteoporosis Diagnosis Table), the next step prior to initiating any treatment is to complete baseline lab work. The minimum necessary lab work prior to treatment must include a comprehensive metabolic panel and a vitamin D level (25[OH]D). Also consider evaluating a complete blood count, intact parathyroid hormone, phosphate and a 24-hour urine collection for calcium, sodium and creatinine. Additional testing is recommended to detect secondary osteoporosis.

Vitamin D Repletion

Vitamin D not only plays a role in calcium absorption, but optimal vitamin D levels may help to enhance the response to pharmacotherapy – especially with bisphosphonates, increase BMD and prevent fractures. If the patient has a vitamin D deficiency to start and it isn't corrected, you may not get as big of a bang for your buck with treatment as you would if the patient has a normal vitamin D level. Vitamin D deficiency is common in patients with osteoporosis, and therefore all patients with osteoporosis should be considered at risk for deficiency.

Recommendations for vitamin D repletion

- Ergocalciferol or cholecalciferol 50,000 IU PO weekly x eight weeks
- Recheck vitamin D following eight weeks of therapy
- Recommended maintenance therapy is cholecalciferol 2,000 IU PO daily
- Recheck vitamin D at six months and then yearly
- Maintain vitamin D level of ≥ 30 ng/mL, can consider target range of 40 – 80 ng/mL

Fundamental Measures for Bone Health

- Calcium intake of 1,200 mg/day (dietary plus supplementation)
  - Calcium carbonate
    - Least expensive
    - GI complaints are common

        - Best absorbed when taken with meals
        - Requires gastric acid for absorption – PPIs can inhibit absorption
    - Calcium citrate
        - More expensive
        - More tablets needed to achieve desired dosing
        - Less likely to cause GI complaints
        - Not dependent on gastric acid for absorption
- Limit alcohol intake to no more than two servings per day
- Avoid or stop smoking
- Regular weight-bearing, balance and resistance exercises
- Implement fall prevention strategies

Initial Treatment Selection

When selecting initial therapy, most patients should be started on alendronate. Alendronate is inexpensive to the patient, inexpensive to the healthcare system, and is easy to access. Start alendronate for your patient unless they have any of the following:

- Reduced kidney function, GFR <30 ml/min
- Hypocalcemia, correct prior to initiation of treatment
- Abnormalities of the esophagus that delay esophageal emptying (e.g., stricture, achalasia)
- Inability to stand or sit upright for at least 30 minutes after dosing
- Unable to tolerate due to gastrointestinal disease
    - Use zoledronic acid instead

Results from the FIT found that treatment with alendronate prevented fractures in women across various risk groups:

- Age: RR, 0.49 in women <75 years, 0.62 in women 75 years and older
- BMD: RR, 0.54 in women with a femoral neck BMD <0.59 g/cm, 0.53 in women with BMD ≥0.59 g/cm
- Number of pre-existing vertebral fractures: RR, 0.58 in women with one vertebral fracture, 0.52 in women with two or more

A real-world effectiveness study found oral bisphosphonates reduced clinical vertebral fractures by 24%, lower than in clinical trials, likely related to non-adherence.

If patient is determined to be “very high risk” (i.e., advanced age, frailty, glucocorticoid use, very low T-scores [less than-3] or increased fall risk), may consider initiating treatment with an injectable agent. A referral to bone health or endocrinology can be considered in patients who are very high risk. A referral is recommended if considering use of an anabolic agent (romosozumab, teriparatide or abaloparatide) due to cost, the importance of monitoring patients and tracking administration, and specific considerations for administration and risk stratification.

Additional Information

AMG treatment guidelines and algorithms for bone health:

- Agents for the Treatment of Osteoporosis
- Osteoporosis Screening Guidelines
- Osteoporosis Treatment Algorithm

References

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Osteoporosis Treatment Recommendations – Beyond Orals

Author: Rachelle Davis, PharmD

Executive Summary

PO or IV bisphosphonate are typically recommended as the preferred first line agent for osteoporosis treatment due to cost-effectiveness. Denosumab should be considered as an alternate first-line agent if bisphosphonates are not tolerated or contraindicated.

Acronyms	
AACE	American Association of Clinical Endocrinology
ACE	American College of Endocrinology
ACP	American College of Physicians
BMD	Bone mineral density
ES	Endocrine Society
FREEDOM	Future Revascularization Evaluation in Patients with Diabetes Mellitus
HORIZON-PFT	Health Outcomes and Reduced Incidence with Zoledronic acid Once-Yearly Pivotal Fracture Trial
RANKL	Receptor activator of nuclear factor kappa-B ligand

Key Takeaways

- Zoledronic acid is a once-yearly IV infusion requiring yearly lab monitoring, compared to denosumab which is given subcutaneously every six months and requires lab monitoring every six months
- Timely injections of denosumab are crucial as risk of vertebral fractures increases within one month of discontinuation or missed denosumab dose
- There are limited head-to-head comparative studies between zoledronic acid and denosumab – one cohort study using U.S. claims found no difference in serious adverse effects or effectiveness
- Zoledronic acid is preferred over denosumab due to cost when not contraindicated (renal impairment, bisphosphonate related bone or muscle pain, or infusion reaction)
- Anabolic agents (romosozumab, teriparatide, and abaloparatide) are considered first-line treatment options for patients at very high risk of fracture*; this paper does not discuss the use of anabolic agents as is it recommended to refer patients to endocrinology or bone health if considering the use of one

*Indicators of very high fracture risk in patients with low bone density would include advanced age, frailty, glucocorticoids, very low T scores or increased fall risk (refer to AMG Osteoporosis Treatment Algorithm for treatment initiation recommendations)

Table 1: Comparing and Contrasting Zoledronic Acid and Denosumab (Prolia)

	Zoledronic Acid (Bisphosphonate)	Denosumab (RANKL Inhibitor)
Route of administration	IV infusion (15 mins)	Subcutaneous
Frequency	Once yearly	Every six months
Generic availability	Yes	No
Estimated yearly drug cost *(additional administration fee not included)*	$270	$3,069
Monitoring parameters	• Serum creatinine yearly (avoid in renal impairment) • Vitamin D yearly (maintain above 30 ng/mL)	• Serum creatinine every six months (impairment can increase risk of hypocalcemia) • Calcium every six months (risk for hypocalcemia following injections) • Vitamin D yearly (maintain above 30 ng/mL) • Avoid abrupt discontinuation: risk of vertebral fractures significantly increases within one month of discontinuation of denosumab

Avera Treatment Recommendations		
AMG treatment algorithm	• High risk: second-line agent after alendronate • Very high risk: first-line agent	
ACO considerations	Highly encourage over denosumab if oral agents are not preferred, tolerated or are contraindicated	Covered under Medicare Part B and impacts ACO cost
Avera Health Plans considerations	N/A	Medical drug preauthorization: member must fail or have an intolerance to or contraindication to bisphosphonate therapy (PO and IV) prior to denosumab approval
Contraindications	• Renal impairment • Bisphosphonate-related bone or muscle pain • Infusion reaction	N/A

The HORIZON PFT studied the use of once-yearly zoledronic acid compared to placebo in postmenopausal women with an appropriate diagnosis of osteoporosis. Zoledronic acid resulted in a three-year incidence for vertebral fracture of 3.3% compared to 10.9% with placebo, a 70% reduction (hazard ratio, 0.3; 95% CI, 0.24 to 0.38). The incidence of hip fracture was 1.4% with zoledronic acid and 2.5% with placebo, a 41% reduction (hazard ratio, 0.59; 95% CI, 0.42 to 0.83). Significant findings in the secondary efficacy end points also support the use of zoledronic acid (nonvertebral fracture, any clinical fracture, clinical vertebral fracture, and two or more morphometric vertebral fractures). BMD increased significantly at the total hip, lumbar spine and femoral neck with zoledronic acid compared to placebo. The biochemical markers of bone turnover all decreased significantly in those treated with zoledronic acid as well. Zoledronic acid caused a transient increase in serum creatinine level. There were no reports of spontaneous osteonecrosis of the jaw.

The FREEDOM trial randomized postmenopausal women with osteoporosis to denosumab or placebo every six months for three years. The three-year incidence of new vertebral fracture was 2.3% with denosumab compared to 7.2% with placebo, a 68% relative risk reduction (P<0.001). Denosumab also decreased the risk of nonvertebral fracture by 20% (6.5% vs 8.0%) and hip fracture by 40% (0.7% vs 1.2%). BMD increased significantly at the lumbar spine and total hip, and bone turnover markers were increased with denosumab.

There are limited head-to-head comparative studies between denosumab and zoledronic acid for the treatment of osteoporosis. One cohort study using claims data from a commercial U.S. health plan found that the use of denosumab was not associated with excess risk for serious infections or composite cardiovascular events compared to zoledronic acid. A difference in effectiveness based on risk of incident non-vertebral osteoporotic fracture was not observed either.

Clinical practice guidelines recommend that pharmacologic treatment selection be based off patient-specific factors. AMG Treatment Algorithm recommendations align closely with the recommendations from the AACE/ACE 2020. Other clinical practice guidelines provide similar recommendations, although these tend to favor use of zoledronic acid over denosumab.

Table 2: Treatment Guideline Recommendations for Patients at High Risk of Fracture

	First Line	Alternate First Line
AACE/ACE 2020	Alendronate Risedronate **Zoledronic acid** **Denosumab**	Ibandroate Raloxifene
ACP 2023	Alendronate Risedronate **Zoledronic acid**	**Denosumab** (for those with contraindications to or experience adverse effects of bisphosphonates)
ES 2020	**Bisphosphonate** (PO or IV)	Denosumab

Table 3: Treatment Guidelines for Patients at Very High Risk of Fracture

	First Line	Alternate First Line
AACE/ACE 2020	Zoledronic acid Denosumab Abaloparatide Teriparatide Romosozumab	Alendronate Risedronate
ACP 2023	Romosozumab Teriparatide	Initiate **bisphosphonate** after completion of first-line agent
ES 2020	Abaloparatide x 2 years Teriparatide x 2 years Romosozumab x 1 year	Initiate **bisphosphonate** or **denosumab** after completion of first-line agent

Additional Resources

AMG treatment guidelines and algorithms for bone health:

- Agents for the Treatment of Osteoporosis
- Osteoporosis Screening Guidelines
- Osteoporosis Treatment Algorithm

References

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Considerations for Bisphosphonate Breaks

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Executive Summary

Bisphosphonates remain in bone matrix for many years and produce residual effects on BMD after discontinuation of long-term use. Effects are expected to persist for two to three years for alendronate and three years for zoledronic acid. The combination of residual effects from bisphosphonates and risk for adverse effects suggest that a bisphosphonate drug holiday should be considered for certain patients. Assess for appropriateness of a bisphosphonate holiday after three years of IV therapy or five years of oral therapy. Reassess every two to three years regardless of whether a drug holiday was implemented or not.

Acronyms	
BMD	Bone mineral density
BP	Bisphosphonate
FIT	Fracture Intervention Trial
FLEX	FIT Long-term Extension

Key Takeaways

- Increased risk of atypical femoral fracture with increased therapy duration of bisphosphonates
- Risk of vertebral fracture is reduced with continued bisphosphonate use
- Duration of bisphosphonate treatment and the decision to take a drug break should be individualized based on patient's values, preferences and risk of fracture
- Weigh the risk versus benefit of a bisphosphonate drug holiday on patient specific factors (e.g., fracture before or during therapy, BMD T-Score, fracture risk)
- Drug holidays are not recommended for denosumab due to the significant increased risk of vertebral fractures following discontinuation

Recommendations from the American Society for Bone and Mineral Research are outlined in the figure below but note that these are based on limited data and clinical experience.

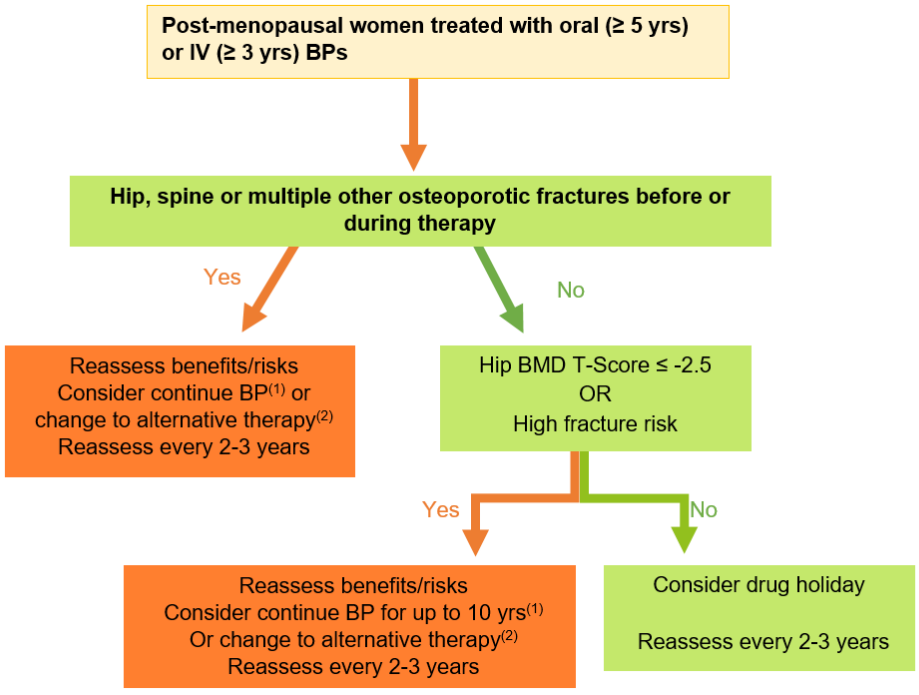

Figure 1: Recommendations from the American Society for Bone and Mineral Research

Multiple other clinical practice guidelines have similar recommendations on when to reassess pharmacologic therapy and the patient's fracture risk, however the American Society for Bone and Mineral Research provides more specificity on individual patient factors that can help to guide the decision on whether to withhold therapy or not.

There is no data to guide the reinstitution of therapy. Guideline recommendations vary slightly; however, it should be based on individual patient characteristics such as increase in fracture risk, decrease in BMD, increase in bone turnover markers or fracture. Consider reassessing patient's risk at intervals of every two to three years, or earlier in patients with a new fracture or considering anticipated accelerated bone loss (e.g., initiation of aromatase inhibitor or glucocorticoid therapy).

Evidence Supporting Bisphosphonate Breaks

The FLEX trial (an extension of FIT) evaluated the effects on BMD in postmenopausal women who continued on alendronate for a total of 10 years compared to patients who discontinued after approximately five years. Results of this study found that women who continued alendronate for five additional years maintained higher BMD at the hip and spine and bone remodeling remained reduced. Those who discontinued after five years of treatment experienced small decreases in BMD and a gradual increase in bone remodeling, however that remained below pretreatment levels. There was no difference in rates of nonvertebral fractures between groups, however a significantly lower risk of clinical vertebral fractures was seen in those who continued on alendronate (5.3% with placebo versus 2.4% with alendronate; RR, 0.45). The authors concluded that in most women, discontinuation of alendronate after five years does not significantly increase risk of fracture, but in women who have a vertebral fracture or very low T score (<-3), there may be benefit to continuing alendronate beyond five years.

An extension of Horizon-PFT was conducted to evaluate the efficacy and safety of continuing zoledronic acid for six years versus discontinuing after three years of treatment. After six years, BMD in both groups remained above pretreatment values, although those who continued on zoledronic acid-maintained BMD gains while those who discontinued did experience some reduction in BMD. There was a 49% lower risk for morphometric vertebral fractures in those who continued treatment but no significant differences in clinically evident vertebral fractures or nonvertebral fractures. Like the FLEX trial, the authors concluded that many women may discontinue treatment after three years, however women at high risk for fracture may benefit from continuing treatment.

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DXA Scans for Monitoring Treatment in Osteoporosis

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Executive Summary

The optimal interval for repeating DXA scans to monitor treatment for osteoporosis is uncertain and different monitoring intervals for DXA scans may be appropriate in specific circumstances (e.g., patients on medications or treatments that cause rapid bone loss or for monitoring anabolic therapies). AACE/ACE guidelines recommend testing every two years (consider checking after one year if significant ongoing risk factors for bone loss) to identify those who have significant bone loss and continue at this frequency until findings are stable.

Acronyms	
AACE	American Association of Clinical Endocrinologists
ACE	American College of Endocrinology
BHOF	Bone Health and Osteoporosis Foundation
BMD	Bone mineral density
BTM	Bone turnover markers
DXA	Dual X-ray absorptiometry
LSC	Least significant change
NOF	Non-ossifying fibromas

Key Takeaways

- Utilize DXA scans during treatment for osteoporosis when there are concerns for adherence or treatment failure
- Consider the entire clinical picture when applying DXA information to clinical situations during osteoporosis treatment and before making decisions regarding treatment changes
- Reassess annually for response to therapy/fracture risk (consider DXA every one to two years)
- In general, stable or increasing BMD on DXA should be considered an indication of successful treatment

Argument against frequent DXA scans:

- Changes in bone density over short intervals are often smaller than the measurement error of most DXA scanners
- DXA changes do not always correlate with probability of fracture
- Weak evidence to support the use of DXA scans for monitoring treatment response
- May be limited to frequency as defined by insurance carrier
- Multifactorial causes for inaccuracies (e.g., inadequate training in DXA testing and interpretation, positioning errors, failure to compare results and comparing results from different machines)

Argument for DXA scans:

- May identify patients who are not adhering to treatment
- May identify patients who have a secondary cause for bone loss
- May identify patients who fail therapy

Treatment failure and consideration for treatment change should be considered only if: BMD decrease that exceeds the LSC for the scanning facility occurs over more than one serial scan completed while the patient is compliant on the treatment being evaluated; and/or the patient experiences more than one low-trauma fracture while on treatment.

Table 1: Guideline Recommendations for Monitoring Drug Therapy

Guideline	Recommendation for Frequency of DXA	Definition of Treatment Success and Failure
AACE/ACE 2020 guidelines	Repeat DXA every 1-2 years until findings are stable; continue with follow-up DXA every 1-2 years or longer depending on clinical circumstances	**Successful treatment**: stable or increasing BMD with no evidence of new fractures or vertebral fracture progression. Consider alternate therapy: recurrent fractures or significant bone loss. **Treatment failure**: two or more fragility fractures
American College of Physicians 2017 guidelines	Recommends against repeat DXA during 5-year pharmacologic treatment period	
NOF 2014 guidelines	Repeat DXA 1-2 years after initiating therapy and then every 2 years. More or less frequent testing may be necessary in certain clinical situations.	
2019 Endocrine Society guidelines	Repeat DXA every 1-3 years to assess the response to treatment.	**Treatment failure**: loss of BMD greater than the LSC over 2 years and BTM decrease on antiresorptive drugs less than the LSC; 2 or more fractures while on therapy

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