Introduction

This Clinician Guide was developed to assist Primary Care physicians and other clinicians in the primary prevention, screening, and treatment of low bone mass and osteoporosis. It is not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners.

Definitions

- Bone mass status is defined by T-score derived by Dual-Energy X-ray Absorptiometry (DXA) measured at total proximal femur (total hip), femoral neck, and lumbar spine:
  - Normal bone mass: ≥ -1.0
  - Low bone mass (formerly referred to as osteopenia): -1.1 to -2.4
  - Osteoporosis: ≤ -2.5
- A fragility fracture is defined as a fracture of any bone, excluding fingers, toes, face or skull, sustained from a fall at standing height or less.

Key Points

- For all adults, encourage a bone-healthy lifestyle to reduce the risk of osteoporosis. This includes regular weight-bearing and muscle-building exercise, smoking cessation, and adequate daily intake of calcium and Vitamin D
- In post-menopausal women with low bone mass (osteopenia), if either of the following risk factors are present, pharmacologic therapy should be considered:
  - A FRAX 10-year risk of hip fracture ≥ 3% or a FRAX 10-year risk of major osteoporotic fracture ≥ 20%
  - Increased risk of falling
- In men and women with osteoporosis, alendronate is preferred therapy. Other bisphosphonates (zoledronic acid, risedronate, ibandronate) may be prescribed if alendronate cannot be used.
- For women, over 65 years who are not receiving prescription anti-fracture medication, rescreening interval is determined by T-score:
  - ≥ -1.4: 10 years
  - -1.5 to -1.9: 5 years
  - -2.0 to -2.4: 2 years
- Consider a ‘drug holiday’ after 5 years of oral and 3 years of intravenous bisphosphonate use
- Bisphosphonate therapy should not be given for greater than 10 years of oral and 6 years of intravenous treatment.
Prevention and Treatment of Osteoporosis

All Adults: Non-pharmacologic primary prevention of Osteoporosis

**Lifestyle Choices**
- For all adults, consider recommending regular weight-bearing and muscle-building exercise for prevention of osteoporosis and falls.
- For all adults who are current smokers, consider recommending smoking cessation for prevention of osteoporosis and fragility fractures.

**Fall Prevention**
- For adults at increased risk of falling, consider safety proofing their residence.
  - Home safety proofing includes removing rugs, adding grab bars, establishing adequate lighting (e.g., nightlights), and securing electrical cord placement.
- For post-menopausal women and men aged 50 years or older, the routine use of hip protectors to reduce the risk of hip fractures is not recommended.

**Supplementation**
- For all adults, advise patients to consume the recommended total daily intake* of calcium and vitamin D.
- Consider prescribing supplemental calcium and vitamin D if recommended daily intake is not achieved through diet alone.
- In adults aged 50 years or older without osteoporosis, do not screen for Vitamin D deficiency.

*USDA recommended daily allowance (RDA):

**Calcium**
- Women:
  - Ages 19-50 years: 1,000 mg
  - Ages ≥ 51 years: 1,200 mg
- Men:
  - Ages 19-70 years: 1,000 mg
  - Ages >70 years: 1,200 mg

**Vitamin D**
- All adults:
  - Ages 19-70 years: 600 IU
  - >70 years: 800 IU

**Clinical Considerations**
- If supplementation is necessary, vitamin D3 (ergocalciferol) is preferred.
- Calcium carbonate contains the most elemental calcium per dose. It should be taken with food to enhance absorption.
- Calcium citrate contains less elemental calcium than the carbonate salt, but it is better absorbed and may be preferred in patients with reduced gastric acid production or high gastric pH requiring long-term H2 antagonist or proton pump inhibitor therapy and in patients who have undergone bariatric surgery. It is more expensive and usually requires more tablets to be taken per day than calcium carbonate.
Low Bone Mass (T-score -1.1 to -2.4): Pharmacologic treatment

Pharmacological Treatment for post-menopausal women

- Consider treating women with low bone mass (and no history of prior fragility fracture) who have at least one of the following additional risk factors:
  - A FRAX 10-year risk of hip fracture ≥ 3% or a FRAX 10-year risk of major osteoporotic fracture ≥ 20%\(^1\)
  - Increased risk of falling\(^2\)

  Preferred therapy
  - Optimize non-pharmacologic therapies, including vitamin D supplementation, calcium intake and fall prevention efforts (via physical activity or therapy, ambulatory assistive devices, and reduction in sedative/hypnotic medications).
  - Consider prescribing alendronate (70 mg/week) as a first-line therapy, particularly in those with a lowest T score in the range of -2.1 to -2.4 and at least one of the following additional risk factors:
    - A FRAX 10-year risk of hip fracture ≥ 3% or a FRAX 10-year risk of major osteoporotic fracture ≥ 20%\(^1\)
    - Increased risk of falling

  Alternative therapy\(^3\)
  - Consider prescribing risedronate, ibandronate, zoledronic acid or raloxifene (the latter for women with a low cardiovascular risk\(^4\)) for women who cannot tolerate or should not take alendronate.

  Therapies to Avoid
  - Do not prescribe hormone replacement therapy (estrogen or estrogen/progesterone) solely for the treatment of low bone mass.
  - Do not prescribe nasal calcitonin for the treatment of low bone mass.

Clinical Considerations

- Calcium supplementation
  - Use calcium citrate in patients taking proton pump inhibitors (PPIs) or H2 blockers.

- Fall risk
  - Hip fracture risk increases with falling. The most common risk factors for falls include:

\(^1\) For women, whose high FRAX score (>3% for hip fracture and >20% for major osteoporotic fracture) is due in part to long-term, daily use of corticosteroids (>5 mg of prednisone or equivalent therapy), please refer to the recommendation for "Treatment for Men and Women Taking Corticosteroid Therapy."

\(^2\) The most common risk factors for falls include:
- A history of falls
- Psychoactive medications (sedatives, antipsychotics and antidepressants) anticonvulsants, or antihypertensive medications
- A high number of medications consumed (>4), independent of medication indication
- Strength, gait and balance impairments
- Visual impairment
- Age >80 years old

\(^3\) There is no recommendation for or against the use of teriparatide (PTH) or denosumab in postmenopausal women with low bone mass. Evidence is insufficient to determine benefits and harms of therapy.

\(^4\) Those at increased risk include postmenopausal women with known coronary artery disease, peripheral vascular disease, or cerebrovascular disease; or a combination of diabetes with 1 additional risk factor (age >65, current smoking, hypertension, hyperlipidemia), or a combination of all 4 of the listed risk factors together (Mosca 2001).
A history of falls
- Psychoactive medications (sedatives, antipsychotics and antidepressants) anticonvulsants, or antihypertensive medications
- A high number of medications consumed (>4), independent of medication indication.
- Strength, gait and balance impairments
- Visual impairment
- Age >80 years old

Chronic kidney disease
- Use bisphosphonates with caution in patients with chronic kidney disease and reduced glomerular filtration rate. Current drug monographs state that an estimated GFR <35 mL/min is a contraindication to bisphosphonate use.

Dental hygiene
- Educate patients starting a bisphosphonate about the importance of regular dental cleanings and good dental hygiene. For those patients who have a planned tooth extraction or dental implant surgery, consider delaying the start of bisphosphonate therapy until 3 months after completion of the dental procedure, or until maxillofacial bone healing is complete. Both considerations are based upon the moderate evidence for association of osteonecrosis of the jaw (ONJ) with bisphosphonate use (0.001% to 0.069% per year increased incidence over non-bisphosphonate users).

Choice of alternative therapies
- Consider significant side effects when choosing alternative therapies for patients who do not tolerate alendronate:
  - Zoledronic acid: There is strong evidence for an acute phase reaction within 3 days of zoledronic acid administration (up to 25% increased risk over placebo of any of the following symptoms: pyrexia, myalgia, headache, arthralgia, chills). A 650-mg dose of acetaminophen initiated 45 minutes before zoledronic acid infusion and continuing every 6 hours for 3 days has been shown to reduce severity of symptoms. It is common practice also to ensure the patient is well hydrated prior to infusion.
  - Raloxifene: There is strong evidence for increased hot flashes (2%-7% increase over placebo) and venous thromboembolic events (0.2%-0.7% increased risk) and death due to stroke (0.07% increased risk over placebo) as side effects of raloxifene.

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5 This can be assessed with the timed Get-Up-and-Go test. The test is performed by observing the time it takes a person to rise from an armchair, walk 3 meters (10 feet), turn, walk back, and sit down again. The average healthy adult older than 60 years can perform this task in less than 10 seconds.
6 Recommendations on interruption of bisphosphonate therapy can be found in the ‘discontinuation’ section of this guideline.
Treatment of Osteoporosis: T-score ≤-2.5 or prior fragility fracture

Women

- Preferred therapy
  - Optimize non-pharmacologic therapies, including vitamin D supplementation, calcium intake and fall prevention efforts (via physical activity or therapy, ambulatory assistive devices, and reduction in sedative/hypnotic medications).
  - Prescribe alendronate (70 mg/week) as a first-line therapy for post-menopausal women with osteoporosis (T-score ≤ -2.5 or a prior fragility fracture).

- Alternative therapy
  - Prescribe alternative bisphosphonates, including ibandronate, risedronate and zoledronic acid, for women who cannot tolerate or should not take alendronate.

- Additional therapeutic options
  - Consult with specialty care about prescription of denosumab or teriparatide (PTH) for women who cannot tolerate or should not take bisphosphonates.
  - Consider prescribing raloxifene for women with a low cardiovascular risk who cannot tolerate or should not take bisphosphonates.

- Therapies to Avoid
  - Do not prescribe hormone replacement therapy (estrogen or estrogen/progesterone) solely for the treatment of osteoporosis.
  - Do not prescribe nasal calcitonin for the treatment of osteoporosis.

- Clinical Considerations
  - Calcium supplementation
    - Use calcium citrate in patients taking proton pump inhibitors (PPIs) or H2 blockers.
  - Chronic kidney disease
    - Use bisphosphonates with caution in patients with chronic kidney disease and reduced glomerular filtration rate. Current drug monographs state that an estimated GFR < 35 mL/min is a contraindication to bisphosphonate use.
  - Dental hygiene
    - Educate patients starting a bisphosphonate about the importance of regular dental cleanings and good dental hygiene. For those patients who have a planned tooth extraction or dental implant surgery, consider delaying the start of bisphosphonate therapy until 3 months after completion of the dental procedure, or until maxillofacial bone healing is complete. Both considerations are based upon the moderate evidence for association of osteonecrosis of the jaw (ONJ) with bisphosphonate use (0.001% to 0.069% per year increased incidence over non-bisphosphonate users). 8
  - Choice of alternative therapies
    - Consider significant side effects when choosing alternative therapies for patients who do not tolerate alendronate:
      - Zoledronic acid: There is strong evidence for an acute phase reaction within 3 days of zoledronic acid administration (up to 25% increased risk over placebo of any of the following symptoms: pyrexia, myalgia, headache, arthralgia, chills). A 650-mg dose of acetaminophen initiated 45 minutes before zoledronic acid infusion and continuing every 6 hours for 3 days has been
shown to reduce severity of symptoms. It is common practice also to ensure the patient is well hydrated prior to infusion.

- **Raloxifene:** There is strong evidence for hot flashes (2%-7% increase over placebo) and venous thromboembolic events (0.2%-0.7% increased risk) and death due to stroke (0.07% increased risk over placebo) as side effects of raloxifene.

**Men**

- Consider prescribing alendronate (70 mg/week) as a first-line therapy for men with osteoporosis (T-score ≤ -2.5 or a prior fragility fracture).

**Men and Women Taking Corticosteroid Therapy**

- Consider prescribing alendronate (70 mg/week) or risedronate (35 mg/week) as a first-line therapy for men and women who are taking oral corticosteroid medication at a dose of ≥ 5 mg/day prednisone or equivalent for a duration of 3 months or more and have a FRAX 10-year risk of hip fracture ≥ 3%.
- Consult with specialty care about prescription of teriparatide (PTH) for glucocorticoid-treated patients who cannot tolerate or should not take bisphosphonates.

**Discontinuation of Bisphosphonate Treatment**

- In adults taking bisphosphonates for the treatment of osteoporosis or low bone mass, consider discontinuing therapy after 5 years of oral (alendronate, risedronate, ibandronate) or 3 years of intravenous (zoledronic acid) therapy.
  - Refer to Figures 1,2 and 4
- In adults taking bisphosphonate therapy for the treatment of osteoporosis or low bone mass, bisphosphonate therapy is generally not recommended after 10 years of continuous use of oral (alendronate, risedronate, ibandronate) or 6 years of continuous use of intravenous (zoledronic acid) therapy.
  - Refer to Figures 3-4
Screening for Osteoporosis

Women

- Post-menopausal Women
  - For postmenopausal women aged 65 years and older who are not taking prescription antifracture medication, consider offering a bone mineral density (BMD) test by DXA.
  - For postmenopausal women under age 65 with a 10-year fracture risk of ≥ 9.3%, consider offering a BMD test by DXA.

- Pre-menopausal Women
  - For pre-menopausal women, routine screening for osteoporosis is generally not recommended.

Men

- For men aged 70 years or older and/or with previous fragility fracture, consider offering screening for osteoporosis with a bone mineral density (BMD) test by DXA.

Bone Mineral Density Testing with Dual Energy X-ray Absorptiometry (DXA)

- Measurement Sites
  - Total proximal femur (total hip), femoral neck, and lumbar spine
- Alternative Measurement Sites
  - Forearm (distal one-third of the radius) is acceptable for patients in whom hip and spine BMD cannot be measured or interpreted.

Interpretation

- The lowest T-score from the measurements of the total hip, femoral neck, and lumbar spine (L1 to L4, composite score) is recommended to establish a diagnosis of osteoporosis (T-score ≤ -2.5) or low BMD (T-score -1.1 to -2.4).

DXA Screening Intervals

- For women aged 65 years or older who are not taking prescription antifracture medication (and who have had a baseline BMD test), future rescreening for low BMD with DXA is an option.
  - If DXA testing is obtained, suggested rescreening intervals based on initial T-score (lowest T-score from total hip, femoral neck, or lumbar spine) are as follows:

<table>
<thead>
<tr>
<th>Initial T-Score</th>
<th>Suggested Minimum Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ -1.4</td>
<td>10 years</td>
</tr>
<tr>
<td>-1.5 to -1.9</td>
<td>5 years</td>
</tr>
<tr>
<td>-2.0 to -2.4</td>
<td>2 years</td>
</tr>
</tbody>
</table>

- Evidence is insufficient to recommend a rescreening interval for women aged < 65 years or men.

Clinical Considerations

- Clinicians should assess the patient’s willingness to initiate treatment before deciding to rescreen.
- Clinicians should consider calculating a current FRAX score using the patient’s most recent T-score to make rescreening and treatment decisions.
FIGURE 1: BISPHOSPHONATE “DRUG HOLIDAY” ALGORITHM

Patient has been taking: oral bisphosphonates for a cumulative duration of 5-9 years, or IV bisphosphonates for a cumulative duration of 3-5 years

Order bone density test

Does the patient also meet any of the following indications?
1. Any history of two osteoporotic fractures while on bisphosphonate therapy for six months or more
2. An absolute reduction in bone density of 5% or more between two successive bone density measurements at the same site while consistently taking bisphosphonate therapy
3. T-score < -3.5 at any site or Z score < -2.0

Has patient been adherent to taking bisphosphonate therapy as prescribed?

Is the patient taking an oral bisphosphonate, and has a probable cause of malabsorption? (e.g., PPI therapy, Celiac disease, Crohn disease, history of gastric bypass or bowel resection)

Does the patient have a history of one fragility fracture or a post-therapy T-score of < -2.5?

Ensure adherence to bisphosphonate therapy, and continue therapy for a total duration of up to 10 years (for oral) or a total duration of up to 6 years (for IV) prior to re-evaluation with BMD test

Order labs for evaluation of secondary causes of osteoporosis:
- Comprehensive metabolic panel (which includes calcium, albumin, total protein)
- Complete blood count
- 25-OH vitamin D
- 24-hour urine for calcium and creatinine
- TSH
- TTG and serum IgA
- (In men) 8 am total testosterone

Go to Figure 2 algorithm (“drug holiday in lower risk patients”)

Switch to IV zolendronate and continue therapy for 2-3 years prior to re-evaluation with BMD test

Go to Figure 4 algorithm (“secondary osteoporosis”)
### FIGURE 2: CONSIDERATIONS FOR DRUG HOLIDAY IN LOWER-RISK PATIENTS

#### Consider risk for fragility fracture

<table>
<thead>
<tr>
<th>Favors continuing therapy</th>
<th>Favors bisphosphonate holiday with monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased fall risk (e.g., history of falls, deconditioning, dementia, significant diabeticpolyneuropathy, Parkinson’s).</td>
<td>Normal gait and balance, does not require assistance to stand up or walk (e.g., normal Timed Up and Go (TUG) Test).</td>
</tr>
<tr>
<td>Age ≥70</td>
<td>Age &lt;70</td>
</tr>
<tr>
<td>Taking high risk medications (aromatase inhibitor, androgen deprivation therapy (in men), &gt;5 mg/d of prednisone x 3+ months)</td>
<td>Not taking high risk medications</td>
</tr>
<tr>
<td>Prolonged suppressed TSH (e.g., due to history of thyroid cancer) or history of hyperparathyroidism or rheumatoid arthritis</td>
<td>Normal thyroid and parathyroid function; no history of rheumatoid arthritis</td>
</tr>
</tbody>
</table>

#### Consider patient values

<table>
<thead>
<tr>
<th>Favors continuing therapy</th>
<th>Favors bisphosphonate holiday with monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concerned about risk of fragility fracture (which is more than 10 times more likely than atypical femur fracture or ONJ), and downstream consequences of fragility fracture (e.g., increased frailty, loss of independence)</td>
<td>Concerned about the rare but serious complications of ONJ (≤1%) and/or atypical femur fracture (which goes up with length of use)</td>
</tr>
<tr>
<td>Has no medication side effects</td>
<td>Has medication side effects</td>
</tr>
<tr>
<td>Cost is not a problem</td>
<td>Cost is a problem</td>
</tr>
<tr>
<td>Adherence is not challenging</td>
<td>Adherence is challenging</td>
</tr>
</tbody>
</table>

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**Continue**

- Ensure adherence to bisphosphonate therapy, and **continue therapy** for a total duration of up to 10 years (for oral) or a total duration of up to 6 years (for IV) prior to re-evaluation with BMD

**Discontinue**

- Measure bone density in 2-3 years or upon occurrence of a new fragility fracture
- Currently under development: Figure 5 (“monitoring”)
FIGURE 3: BISPHOSPHONATE DISCONTINUATION ALGORITHM

Patient has been taking: oral bisphosphonates for a cumulative duration of 10+ years, or IV bisphosphonates for a cumulative duration of 6+ years

Yes

STOP BISPHOSPHONATE

Order bone density test

BMD ≤ -2.5 and/or history of fragility fracture

Yes

Does the patient also meet any of the following indications?

4. Any history of 2 osteoporotic fractures while on bisphosphonate therapy for 6 months or more
5. An absolute reduction in bone density of 5% or more between two successive bone density measurements at the same site while consistently taking bisphosphonate therapy
6. T score ≤ -3.5 or Z score ≤ -2.0 at any site
7. Takes one of the following medications currently:
   - Glucocorticoids (prednisone ≥5 mg/d x 3+ months)
   - Aromatase inhibitors
   - Androgen deprivation therapy (in men)

Order labs for evaluation of secondary causes of osteoporosis:
- Comprehensive metabolic panel (which includes calcium, albumin, total protein)
- Complete blood count
- 25-OH vitamin D
- 24-hour urine for calcium and creatinine
- TSH
- TTG and serum IgA
- (In men) 8 am total testosterone

BMD > -2.5 and no history of fragility fracture

Yes

Measure bone density in 2-3 years or upon occurrence of a new fragility fracture

Currently under development: Figure 5 algorithm (“monitoring”)

Go to Figure 4 algorithm (“secondary osteoporosis”)
FIGURE 4: EVALUATION FOR SECONDARY CAUSES OF OSTEOPOROSIS

**MEDICAL HISTORY**

Assess medication causes:
- Glucocorticoids
- Aromatase inhibitors
- Androgen deprivation therapy
- Anti-epileptics (e.g., phenytoin, phenobarbital)
- Excess thyroid replacement
- GnRH agonists (e.g., Lupron)

Assess for history, signs or symptoms of endocrine or metabolic disease:
- Primary hyperparathyroidism
- Hypogonadism
- Hypopituitarism
- Hyperprolactinemia
- Cushing syndrome
- Hyperthyroidism
- Diabetes mellitus (Type I)
- Anorexia nervosa
- Acromegaly

Assess for any known history of bone marrow-related disorders:
- Multiple myeloma or myelodysplasia
- Thalassemia
- Systemic mastocytosis

Assess for other conditions associated with low bone mass:
- Rheumatoid arthritis
- History of organ transplantation
- Chronic kidney disease
- Immobilization (paraplegia, quadriplegia, muscular dystrophy)
- Vitamin D deficiency
- Calcium deficiency

**INITIAL LABORATORY TESTING**

Ask patient to complete the following tests (can be done before office visit):
- Comprehensive metabolic panel (which includes calcium, albumin, total protein)
- Complete blood count
- 25-OH vitamin D
- (In men) 8 am total testosterone
- 24-hour urine for calcium and creatinine
- TSH
- TTG and serum IgA

If any conditions emerge from testing, work up and treat findings appropriately:
- Multiple myeloma
- Hyperparathyroidism/hypercalcemia
- Secondary hyperparathyroidism due to renal disease
- Vitamin D deficiency
- Hypogonadism in men
- Hyperthyroidism
- Malabsorption (can be due to PPI therapy) or inadequate calcium intake (low 24-hour urine calcium)
- Familial hypercalciuria (high 24-hour calcium despite normal supplementation or no supplementation)

Identify a secondary cause for osteoporosis?

YES
Treat secondary cause and recheck BMD test in 2-3 years or upon occurrence of fragility fracture

NO
Consult specialty care
<table>
<thead>
<tr>
<th>Recommendation Language</th>
<th>Strength*</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start, initiate, prescribe, treat, etc.</td>
<td>Strong affirmative</td>
<td>Provide the intervention. Most individuals should receive the intervention; only a small proportion will not want the intervention.</td>
</tr>
<tr>
<td>Consider starting, etc.</td>
<td>Weak affirmative</td>
<td>Assist each patient in making a management decision consistent with personal values and preferences. The majority of individuals in this situation will want the intervention, but many will not. Different choices will be appropriate for different patients.</td>
</tr>
<tr>
<td>Consider stopping, etc.</td>
<td>Weak negative</td>
<td>Assist each patient in making a management decision consistent with personal values and preferences. The majority of individuals in this situation will not want the intervention, but many will. Different choices will be appropriate for different patients.</td>
</tr>
<tr>
<td>Stop, do not start, etc.</td>
<td>Strong negative</td>
<td>Do not provide the intervention. Most individuals should not receive the intervention; only a small proportion will want the intervention.</td>
</tr>
</tbody>
</table>

*Refers to the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects.

**DISCLAIMER**

This guideline is informational only. It is not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners, considering each patient’s needs on an individual basis. Guideline recommendations apply to populations of patients. Clinical judgment is necessary to design treatment plans for individual patients.