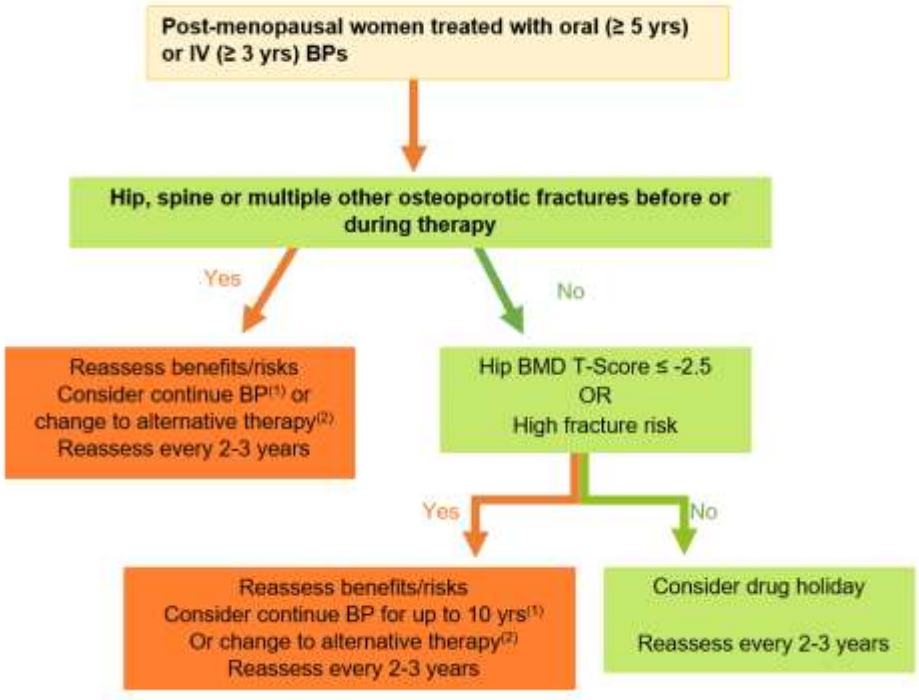
Take a Break…from Bisphosphonates! Considerations for Bisphosphonate Drug Holidays

Executive Summary: Weigh the risk vs. benefit of bisphosphonate drug holidays based on patient specific factors. Assess for appropriateness of a bisphosphonate holiday after 3 years of IV therapy or 5 years of oral therapy. Reassess every 2-3 years regardless of whether a drug holiday was implemented or not.

Note: Drug holidays are not recommended for denosumab due to the significant increased risk of vertebral fractures following discontinuation

Bisphosphonates remain in bone matrix for many years and produce residual effects on bone mineral density (BMD) after discontinuation of long term use. Effects are expected to persist for 2-3 years for alendronate and 3 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. Bisphosphonate therapy duration should be individualized based on patient's values, preferences, risk of fracture, and risk/benefit analysis.[1]

Risks associated with continuation: risk of atypical femoral fracture increases with therapy duration
Benefits associated with continuation: risk of vertebral fracture is reduced in high-risk patients



Recommendations from the American Society for Bone and Mineral Research are outlined in the figure above, but note that these are based on limited data and clinical experience[1].

Multiple other Clinical Practice Guidelines[2-5] 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 2-3 years, or earlier in patients with a new fracture, or in light of anticipated accelerated bone loss (e.g. initiation of aromatase inhibitor or glucocorticoid therapy)[1].

Evidence supporting bisphosphonate holidays

The FLEX trial[6] (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 5 years. Results of this study found that women who continued alendronate for 5 additional years maintained higher BMD at the hip and spine, and bone remodeling remained reduced. Those who discontinued after 5 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 vs 2.4% with alendronate; RR, 0.45). The authors concluded that in most women, discontinuation of alendronate after 5 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 5 years.

An extension of Horizon-PFT[7] was conducted to evaluate the efficacy and safety of continuing zoledronic acid for 6 years versus discontinuing after 3 years of treatment. After 6 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 on treatment, but no significant differences in clinically evident vertebral fractures or nonvertebral fractures. Similarly to the FLEX trial, the authors concluded that many women may discontinue treatment after 3 years, however women at high risk for fracture may benefit from continuing treatment.

Sources:

1. Adler RA, Fuleihan GE, Bauer DC, et al. Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2016;31(1):16-35. DOI: 10.1002/jbmr.2708
2. Eastell R, Rosen, CJ, Black DM, et al. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol & Metab*. 2019;104:1595-1622. DOI: 10.1210/jc.2019-00221
3. Qaseern A, Forciea MA, McLean RM, et al. Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Med and Women: A Clinical Practice Guideline Update From the American College of Physicians. *Ann Intern Med*. 2017;166:818-39. DOI: 10.7326/M15-1361
4. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis – 2020 Update. *Endocr Pract*. 2020;26:1-44. https://doi.org/10.4158/GL-2020-0524SUPPL

5. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int*. 2014;25(10):2359-81. DOI: 10.1007/s00198-014-2794-2
6. Black DM, Schwartz AV, Ensrud KE, et al. Effects of Continuing or Stopping Alendronate After 5 Years of Treatment: The Fracture Intervention Trial Long-Term Extension (FLEX): A Randomized Trial. *JAMA*. 2006;296(24):2927-38. DOI: 10.1001/jama.296.24.2927
7. Black DM, Reid, IR, Boonen S, et al. The Effect of 3 Versus 6 Years of Zoledronic Acid Treatment of Osteoporosis: A Randomized Extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res*. 2012;27(2):243-54. DOI: 10.1002/jbmr.1494

When and How to Use DXA Scans for Monitoring Treatment in Osteoporosis – The Biggest Gray Area in Osteoporosis Management

Executive Summary: 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.

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)[1]. AACE/ACE guidelines recommend testing every 2 years (consider checking after 1 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[2].

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

In general, stable or increasing BMD on DXA should be considered an indication of successful treatment.

Treatment failure and consideration for treatment change should be considered only if: BMD decrease that exceeds the LSC (least significant change) 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.

Guideline recommendations for monitoring drug therapy

Guideline	Recommendation for frequency of DXA	Definition of treatment success and failure
AACE/ACE 2020 guidelines[2]	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: 2 or more fragility fractures
American College of Physicians 2017[3] guidelines	Recommends against repeat DXA during the 5-year pharmacologic treatment period	
NOF 2014 guidelines[4]	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[5]	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

Sources:

1. American College of Rheumatology. Don't routinely repeat DXA scans more often than once every two years. February 21, 2013. Accessed May 7, 2021. Choosing Wisely website. https://www.choosingwisely.org/clinician-lists/american-college-rheumatology-routine-repeat-dxa-scans-more-than-once-every-two-years/
2. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis – 2020 Update. *Endocr Pract*. 2020;26:1-44. https://doi.org/10.4158/GL-2020-0524SUPPL
3. Qaseern A, Forciea MA, McLean RM, et al. Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Med and Women: A Clinical Practice Guideline Update From the American College of Physicians. *Ann Intern Med*. 2017;166:818-39. DOI: 10.7326/M15-1361
4. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int*. 2014;25(10):2359-81. DOI: 10.1007/s00198-014-2794-2
5. Eastell R, Rosen, CJ, Black DM, et al. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol & Metab*. 2019;104:1595-1622. DOI: 10.1210/jc.2019-00221

You're Diagnosing Your Patient with Osteoporosis, So Now What? Recommendations for Treatment Initiation

Executive Summary: Prior to initiation of pharmacotherapy, ensure 5 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.

Once a patient is diagnosed with osteoporosis, 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-hr urine collection for calcium, sodium and creatinine. Additional testing is recommended to detect secondary osteoporosis.[1]

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.[1]

Recommendations for vitamin D repletion[1]

- Ergocalciferol or cholecalciferol 50,000 IU PO weekly x 8 weeks
- Recheck vitamin D following 8 weeks of therapy
- Recommended maintenance therapy is cholecalciferol 2,000 IU PO daily
- Recheck vitamin D at 6 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[1]

- 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 – proton pump inhibitors (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 2 servings per day
- Avoid or stop smoking
- Regular weight-bearing, balance, and resistance exercises
- Implement fall prevention strategies

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 Fracture Intervention Trial (FIT)[2] found that treatment with alendronate prevented fractures in women across various risk groups:

- Age: relative risk [RR], 0.49 in women <75 years, 0.62 in women 75 years and older
- Bone mineral density (BMD): RR, 0.54 in women with a femoral neck BMD <0.59 g/cm^2, 0.53 in women with BMD ≥0.59 g/cm^2
- Number of preexisting vertebral fractures: RR, 0.58 in women with 1 vertebral fracture, 0.52 in women with 2 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[3].

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.[1] 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.

For additional information:
AMG treatment guidelines and algorithms for Bone Health:

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

Avera Standardized Patient Education Resources

- Osteoporosis: What is it and who is at risk?
- Preventing Bone Loss
- Detecting Osteoporosis
- Treatments for Osteoporosis

Sources

1. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis – 2020 Update. *Endocr Pract*. 2020;26:1-44. https://doi.org/10.4158/GL-2020-0524SUPPL
2. Ensrud KE, Black DM, Palermo L, et al. Treatment with Alendronate Prevents Fractures in Women at Highest Risk: Results From the Fracture Intervention Trial. *Arch Intern Med*. 1997;157:2617-24. PMID: 9531231
3. Yusuf AA, Cummings SR, Watts NB, et al. Real-world effectiveness of Osteoporosis Therapies for Fracture Reduction in Post-Menopausal Women. *Arch Osteoporos*. 2018;13:33. DOI: 10.1007/s11657-018-0439-3

What to Consider if Your Patient with Osteoporosis Cannot Use an Oral Agent

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.

Comparing and contrasting zoledronic acid and denosumab (Prolia)

	Zoledronic Acid (bisphosphonate)	**Denosumab (RANKL inhibitor)**
Route of administration	IV infusion (15 minutes)	Subcutaneous
Frequency	Once yearly	Every 6 months
Generic Availability	Yes	No
Estimated yearly drug cost *(additional administration fee not included in this price information)*	$270	$3,069
Monitoring Parameters	Serum creatinine yearly (avoid in renal impairment) Vitamin D yearly (maintain above 30 ng/mL)	Serum creatinine every 6 months (impairment can ↑ risk of hypocalcemia) Calcium every 6 months (risk for hypocalcemia following injections) Vitamin D yearly (maintain above 30 ng/mL) Avoid abrupt discontinuation: Risk of vertebral fractures significantly increases within 1 month of discontinuation of denosumab
Avera Treatment Recommendations		
AMG Treatment Algorithm	High risk: Second line agent after alendronate Very high risk: First line agent	High risk: Second line agent after alendronate Very high risk: First line agent
ACO Considerations	Highly encourage zoledronic acid over denosumab if oral agents are not preferred, tolerated, or are contraindicated Denosumab is covered under Medicare Part B and impacts ACO cost	
Avera Health Plan Considerations		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	

The HORIZON Pivotal Fracture Trial (PFT)[1] 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 3 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 2 or more morphometric vertebral fractures). Bone mineral density 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[2] randomized postmenopausal women with osteoporosis to denosumab or placebo every 6 months for 3 years. The 3 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%). Bone mineral density 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[3].

Clinical Practice Guidelines[3-5] recommend that pharmacologic treatment selection be based off of 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.

Treatment Guideline Recommendations

	First Line	Alternate First Line
AACE/ACE 2020[4] *High Risk/no prior fractures*	Alendronate Risedronate **Zoledronic acid** **Denosumab**	Ibandroate Raloxifene
AACE/ACE 2020[4] *Very High Risk/prior fractures*	**Zoledronic acid** **Denosumab** Abaloparatide Teriparatide Romosozumab	Alendronate Risedronate
ACP 2017[5]	Alendronate Risedronate **Zoledronic acid** **Denosumab** *Clinicians should select generic drugs when possible*	
ES 2019[6]	**Bisphosphonate** (PO or IV)	**Denosumab**

For additional information:
AHID policy on Prolia

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Sources:

1. Black DM, Delmas PD, Eastell R, et al. Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis. *N Engl J Med*. 2007;356(18):1809-22. DOI: 10.1056/NEJMoa067312
2. Cummings ST, San Martin J, McClung MR, et al. Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporsis. *N Engl J Med*. 2009;361:756-65. DOI: 10.1056/NEJMoa0809493
3. Choi, N, Solomon DH, Tsacogianis TN, et al. Comparative Safety and Effectiveness of Denosumab Versus Zoledronic Acid in Patients with Osteoporosis: A Cohort Study. *J Bone Miner Res*. 2017;32:611-7. DOI: 10.1002/jbmr.3019
4. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis – 2020 Update. *Endocr Pract*. 2020;26:1-44. https://doi.org/10.4158/GL-2020-0524SUPPL
5. Qaseern A, Forciea MA, McLean RM, et al. Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Med and Women: A Clinical Practice Guideline Update From the American College of Physicians. *Ann Intern Med*. 2017;166:818-39. DOI: 10.7326/M15-1361
6. Eastell R, Rosen, CJ, Black DM, et al. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol & Metab*. 2019;104:1595-1622. DOI: 10.1210/jc.2019-00221