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Management of Postmenopausal Osteoporosis

Committee on Clinical Practice Guidelines–Gynecology. This Clinical Practice Guideline was developed by the ACOG Committee on Clinical Practice Guidelines–Gynecology in collaboration with JoAnn V. Pinkerton, MD; David Chelmow, MD; and Catherine T. Witkop, MD, MPH.

PURPOSE: To provide updated evidence-based recommendations for the treatment of postmenopausal osteoporosis.

TARGET POPULATION: Postmenopausal patients with primary osteoporosis.

METHODS: This guideline was developed using an a priori protocol in conjunction with a writing team consisting of two specialists in obstetrics and gynecology appointed by the ACOG Committee on Clinical Practice Guidelines–Gynecology and one external subject matter expert. ACOG medical librarians completed a comprehensive literature search for primary literature within Cochrane Library, Cochrane Collaboration Registry of Controlled Trials, EMBASE, PubMed, and MEDLINE. Studies that moved forward to the full-text screening stage were assessed by two authors from the writing team based on standardized inclusion and exclusion criteria. Included studies underwent quality assessment, and a modified GRADE (Grading of Recommendations Assessment, Development, and Evaluation) evidence-to-decision framework was applied to interpret and translate the evidence into recommendation statements.

RECOMMENDATIONS: This Clinical Practice Guideline includes updated recommendations on who should receive osteoporosis pharmacotherapy, the benefits and risks of available pharmacotherapy options, treatment monitoring and follow-up, and the role of calcium and vitamin D in the management of postmenopausal osteoporosis. Recommendations are classified by strength and evidence quality. Ungraded Good Practice Points are included to provide guidance when a formal recommendation could not be made because of inadequate or nonexistent evidence.

INTRODUCTION

Osteoporosis is a common generalized skeletal disorder characterized by low bone mineral density (BMD) and loss of bone mass, microarchitectural deterioration, and a decline in bone quality, which increase vulnerability to fracture (1). It is a silent disease until a fracture occurs. Approximately 71% of osteoporotic fractures in people aged 50 years and older occur in women (2). Individuals with osteoporosis and an elevated or high risk of fracture can be identified through screening and risk assessment. Bone loss can be slowed or prevented with pharmacologic therapy.

Since publication of the American College of Obstetricians and Gynecologists (ACOG) *Osteoporosis* Practice Bulletin in 2012, there have been advances in the treatment of osteoporosis, including the use of drug holidays from bisphosphonates to possibly decrease rare adverse effects and the development of new medications to help provide more targeted treatment. The purpose of this Clinical Practice Guideline is to provide evidence-based clinical recommendations for the management of postmenopausal osteoporosis. Osteoporosis prevention, screening, and diagnosis is addressed in a separate ACOG Clinical Practice Guideline (3).

SUMMARY OF RECOMMENDATIONS

Candidates for Pharmacotherapy

Before starting pharmacotherapy for osteoporosis, evaluate patients for secondary causes of bone loss. **(GOOD PRACTICE POINT)**

ACOG recommends pharmacologic osteoporosis treatment in patients who have a high risk of fracture. **(STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE)**

Pharmacotherapy Options

ACOG recommends bisphosphonates as initial therapy for most postmenopausal patients at increased risk of fracture. **(STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE)**

ACOG suggests discontinuation of bisphosphonates to allow a drug holiday for low-to-moderate risk patients who are stable after 5 years of treatment with oral bisphosphonates or after 3 years of treatment with intravenous zoledronic acid. Longer treatment, of up to 10 years for oral bisphosphonates or up to 6 years for intravenous zoledronic acid, is suggested for patients at high risk of fracture. **(CONDITIONAL RECOMMENDATION, LOW-QUALITY EVIDENCE)**

ACOG recommends using denosumab as initial therapy for postmenopausal patients at increased risk of fracture who prefer every 6-month subcutaneous administration. **(STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE)**

Patients who discontinue denosumab therapy should be transitioned to treatment with another antiresorptive agent. **(GOOD PRACTICE POINT)**

ACOG suggests raloxifene for postmenopausal patients at increased risk of vertebral fracture and breast cancer who are at low risk of venous thromboembolism and do not have significant vasomotor symptoms. **(CONDITIONAL RECOMMENDATION, HIGH-QUALITY EVIDENCE)**

ACOG recommends the parathyroid hormone analogs, teriparatide and abaloparatide, for the treatment of postmenopausal osteoporosis for up to 2 years in patients who are at very high risk of fracture or who continue to sustain fractures or have significant bone loss while taking antiresorptive therapy. **(STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE)**

ACOG recommends the sclerostin-binding inhibitor romosozumab for the treatment of postmenopausal osteoporosis for up to 1 year in patients who are not at increased risk of cardiovascular disease or stroke and have a very high risk of fracture or for whom other treatments have not been effective. **(STRONG RECOMMENDATION, MODERATE-QUALITY EVIDENCE)**

STRENGTH OF RECOMMENDATION

STRONG

ACOG recommends:
Benefits clearly outweigh harms and burdens. Most patients should receive the intervention.

ACOG recommends against:
Harms and burdens clearly outweigh the benefits. Most patients should not receive the intervention.

CONDITIONAL

ACOG suggests:
The balance of benefits and risks will vary depending on patient characteristics and their values and preferences. Individualized, shared decision making is recommended to help patients decide on the best course of action for them.

QUALITY OF EVIDENCE

HIGH

Randomized controlled trials, systematic reviews, and meta-analyses without serious methodologic flaws or limitations (eg, inconsistency, imprecision, confounding variables)
Very strong evidence from observational studies without serious methodologic flaws or limitations
There is high confidence in the accuracy of the findings and further research is unlikely to change this

MODERATE

Randomized controlled trials with some limitations
Strong evidence from observational studies without serious methodologic flaws or limitations

LOW

Randomized controlled trials with serious flaws
Some evidence from observational studies

VERY LOW

Unsystematic clinical observations
Very indirect evidence from observational studies

GOOD PRACTICE POINTS

Ungraded Good Practice Points are incorporated when clinical guidance is deemed necessary in the case of extremely limited or non-existent evidence. They are based on expert opinion as well as review of the available evidence.

Treatment Monitoring

ACOG suggests dual energy X-ray absorptiometry (DXA) testing every 1–3 years during osteoporosis pharmacotherapy, depending on clinical circumstances, until findings are stable. **(CONDITIONAL RECOMMENDATION, MODERATE–QUALITY EVIDENCE)**

Nonpharmacologic Management: Calcium and Vitamin D

Counsel patients who are receiving osteoporosis pharmacotherapy and patients with postmenopausal osteoporosis who cannot tolerate pharmacologic therapy to consume the recommended daily allowance of calcium and vitamin D through diet (preferably), supplementation, or both. **(GOOD PRACTICE POINT)**

METHODS

ACOG Clinical Practice Guidelines provide clinical management recommendations for a condition or procedure by assessing the benefits and harms of care options through a systematic review of the evidence. This guideline was developed using an *a priori* protocol in conjunction with a writing team consisting of two specialists in obstetrics and gynecology appointed by the ACOG Committee on Clinical Practice Guidelines–Gynecology and one external subject matter expert. A full description of the Clinical Practice Guideline methodology is published separately (4). The following description is specific to this Clinical Practice Guideline.

Literature Search

ACOG medical librarians completed a comprehensive literature search for primary literature within Cochrane Library, Cochrane Collaboration Registry of Controlled Trials, EMBASE, PubMed, and MEDLINE. Parameters for the search included human-only studies published in English. The search was restricted to studies from 2012 to 2018, based on the completion date of the previous literature search performed for ACOG Practice Bulletin 129, *Osteoporosis*. For new clinical questions, the search period was not restricted. The MeSH terms and keywords used to guide the literature search can be found in Appendix A. An updated literature search was completed in February 2020 and reviewed by two members of the writing team using the same systematic process as the original literature search. Two additional supplemental literature searches were performed in February 2021 and in September 2021 to ensure any newly published high-level sources were addressed in the final manuscript.

Study Selection

A title and abstract screen of all studies was completed by ACOG research staff. Studies that moved forward to the full-text screening stage were assessed by two authors from the writing team (a subject matter expert and a specialist in obstetrics and gynecology) based on standardized inclusion and exclusion criteria. To be considered for inclusion, studies had to be conducted in countries ranked very high on the United Nations Human Development Index (5); published in English; and include participants who identified as female or women, were postmenopausal, and were diagnosed with primary osteoporosis (ie, osteoporosis that was not due to medication use or a medical condition). Although systematic reviews, randomized controlled trials (RCTs), and prospective cohort studies were prioritized, case-control studies were considered for topics with limited evidence, particularly for rare outcomes. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the included and excluded studies can be found in Appendix B. Included studies underwent quality assessment and had key details extracted (study design, sample size, details of interventions, outcomes) and were organized into summary evidence tables (Appendix C).

Recommendation Development

A modified GRADE (Grading of Recommendations Assessment, Development, and Evaluation) evidence-to-decision framework was applied to interpret and translate the evidence into draft recommendation statements, which were classified by strength and evidence quality (6, 7). Ungraded Good Practice Points were incorporated to provide clinical guidance in the case of extremely limited or nonexistent evidence. They are based on expert opinion as well as review of the available evidence (8). The recommendations and supporting evidence tables were then reviewed, revised as appropriate, and affirmed by the Committee on Clinical Practice Guidelines–Gynecology at a meeting. The guideline manuscript was then written and subsequently reviewed and approved by the Committee on Clinical Practice Guidelines and other internal review bodies before continuing to publication.

Use of Language

When describing research findings, this document uses the race–ethnicity and gender terminology reported by the investigators. ACOG recognizes and supports the gender diversity of patients who seek obstetric and gynecologic care, including people who are cisgender, transgender, gender nonbinary, or otherwise gender expansive. ACOG's goal is to use language that is inclusive of gender-diverse individuals. Therefore, this document uses the terms "woman," "women," "patient," and "individual." ACOG advocates for inclusive, thoughtful, affirming care, including the use of language that reflects a patient's identity.

CLINICAL OVERVIEW

Epidemiology

In the United States, one in two women older than 50 years will experience an osteoporotic fracture (9). Postmenopausal women who experience a vertebral or

nonvertebral fracture are at increased risk of experiencing another fracture within the subsequent 1–2 years (10, 11). However, only 24% of women aged 60 and older receive osteoporosis treatment during the first year after a fracture (12).

Health Inequities

Black women are significantly less likely to receive osteoporosis treatment compared with White women (13–15). In a study of 1,000 women aged 60 and older receiving care at a primary care practice, African American women received fewer prescriptions for osteoporosis treatment after diagnosis than White women (79.6% vs 89.2%, $P<.05$) (13). In a secondary analysis of data from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study, women with osteoporosis who self-identified as African American were less likely to receive therapy than those who identified as Caucasian (14). In a post hoc analysis of data from the Women's Health Initiative study, Black women with osteoporosis were significantly less likely to receive treatment compared with White women (odds ratio 0.55; 95% CI 0.41–0.72), whereas treatment rates among White women and Hispanic women were similar (15). In a study of outcomes after major fragility fracture, Black women had higher rates of 1-year mortality (19.6% vs 15.4%; $P<.001$); destitution (2.4% vs 2.0%; $P=.006$); and a composite outcome combining death, debility, and destitution (24.6% vs 20.2%; $P<.001$) compared with White women (16).

Although these studies did not investigate the underlying causes of the observed patient-level differences in osteoporosis treatment and outcomes, racial inequities in health care reflect racism and discrimination at the structural, institutional, and individual levels (17–20). System-level structures, policies, and practices that promote inequity, such as varying geographic availability of health care institutions, lack of health care delivery in one's language or at one's health literacy level, and high health care costs and insurance premiums, all play a critical role in reducing access to care and in decreasing the quality of care provided (18). Individual practitioner-level factors, including implicit biases, also contribute to health inequities (18). For example, in the case of osteoporosis, several studies showed that racial disparities in DXA testing and treatment rates persisted even after accounting for insurance status and socioeconomic factors, suggesting that health practitioner bias may have influenced clinical decision making (13, 21, 22).

It also is important to consider the social factors that affect health care access and health outcomes (17). In one study, among patients who received referral for DXA testing, African American women were less likely to complete screening than Caucasian women (20.8% vs 27.0%, $P<.05$) (13), which may reflect patient mistrust of the health care system because of historic and ongoing systemic racism or may be related to social determinants of health (eg, limited access to transportation), or a complex interplay of these factors (17, 18). Additional research that is explicitly focused on racial inequities along the entire spectrum of osteoporosis care is needed to help identify strategies and interventions to help ensure quality care for all patients.

Diagnosis

Dual energy X-ray absorptiometry, which measures BMD, is the preferred test for identifying bone loss and assessing risk of fracture. Hip and lumbar spine measurements by DXA provide the most accurate and precise measurements of BMD. Results from a DXA test are reported as a T-score, which is calculated by comparing an individual's BMD measurements at the hip or spine with the peak mean BMD in a healthy, young-adult female population. The World Health Organization defines osteoporosis as a BMD T-score of less than or equal to –2.5 standard deviations (23). Osteoporosis also can be diagnosed clinically, regardless of a normal T score, if an individual develops a fragility fracture (defined as a fracture that occurs from a fall at less than standing height, most commonly of the spine, hip, wrist, humerus, rib, or pelvis). For more information, see ACOG Clinical Practice Guideline 1, *Osteoporosis Prevention, Screening, and Diagnosis* (3).

Management

The primary goal of osteoporosis management is to reduce fracture risk by slowing or stopping bone loss, increasing bone mass, improving bone architecture or quality, maintaining or increasing bone strength, and minimizing falls. In addition to lifestyle and environmental interventions, such as aerobic and weight-bearing exercise, adequate intake of calcium and vitamin D, and fall-prevention strategies (3), pharmacologic therapy generally is indicated for individuals at high risk of fracture.

Osteoporosis medications are classified as antiresorptive or anabolic, depending on their primary mechanism of action. Antiresorptive agents increase BMD and decrease bone turnover by inhibiting the activity of osteoclasts, which decrease bone formation by osteoblasts. Antiresorptive treatments approved by the U.S. Food and Drug Administration (FDA) include bisphosphonates, the targeted RANK-ligand inhibitor denosumab, selective estrogen receptor modulators, hormone therapy, and calcitonin. Anabolic agents increase bone density by stimulating bone formation and include parathyroid hormone analogs and sclerostin-binding inhibitors.

Osteoporosis is a lifelong problem that requires evolving management, which may include intervals on and off medical treatment. Considerations for the use of osteoporosis pharmacologic therapy include the following:

- type of treatment
- timing of initiation
- length of treatment
- use of drug holidays to reduce the risk of adverse events
- bone loss management when therapy is discontinued
- timing of therapy re-initiation
- indications for referral to an endocrinologist or other osteoporosis specialist

CLINICAL RECOMMENDATIONS AND EVIDENCE SUMMARY

Secondary Causes of Bone Loss

Before starting pharmacotherapy for osteoporosis, evaluate patients for secondary causes of bone loss. (GOOD PRACTICE POINT)

Expert guidelines recommend evaluation for remediable and secondary causes of bone loss before initiation of osteoporosis treatment (Box 1 and Box 2) (24), particularly in patients with very low BMD or with a history of multiple or recent fractures (25). Secondary causes should be corrected if possible. If bone loss persists, osteoporosis treatment should be initiated as necessary (see "Candidates for Pharmacotherapy" later in this document). The need for continued medications associated with bone loss should be assessed in conjunction with the prescribing physician. Referral to an endocrinologist or other osteoporosis specialist should be considered for patients with unclear etiology or secondary causes of osteoporosis (see "Referral" later in this document) (11, 24).

Secondary osteoporosis is a concern for breast cancer patients and survivors who are treated with chemotherapy or aromatase inhibitors because both treatments are associated with decreased BMD and an increased incidence of fractures (26–28). Recommended risk assessment before initiation of aromatase inhibitor treatment or chemotherapy in patients with breast cancer includes BMD testing, a bone-related medical history (eg, new back pain, occurrence of fractures or falls), use of a validated risk-assessment tool (eg, FRAX calculator), and a physical examination (26). Expert guidelines recommend repeat BMD testing with DXA every 2 years, or as often as every year based on clinical indications (ie, new risk factors for bone loss, surgery, or a significant change in medical therapy) (26, 29). All breast cancer patients and survivors should be counseled regarding lifestyle and nutritional modifications–including physical activity, weight-bearing exercise, and sufficient calcium and vitamin D

Box 1. Common Causes of Bone Loss or Secondary Osteoporosis*

Conditions, disorders, and diseases

- AIDS or HIV
- Anorexia nervosa
- Diabetes mellitus (type 1 and type 2)
- Diminished ovarian reserve
- Gastric bypass
- Hyperparathyroidism
- Hypocalcemia
- Premature menopause (induced or surgical)
- Primary ovarian insufficiency
- Renal impairment
- Rheumatoid arthritis
- Turner's syndrome
- Vitamin D deficiency

Medications

- Antiepileptic drugs (eg, phenytoin, carbamazepine, primidone, and phenobarbital)
- Antiretroviral drugs
- Aromatase inhibitors
- Cancer chemotherapeutic agents
- Depot medroxyprogesterone acetate†
- Glucocorticoids
- Gonadotropin-releasing hormone agonists
- Gonadotropin-releasing hormone antagonists
- Heparin

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

*This is not intended to be an all-inclusive list of causes of secondary osteoporosis.

†Although the use of depot medroxyprogesterone acetate is associated with loss of bone mineral density, available evidence suggests that decreases in bone density appear to be substantially or fully reversible after discontinuation. High-quality studies are needed to determine whether depot medroxyprogesterone acetate affects fracture risk in adolescents or adults later in life. (Depot medroxyprogesterone acetate and bone effects. Committee Opinion No. 602. American College of Obstetricians and Gynecologists. Obstet Gynecol 2014;123:1398–402.)

Data from Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, et al. Screening for osteoporosis to prevent fractures: US Preventive Services Task Force recommendation statement. US Preventive Services Task Force. JAMA 2018;319:2521-31. doi: 10.1001/jama.2018.7498; Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, 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(suppl 1):1-46. doi: 10.4158/GL-2020-0524SUPPL; *and* Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's guide to prevention and treatment of osteoporosis. National Osteoporosis Foundation [published erratum appears in Osteoporos Int 2015;26:2045-7]. Osteoporos Int 2014;25:2359-81. doi: 10.1007/s00198-014-2794-2.

Box 2. Initial Evaluation for Secondary Osteoporosis

- Complete blood count
- Metabolic profile (calcium, renal function, phosphorus, and magnesium)
- 24-hour collection for calcium, sodium, and creatinine excretion
- Liver function tests
- Thyroid-stimulating hormone with or without free T4
- 25-hydroxyvitamin D

Data from Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, 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(suppl 1):1-46. doi: 10.4158/GL-2020-0524SUPPL; *and* Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's guide to prevention and treatment of osteoporosis. National Osteoporosis Foundation [published erratum appears in Osteoporos Int 2015;26:2045-7]. Osteoporos Int 2014;25:2359-81. doi: 10.1007/s00198-014-2794-2.

intake—to help support bone health (26). Available osteoporosis pharmacotherapy options for breast cancer patients at high risk of fracture include bisphosphonates and the targeted RANK-ligand inhibitor, denosumab (29).

Candidates for Pharmacotherapy

ACOG recommends pharmacologic osteoporosis treatment in patients who have a high risk of fracture. **(STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE)**

Pharmacotherapy is recommended to decrease the risk of fracture in patients who meet any of the criteria listed in Box 3 and who do not have contraindications for the type of treatment being recommended (11, 24, 25). (See individual medication sections later in this document for discussion of drug-specific contraindications.)

Pharmacologic therapy has been shown in high-quality studies to be effective for fracture prevention. The U.S. Preventive Services Task Force review of the evidence on osteoporosis screening and treatment found that drug therapies are effective in reducing the incidence of fractures in postmenopausal patients at high risk and that the potential harms are generally small to moderate (30, 31). The benefits of osteoporosis pharmacotherapy also have been demonstrated in more recent meta-analyses (32, 33).

Osteoporosis Pharmacotherapy Options

Pharmacotherapy options for osteoporosis are listed in Table 1. Osteoporosis medications are indicated for prevention, treatment, or both. Osteoporosis agents that are FDA-approved for prevention have been shown to significantly increase BMD, whereas medications indicated for osteoporosis treatment have been shown to significantly reduce the risk of fracture.

When selecting a medication for osteoporosis management, important considerations include benefits and risks, individual clinical factors, and patient values and preferences. All the medications listed in Table 1 improve BMD compared with placebo, but the more relevant clinical outcome is demonstration of fracture reduction in women with osteoporosis in clinical trials (11, 24, 31). Although prospective head-to-head trial data on fracture prevention are not available for the various FDA-

Box 3. Indications for Osteoporosis Pharmacotherapy

After evaluation for remediable secondary causes, pharmacotherapy for postmenopausal osteoporosis is recommended for patients who meet any of the following criteria:

- T-score −2.5 or lower by DXA of the femoral neck, total hip, lumbar spine, or distal 1/3 radius*
- History of fragility fracture, including asymptomatic vertebral fracture
- T-score between −1.0 and −2.5 and increased risk of fracture, as determined by a formal clinical risk-assessment tool†

Abbreviation: DXA, dual energy X-ray absorptiometry.

*Hip (femoral neck) and lumbar spine measurements by DXA provide the most accurate and precise measurements of bone mineral density. When one or both these sites cannot be evaluated (eg, in the case of bilateral hip replacements, lumbar spine surgery, or both), bone mineral density measurement at the forearm (distal one third of the radius) can be used for diagnosis.

†For example, using the U.S. Fracture Risk Assessment Tool (FRAX) tool, this would be a 10-year hip fracture probability of 3% or greater or a 10-year major osteoporotic fracture probability of 20% or greater.

Data from Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, 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(suppl 1):1-46. doi: 10.4158/GL-2020-0524SUPPL; Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's guide to prevention and treatment of osteoporosis. National Osteoporosis Foundation [published erratum appears in Osteoporos Int 2015;26:2045-7]. Osteoporos Int 2014;25:2359-81. doi: 10.1007/s00198-014-2794-2; *and* Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2019;104:1595-622. doi: 10.1210/jc.2019-00221.

Table 1. Medications for Postmenopausal Osteoporosis			
Category	**Examples (Mode of Administration)**	**Indication**	**Demonstrated Fracture Risk Reduction**
Antiresorptive agents			
Bisphosphonate*†‡	Alendronate (PO) Risedronate (PO) Zoledronic acid (IV)	Prevention and treatment	Vertebral Nonvertebral Hip
	Ibandronate (PO)	Prevention and treatment	Vertebral
	Ibandronate (IV)	Treatment	
Targeted monoclonal-antibody RANK-ligand inhibitor*‡§	Denosumab (SQ)	Prevention‖ and treatment	Vertebral Nonvertebral Hip
Selective estrogen receptor modulator*‡§	Raloxifene (PO)	Prevention and treatment for patients at increased risk of breast cancer	Vertebral
Hormone therapy*¶#	Estrogen with or without progestogen (multiple regimens)	Prevention	Vertebral Nonvertebral Hip
	Conjugated estrogen plus bazedoxifene (PO)	Prevention	N/A
Calcitonin**	Salmon calcitonin (intranasally or SQ)	Treatment	Vertebral††
Anabolic agents			
Parathyroid hormone analog*§	Abaloparatide (SQ) Teriparatide (SQ)	Treatment for patients at very high risk of fracture	Vertebral Nonvertebral
Sclerostin-binding inhibitor*‡‡	Romosozumab (SQ)		Vertebral Nonvertebral Hip

Abbreviations: PO, orally; IV, intravenously; RANK, receptor activator of nuclear factor kappa beta; SQ, subcutaneously; N/A, data not available.

*Barrionuevo P, Kapoor E, Asi N, Alahdab F, Mohammed K, Benkhadra K, et al. Efficacy of pharmacological therapies for the prevention of fractures in postmenopausal women: a network meta-analysis [published erratum appears in J Clin Endocrinol Metab 2021;106:e1494].

†Fink HA, MacDonald R, Forte ML, Rosebush CE, Ensrud KE, Schousboe JT, et al. Long-term drug therapy and drug discontinuations and holidays for osteoporosis fracture prevention: a systematic review. Ann Intern Med 2019;171:37-50. doi: 10.7326/M19-0533.

‡Wu CH, Hung WC, Chang IL, Tsai TT, Chang YF, McCloskey EV, et al. Pharmacologic intervention for prevention of fractures in osteopenic and osteoporotic postmenopausal women: systemic review and meta-analysis. Bone Rep 2020;13:100729. doi: 10.1016/j.bonr.2020.100729.

§Simpson EL, Martyn-St James M, Hamilton J, Wong R, Gittoes N, Selby P, et al. Clinical effectiveness of denosumab, raloxifene, romosozumab, and teriparatide for the prevention of osteoporotic fragility fractures: a systematic review and network meta-analysis. Bone 2020;130:115081. doi: 10.1016/j.bone.2019.115081.

‖Denosumab is FDA-approved to increase bone mass in breast cancer patients treated with aromatase inhibitors. (Denosumab injection. Drug label information. In: DailyMed. National Library of Medicine; 2021. Accessed December 7, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=49e5afe9-a0c7-40c4-af9f-f287a80c5c88)

¶Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. Women's Health Initiative Investigators. JAMA 2003;290:1729-38. doi: 10.1001/jama.290.13.1729.

#Jackson RD, Wactawski-Wende J, LaCroix AZ, Pettinger M, Yood RA, Watts NB, et al. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. Women's Health Initiative Investigators. J Bone Miner Res 2006;21:817-28. doi: 10.1359/jbmr.060312.

Continued

[**]Chesnut CH III, Silverman S, Andriano K, Genant H, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 2000;109:267-76. doi: 10.1016/s0002-9343(0000490-3).

[††]Available data show that salmon calcitonin nasal spray is associated with a reduced risk of recurrent but not initial vertebral fracture. (Chesnut CH III, Silverman S, Andriano K, Genant H, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 2000;109:267-76. doi: 10.1016/s0002-9343(0000490-3.))

[‡‡]Liu Y, Cao Y, Zhang S, Zhang W, Zhang B, Tang Q, et al. Romosozumab treatment in postmenopausal women with osteoporosis: a meta-analysis of randomized controlled trials. Climacteric 2018;21:189-95. doi: 10.1080/13697137.2018.1433655.

approved agents, results from systematic reviews and meta-analyses show that bisphosphonates (ie, alendronate, risedronate, zoledronic acid) and denosumab effectively reduce the risk of vertebral, nonvertebral, and hip fractures (1, 32, 34). Given their broad-spectrum antifracture efficacy, these antiresorptive agents are considered as first-line therapy for most patients with osteoporosis and elevated fracture risk (32).

In patients with severe bone loss, very high fracture risk, or both (eg, a T-score of -3 or lower, T score of less than 2.5 and a fracture within the past 12 months, or a history of severe or multiple vertebral fractures), it may be appropriate to choose an anabolic agent as initial therapy (11, 24, 35) because they have been shown to be more effective than antiresorptive therapies for increasing BMD and bone formation and decreasing the risk of vertebral fractures (33, 36, 37). Raloxifene may be appropriate in select patients who need spine-specific therapy and are at elevated risk of breast cancer (24). Because of the risks associated with hormone therapy and the low efficacy of calcitonin, these treatments generally are reserved for use in patients who cannot tolerate other osteoporosis therapies.

In addition to efficacy, mode of administration (injectable vs oral), dosing frequency, and cost are important considerations for patients who are deciding among the various osteoporosis treatments (Table 1) (38). A systematic review of studies on patient decision making regarding osteoporosis medications found that oral therapies generally are preferable to injectable agents unless oral treatments require more frequent dosing (38). The most cost-effective initial therapy for postmenopausal osteoporosis is generic oral alendronate or generic parenteral zoledronic acid (39). Additional important considerations for shared decision making about osteoporosis pharmacotherapy include drug contraindications and adverse effects, ease and convenience of administration, and duration of treatment.

Bisphosphonates

ACOG recommends bisphosphonates as initial therapy for most postmenopausal patients at increased risk of fracture. **(STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE)**

Bisphosphonates prevent and treat osteoporosis by inhibiting osteoclast-mediated bone resorption. Four bisphosphonates are approved for use in the United States (alendronate, risedronate, ibandronate, and zoledronic acid). The bisphosphonates differ in binding affinity, dose frequency, and route of administration. They all have been studied extensively in large RCTs that have demonstrated antifracture benefit (1, 32, 40, 41). A network meta-analysis of studies on bisphosphonates found that they significantly reduce vertebral fractures: zoledronic acid (relative risk [RR] 0.38; 95% CI 0.25–0.58), risedronate (RR 0.61; 95% CI 0.48–0.78), alendronate (RR 0.57; 95% CI 0.45–0.71), and ibandronate (RR 0.67; 95% CI 0.48–0.93) (32). Similarly, a systemic review and meta-analysis showed that bisphosphonates were associated with an overall 50% reduction in vertebral fractures in postmenopausal women with osteoporosis or osteopenia (41). Alendronate, risedronate, and zoledronic acid also significantly reduce nonvertebral fractures and hip fractures (32). In addition, zoledronic acid (42) and risedronate (43) have been shown to reduce the incidence of vertebral and nonvertebral fragility fractures in postmenopausal women with osteopenia. Ibandronate improves bone density and reduces vertebral fractures, but evidence is lacking for its prevention of hip and nonvertebral fractures (32).

Implementation and Safety Considerations

Lack of adherence to taking oral bisphosphonates as directed is an issue and limits their effectiveness in preventing fracture (44). Bisphosphonates are poorly absorbed orally; therefore, oral therapies need to be taken in the early morning on an empty stomach with water 30–60 minutes before eating, and patients need to stay upright to avoid esophageal irritation. Other adherence issues are attributed to the need for weekly instead of monthly dosing and adverse effects of the medication (44, 45).

Adverse effects of oral bisphosphonates include musculoskeletal aches and pains, gastrointestinal irritation, and esophageal reflux and ulceration (1). Potential rare risks identified in postmarketing surveillance include osteonecrosis of the jaw, atypical fractures of the femoral shaft, and esophageal cancer (1). Patients should be cautioned that pain in the thigh or groin may be a

prodrome to an atypical femoral fracture, which is more common in individuals taking bisphosphonates for more than 5 years (24, 46). The American College of Radiology recommends bilateral imaging with radiography followed by magnetic resonance imaging, if needed, for patients on long-term bisphosphonate therapy who present with thigh or groin pain (47).

Premenopausal patients who are considering the use of bisphosphonates for the treatment of secondary osteoporosis should be counseled about the unknown long-term effects on bone and the potential for teratogenicity. Although no serious outcomes have been reported, published data regarding the use of bisphosphonates in premenopausal women and potential effects on pregnancy outcomes and lactation are limited to case reports (48).

Intravenous bisphosphonates should be offered to patients with contraindications for oral bisphosphonates, which include esophageal disorders (eg, achalasia, esophageal stricture, esophageal varices, Barrett's esophagus), hypocalcemia, an inability to follow the dosing requirements, and conditions associated with gastrointestinal malabsorption (eg, gastric bypass) (24, 49). Bisphosphonates generally are contraindicated in patients with acute renal failure or reduced kidney function (ie, estimated glomerular filtration rate of less than 35 mL/min for zoledronic acid and alendronate or less than 30 mL/min for risedronate and ibandronate) (11, 49, 50).

Duration of Treatment and Drug Holidays

ACOG suggests discontinuation of bisphosphonates to allow a drug holiday for low-to-moderate risk patients who are stable after 5 years of treatment with oral bisphosphonates or after 3 years of treatment with intravenous zoledronic acid. Longer treatment, of up to 10 years for oral bisphosphonates or up to 6 years for intravenous zoledronic acid, is suggested for patients at high risk of fracture. **(CONDITIONAL RECOMMENDATION, LOW-QUALITY EVIDENCE).**

The concept of drug holidays (ie, stopping bisphosphonates and restarting therapy later if needed) was developed because of the uncertainty about the antifracture benefits of long-term bisphosphonate use beyond 5 years and concern that persistence of bisphosphonates in bone might increase the risk of atypical femoral fracture and osteonecrosis of the jaw (46). Longer duration of bisphosphonate treatment is associated with an increased risk of atypical femoral fracture, although the absolute incidence remains low (51). In a 10-year prospective cohort study of 196,129 women aged 50 or older receiving bisphosphonate treatment, the incidence of atypical femoral fracture increased with duration of bisphosphonate use, from 0.07 per 10,000 person-years among women with less than 3 months of bisphosphonate use to 13.10 per 10,000 person-years among those treated for 8 years or more (51). It is unclear whether there is an increased risk of osteonecrosis of the jaw with extended bisphosphonate use (46). However, these potential risks need to be weighed against the potential benefits of continued fracture reduction (1, 46).

Most of the data on long-term bisphosphonate treatment come from two randomized, placebo-controlled trials on the use of alendronate for 10 years or zoledronic acid for 6 years (52, 53). In the alendronate extension trial, postmenopausal women who discontinued treatment had small but statistically significant reductions in BMD at the total hip and spine and an increased risk of clinical vertebral fractures compared with participants who continued alendronate therapy for an additional 5 years (5.3% for discontinuation/placebo and 2.4% for extended use; RR 0.45; 95% CI 0.24–0.85); however, the rates of other types of fracture were similar between groups (52). Similarly, in the long-term study of zoledronic acid, participants who discontinued treatment had a small but statistically significant reduction in BMD at the femoral neck and other sites as well as a higher incidence of new morphometric vertebral fracture compared with those who received an additional 3 years of treatment (6.2% vs 3.0%; odds ratio 0.51; 95% CI 0.26–0.95), yet the rates of clinical vertebral and nonvertebral fractures were not significantly different between the two groups (53).

Based on available evidence on long-term efficacy and safety, and in line with other osteoporosis treatment guidelines, a bisphosphonate holiday can be considered for low-to-moderate risk patients who are stable after 5 years of treatment with oral bisphosphonates or after 3 years of treatment with intravenous zoledronic acid (1, 11, 24, 40, 46). Longer treatment, of up to 10 years for oral bisphosphonates or up to 6 years for intravenous zoledronic acid, is suggested for patients at high risk of fracture (ie, with osteoporotic fractures either before or during therapy, or a hip T-score of -2.5 or lower, or with other significant risk factors as determined by a validated clinical risk-assessment tool such as FRAX) (3, 11, 24, 46).

The optimal length of bisphosphonate holidays is unclear because the duration of therapeutic effect after discontinuation of bisphosphonates may vary depending on the binding affinity of the drug, its half-life, and individual patient characteristics. Expert guidelines on osteoporosis management recommend re-evaluation of patients 2–4 years after bisphosphonate discontinuation (11, 46). Resumption of treatment should be considered in patients with new fractures, additional risk factors for fractures, or significant decreases in BMD (11, 24, 46).

Targeted RANK-ligand Inhibitor (Denosumab)

ACOG recommends using denosumab as initial therapy for postmenopausal patients at increased risk of fracture who prefer every 6-month subcutaneous administration. **(STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE)**

Denosumab is a human monoclonal antibody that interferes with osteoclast production and activity by inhibition of the RANK (receptor activator of nuclear factor kappa beta) ligand. Metanalyses of studies on denosumab have revealed a significant reduction in vertebral fracture (RR 0.32; 95% CI 0.22–0.45) and nonvertebral fracture (RR 0.80; 95% CI 0.67–0.96), as well as hip fracture (RR 0.56; 95% CI 0.35–0.90) compared with placebo (32). Continued improvement in BMD and sustained fracture reduction have been reported with long-term use of up to 10 years (54). In a systematic review of nine RCTs that compared denosumab and bisphosphonates, denosumab showed greater improvement in bone strength (ie, BMD, bone porosity, bone turnover markers), and there was no difference in adverse events (55). Denosumab is administered subcutaneously every 6 months, which makes it a good option for patients unwilling or unable to take oral medications or for patients who have concerns about receiving an infusion of intravenous bisphosphonate. Patients for whom treatment cost is a concern may prefer generic intravenous zoledronic acid, which has been found to be more cost-effective than denosumab for fracture prevention (39).

Unlike bisphosphonates, denosumab can be used in patients with decreased glomerular filtration rates (11). However, as with bisphosphonates, denosumab is contraindicated in patients with hypocalcemia, and rare cases of osteonecrosis of the jaw and atypical femoral fractures have been reported (56). A survey of 3,591 participants from an RCT on denosumab use up to 10 years found that the overall rate of osteonecrosis of the jaw was low (5.2 per 10,000 person-years), and most cases resolved with treatment (57). Theoretical concerns about immunosuppression leading to increased rates of cancer have not been substantiated in clinical trials up to 10 years in duration (54).

Patients who discontinue denosumab therapy should be transitioned to treatment with another antiresorptive agent. **(GOOD PRACTICE POINT)**

Unlike with bisphosphonates, a drug holiday is not recommended for denosumab because of the increased risk of rapid bone loss and vertebral fractures within a few months of treatment cessation (34, 58). Patients should be counseled about the importance of consistent use and should be switched to treatment with another antiresorptive agent on discontinuation of denosumab to avoid potential rebound effects (11, 24). The duration of continued treatment will depend on clinical factors, such as the patient's individual risk of fracture, as well as the antiresorptive agent used. Clinical data are available for up to 10 years of denosumab use (54).

Selective Estrogen Receptor Modulators

ACOG suggests raloxifene for postmenopausal patients at increased risk of vertebral fracture and breast cancer who are at low risk of venous thromboembolism and do not have significant vasomotor symptoms. **(CONDITIONAL RECOMMENDATION, HIGH-QUALITY EVIDENCE)**

Raloxifene, a selective estrogen receptor modulator, is indicated for the prevention and treatment of postmenopausal osteoporosis as well as for the prevention of invasive breast cancer (59). It is often used to manage postmenopausal osteoporosis in patients who also are at increased risk of breast cancer (11, 59). By acting as an estrogen agonist in bone, it reduces bone resorption and turnover (59). Although raloxifene has been found to significantly reduce the risk of vertebral fractures in randomized controlled studies compared with placebo (RR 0.59; 95% CI 0.46–0.76) (32), no effect has been demonstrated on nonvertebral or hip fractures (32–34, 41). Raloxifene is associated with increases in BMD, which are maintained with long-term use of up to 8 years (60). Raloxifene also has been shown to reduce the risk of invasive breast cancer compared with placebo in postmenopausal women with osteoporosis (RR 0.44; 95% CI 0.24–0.80) (61). Adverse effects of raloxifene include venous thromboembolism, death from stroke (observed in patients with coronary heart disease or at increased risk of major coronary events), leg cramps, and hot flashes (59). Raloxifene is contraindicated in patients with current or past venous thromboembolism and should be used with caution in individuals with hepatic impairment (59). Other selective estrogen receptor modulators that have been investigated for osteoporosis management but are not FDA-approved for this indication include tamoxifen, bazedoxifene (alone), and ospemifene (32, 62).

Hormone Therapy

Estrogen/Estrogen–Progestogen

Estrogen therapy alone (for patients without a uterus) or combined with a progestogen can be considered as an option for the prevention of bone loss and fracture in women at increased risk who meet all the following criteria: are younger than 60 years or within 10 years of menopause; are at low risk of venous thromboembolism,

breast cancer, and cardiovascular disease; have bothersome menopausal symptoms; and for whom other therapies such as bisphosphonates or denosumab are not appropriate (11). Only certain formulations of hormone therapy are FDA-approved for the prevention of osteoporosis (11). In general, because of the associated risks, the use of hormone therapy should be limited to the lowest effective dose for the shortest duration necessary (63). Discontinuation of hormone therapy should include an assessment of benefits and risks.

In the Women's Health Initiative trial, among women without osteoporosis, estrogen alone or combined with progestin reduced the overall risk of clinical fracture compared with placebo (estrogen: hazard ratio [HR] at 7 years 0.71; 95% CI 0.64–0.80 and estrogen–progestin: HR at 5 years 0.76; 95% CI 0.69–0.83) and hip fracture (estrogen: HR at 7 years 0.65; 95% CI 0.45–0.94 and estrogen–progestin: HR at 5 years 0.67; 95% CI 0.47–0.96) (64, 65). However, the potential antifracture benefits of hormone therapy need to be weighed against the reported risks. In the Women's Health Initiative study, estrogen plus progestin increased the risk of coronary artery disease in women older than 60 years or more than 10 years from menopause, and it slightly increased the risk of breast cancer, stroke, and venous thromboembolism. Harms reported across age groups included an increased risk of cardiovascular disease (including stroke) and cognitive impairment, and estrogen–progestin was associated with an increased risk of invasive breast cancer (1). No increased risk of all-cause mortality has been found for either hormone therapy regimen.

Relatively rapid bone loss and loss of protection from fracture occurs after discontinuation of hormone therapy (66). This can be prevented by switching to a bisphosphonate or another antiresorptive agent.

Conjugated Estrogen/Bazedoxifene

The combination of conjugated estrogen and the SERM bazedoxifene is FDA-approved for the prevention of bone loss and the treatment of vasomotor symptoms (67). In RCTs, conjugated estrogen/bazedoxifene has been associated with a small but statistically significant increase in BMD at the lumbar spine and hip compared with placebo (68, 69); however, no fracture data are available (11).

Calcitonin

Calcitonin salmon nasal spray is indicated for the treatment of postmenopausal osteoporosis in individuals who are more than 5 years past menopause and for whom alternative treatments are not suitable (70). In a 5-year, double-blind, randomized controlled study, intranasal calcitonin spray was associated with a statistically significant increase in lumbar spine BMD from baseline (1% to 1.5%, $P<.01$) and a reduced risk of recurrent vertebral fracture (RR 0.67; 95% CI 0.47–0.97) compared with placebo (71). However, a reduction in nonvertebral and hip fracture has not been demonstrated (32). Calcitonin is rarely used because there are more effective osteoporosis therapies available. In addition, there have been safety concerns about a possible increased risk of malignancy. Although an FDA review found insufficient evidence of a causal association to warrant a black box label, it advises shared decision making regarding the benefits and risks for individual patients (72).

Parathyroid Hormone Analogs

ACOG recommends the parathyroid hormone analogs, teriparatide and abaloparatide, for the treatment of postmenopausal osteoporosis for up to 2 years in patients who are at very high risk of fracture or who continue to sustain fractures or have significant bone loss while taking antiresorptive therapy. **(STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE)**

Teriparatide and abaloparatide are indicated for the treatment of postmenopausal osteoporosis in patients at very high risk of fracture (such as those with a history of severe or multiple vertebral fractures, a T-score of -3 or lower, or multiple risk factors) and for the treatment of osteoporosis that is unresponsive to antiresorptive therapy (ie, new or recurrent fragility fractures or progressive loss of BMD during treatment) (11, 24, 73, 74). Parathyroid hormone analogs are also recommended as an initial treatment option in patients at very high risk of fracture (11, 24). Unlike antiresorptive agents, anabolic medications such as teriparatide and abaloparatide can restore bone mass and structure that is already lost in patients with very advanced osteoporosis. Anabolic therapy needs to be followed by treatment with an antiresorptive agent such as a bisphosphonate or denosumab to preserve the BMD gains (11, 24). Treatment is restricted to 2 years in a patient's lifetime because research with high-dose teriparatide and abaloparatide in laboratory rats found an increased incidence of osteosarcoma (73, 74). Parathyroid hormone analogs should not be used in patients with Paget's disease of the bone, unexplained elevations of alkaline phosphatase, or hypercalcemic disorders such as primary hyperparathyroidism, and caution is advised when used in patients with urolithiasis or preexisting hypercalciuria (73, 74).

Teriparatide

Teriparatide significantly reduces the risk of nonvertebral (RR 0.62; 95% CI 0.47–0.80) and vertebral fracture (RR 0.27; 95% CI 0.19–0.38) compared with placebo (32). There are conflicting data on teriparatide's efficacy to reduce the risk of hip fracture. Although a statistically

significant reduction was demonstrated in one meta-analysis (33), another network meta-analysis showed that teriparatide was associated with a nonsignificant decrease in hip fracture (32), which may have been due to the very low incidence of hip fractures in the individual RCTs included in the analysis (11). In another meta-analysis of 11 studies that compared teriparatide with bisphosphonates, teriparatide was found to be more effective in reducing the risk of vertebral fracture (RR 0.57; 95% CI 0.35–0.93) and in increasing BMD at the lumbar spine (at 6, 12, and 18 months) and femoral neck (at 18 months), with similar rates of adverse events (36).

Abaloparatide

A meta-analysis demonstrated that abaloparatide reduces the risk of vertebral fracture (RR 0.14; 95% CI 0.05–0.42) and nonvertebral fracture (RR 0.51; 95% CI 0.29–0.87) compared with placebo (32). However, the reduction in hip fracture in the meta-analysis was not statistically significant (11, 32). In a prospective analysis of BMD response among participants in the Abaloparatide Comparator Trial In Vertebral Endpoint (ACTIVE) trial, a significantly greater proportion of patients treated with abaloparatide experienced increases in BMD than did those treated with placebo or teriparatide at months 6 (19.1% vs 0.9% for placebo and 6.5% for teriparatide), 12 (33.2% vs 1.5% and 19.8%), and 18 (44.5% vs 1.9% and 32.0%) ($P<.001$) (75). In a post hoc analysis of the ACTIVE trial, among participants with an increased risk of fracture at baseline (FRAX-calculated hip fracture risk of 5% or more; or 10-year probability of major fracture of 10% or more), 18-month treatment with abaloparatide significantly reduced new vertebral fractures (relative risk reduction [RRR], 91%; $P<.001$) as well as all fracture endpoints compared with placebo (76). In the same analysis, abaloparatide was associated with a greater reduced risk of major osteoporotic fractures (RRR 78%; $P<.001$) than teriparatide (RRR 23%; $P=.384$).

In an extension study of the ACTIVE trial that included 1,139 women aged 49 to 86 years with postmenopausal osteoporosis and at high risk of fracture, participants who received 18 months of treatment with abaloparatide followed by 24 months of alendronate had a significantly decreased risk of vertebral fracture (RRR 84%; $P<.001$) compared with participants who received 18 months of placebo followed by 24 months of alendronate (77). Abaloparatide followed by alendronate was also associated with a significantly decreased risk of nonvertebral fracture (RRR 39%; $P<.05$), clinical fracture (RRR 34%; $P<.05$), and major osteoporotic fracture (RRR 50%; $P<.05$). Participants in the abaloparatide–alendronate treatment group also experienced additional increases in BMD at the lumbar spine, total hip, and femoral neck compared with the placebo–alendronate group, although there was less of a between-group difference than in the original trial (77).

Sclerostin-Binding Inhibitors

ACOG recommends the sclerostin-binding inhibitor romosozumab for the treatment of postmenopausal osteoporosis for up to 1 year in patients who are not at increased risk of cardiovascular disease or stroke and have a very high risk of fracture or for whom other treatments have not been effective. **(STRONG RECOMMENDATION, MODERATE-QUALITY EVIDENCE).**

The anabolic agent romosozumab is a humanized monoclonal antibody that binds to and inhibits the activity of the protein sclerostin, which simultaneously increases bone formation and decreases bone breakdown. It is indicated for the treatment of postmenopausal osteoporosis in patients at very high risk of fracture (such as those with a history of severe or multiple vertebral fractures, a T-score of -3 or lower, or multiple risk factors) or for whom other treatments have not been effective (ie, new or recurrent fragility fractures or progressive loss of BMD during treatment) (35, 78). Like teriparatide and abaloparatide, romosozumab is also recommended as an initial treatment option for patients at very high risk of fracture (35).

In the FRAME (Fracture Study in Postmenopausal Women With Osteoporosis) RCT of 7,180 women with postmenopausal osteoporosis, 12-month treatment with romosozumab was associated with a significantly reduced risk of vertebral fracture (RR 0.27; 95% CI 0.16–0.47) and clinical fractures (HR 0.64; 95% CI 0.46–0.89) compared with placebo, with BMD increases of 13.3% in the lumbar spine and 6.8% in the total hip (79). A systematic review and meta-analysis of six RCTs that compared romosozumab with other therapies (alendronate, teriparatide) and placebo showed a similar decreased risk of vertebral fracture (RR 0.37; 95%, CI 0.18–0.77), nonvertebral fracture (RR 0.78; 95% CI 0.66–0.92), and hip fracture (RR 0.59; 95% CI 0.44–0.79), as well as a significant increase in BMD (at the lumbar spine, total hip, and femoral neck), with no significant difference in the incidence of adverse events (80).

As with other types of anabolic therapy, romosozumab treatment should be followed with an antiresorptive therapy to help maintain the therapeutic effects (35). In the FRAME study, 12 months of treatment with romosozumab followed by 12 months of denosumab was associated with a significantly lower risk of vertebral fracture compared with 12 months of placebo followed by 12 months of denosumab (RR 0.25; 95% CI 0.16–0.40) (79). Those in the romosozumab–denosumab group continued to have significant increases in BMD at the lumbar spine, femoral neck, and total hip after the

transition to denosumab. In another RCT that included 4,093 postmenopausal women with osteoporosis and a previous fragility fracture, a treatment regimen of 12 months of romosozumab followed by 12 months of alendronate was more effective than treatment with alendronate alone for 24 months (81). The romosozumab–alendronate regimen was associated with a significantly decreased risk of vertebral fracture (RR 0.52; 95% CI 0.40–0.66), nonvertebral fracture (HR 0.81; 95% CI 0.66–0.99), and hip fracture (HR 0.62; 95% CI 0.42– 0.92) and significantly greater gains in BMD (total hip, femoral neck, and lumbar spine), which were maintained at 36 months. Although romosozumab is currently indicated for up to 12 months of treatment, RCT data from phase 2 extension trials suggest that a second 12-month course, particularly when followed by 12 months of denosumab, is associated with continued significant increases in BMD with no additional safety concerns (82, 83).

Romosozumab may increase the risk of myocardial infarction, stroke, and cardiovascular death, and the drug label includes a black box warning against its use in patients with a recent history (within 1 year) of myocardial infarction or stroke and recommends caution for use in patients with other cardiovascular risk factors (78). Administration of romosozumab is contraindicated in patients with hypocalcemia, which should be corrected before use. Other reported but rare adverse events include osteonecrosis of the jaw and atypical femoral fractures (78).

Treatment Monitoring

ACOG suggests DXA testing every 1–3 years during osteoporosis pharmacotherapy, depending on clinical circumstances, until findings are stable. (CONDITIONAL RECOMMENDATION, MODERATE–QUALITY EVIDENCE)

Osteoporosis treatment monitoring aims to identify patients who have progressive bone loss (24). In addition, there is evidence to suggest that clinician monitoring, communication, and support may help improve treatment adherence (84, 85). Expert guidelines on osteoporosis management generally recommend repeat BMD testing (ideally on the same DXA machine as prior measurements) after 1–3 years, depending on disease severity and clinical features (11, 24, 47). Patients with a progressive loss of BMD or a new or recurrent fragility fracture should be evaluated for causes of suboptimal response to therapy, such as poor medication adherence, secondary osteoporosis, or use of medications that can cause bone loss (24). Expert guidelines also recommend evaluation of renal function and serum calcium and vitamin D levels every 1–2 years during osteoporosis pharmacotherapy (11, 24).

Vertebral fracture assessment may be indicated in addition to BMD testing for patients with significant height loss or a self-reported prior vertebral fracture or who are receiving glucocorticoid therapy (eg, prednisone, 5 mg/d or more for 3 months or longer) (3, 47). Assessment can be performed using either lateral thoracic and spine X-ray or lateral vertebral fracture assessment, which is available on most DXA machines.

Nonpharmacologic Interventions

Calcium and Vitamin D

Counsel patients who are receiving osteoporosis pharmacotherapy and patients with postmenopausal osteoporosis who cannot tolerate pharmacologic therapy to consume the recommended daily allowance of calcium and vitamin D through diet (preferably), supplementation, or both. (GOOD PRACTICE POINT)

Both the Endocrine Society (11) and International Osteoporosis Foundation (86) recommend calcium and vitamin D supplementation as an adjunct to osteoporosis pharmacologic treatment because nearly all validation studies of osteoporosis pharmacotherapy have included calcium and vitamin D supplementation in both the intervention and control groups. However, these groups as well as the American Association of Clinical Endocrinologists and National Osteoporosis Foundation also acknowledge that dietary intake of the RDA of calcium is preferable to supplementation because excess intake has no proven benefit but is associated with an increased risk of renal calculi (11, 24, 25, 86). The RDA for calcium is 1,000 mg per day from ages 19 to 50 years and 1,200 mg per day in older women (87). For vitamin D, the RDA is 600 international units per day to age 70 years and 800 international units per day thereafter (87). The RDA of vitamin D is believed to maintain an adequate serum level of 25-hydroxyvitamin D (20 ng/mL) in 97.5% of the population (87).

Evidence to support the use of calcium and vitamin D to prevent fracture in patients unable to take osteoporosis pharmacologic therapy is extrapolated from studies that included a combination of average-risk and high-risk community-dwelling and institutionalized adults. A network meta-analysis of randomized trials of postmenopausal individuals found that compared with placebo, combined calcium (1,000–1,200 mg/d) and vitamin D (800 international units/d) was associated with a reduction in hip fracture (RR 0.81; 95% CI 0.71–0.93) but not a statistically significant decrease in nonvertebral fracture (RR 0.93; 95% CI 0.85–1.01) or vertebral fracture (RR 0.88; 95% CI 0.61–1.27) (32). A National Osteoporosis Foundation meta-analysis of pooled data from eight RCTs (30,970 participants, including community-

dwelling and institutionalized adults) found that calcium (500–1,200 mg/d) plus vitamin D supplementation (400–800 international units/d) was associated with a decreased risk of hip fractures (summary relative risk estimate 0.61; 95% CI 0.46–0.82) and a modest reduced risk of total fractures (summary relative risk estimate 0.86; 95% CI 0.75–0.98) (88, 89). In a more recent meta-analysis of six RCTs (49,282 participants), combined calcium (1,000-1,200 mg/d) and vitamin D (400-800 international units/d) was associated with a reduced risk of hip fracture (RR 0.84; 95% CI 0.72–0.97) and a small decreased risk of any fracture (RR 0.94; 95% CI 0.89–0.99) (90). In contrast to these findings, the U.S. Preventive Services Task Force systematic review found that supplementation with calcium and vitamin D had no effect on total fracture incidence (91). However, the Task Force review focused on an average-risk population (ie, without vitamin D deficiency, osteoporosis, or prior fracture) and did not include high-risk patients, for whom combined supplementation appears to be effective.

Complementary and Nutritional Alternative Treatments

It is unclear whether soy isoflavones and other complementary and alternative nutritional therapies have a beneficial effect on BMD. Studies are small, have inconsistent results on BMD, and unlike pharmacologic treatments, no study provides information on fracture risk reduction. Given these limitations, no recommendation can be made to use any of these nutritional alternatives, and patients at risk should be counseled regarding effective pharmacologic therapies.

Isoflavones, a class of phytoestrogens found in legumes, are the most studied nutritional approach for osteoporosis. Soybeans and soy products, the most common dietary sources of phytoestrogens, have estrogenic properties that have been hypothesized to have beneficial effects on bone. However, studies of the effect of soy isoflavone supplements on BMD for the prevention of osteoporosis have produced mixed results, and data are not available regarding fracture risk reduction. A 2011 report by the North American Menopause Society concluded that there was not significant evidence showing that isoflavones have a beneficial effect on bone density (92). A more recent nonquantitative systematic review of 23 RCTs on the effect of various phytoestrogens on BMD in perimenopausal and postmenopausal women concluded that soy isoflavones probably increase BMD (93). However, the systematic review included studies with many different isoflavones and study designs, and many of the included studies showed no effect on BMD. A meta-analysis of 26 RCTs found that soy isoflavone treatment, particularly with aglycone isoflavones, was associated with a modest but statistically significant increased weighted mean difference in BMD at the lumbar spine (0.01 g/cm^2; 95% CI 0.01–0.02 g/cm^2) and femoral neck (0.01 g/cm^2; 95% CI 0.00–0.02 g/cm^2), compared with control or placebo (94).

Flax seeds are another source of phytoestrogens that have been investigated for bone loss prevention. However, a systematic review of RCTs that examined the effect of flax interventions on bone turnover markers and BMD found no clear benefit for either outcome (95).

Green tea extract, which has antioxidant properties hypothesized to be beneficial for bone health, also has been studied as an intervention to prevent bone loss. However, it was found to have no effect on BMD in a randomized trial that included 121 postmenopausal women with body mass indexes in the overweight or obese range (96).

In a randomized trial that studied the effects of Fufang, a traditional Chinese herbal treatment, in healthy Chinese postmenopausal women with T-scores of -2 or lower, participants in the treatment group showed a statistically significant 6-month increase in BMD at the lumbar spine but not at the hip (97). However, the increase in lumbar spine BMD was not maintained and was no longer significant at 12 months.

In a systematic review of five RCTs that included postmenopausal women with osteoporosis, treatment with dietary protein (mostly from animal sources), supplemental proteins (whey), or both for up to 24 months had inconsistent effects on BMD, with some studies showing less bone loss at different body sites and other studies showing no change or greater loss of BMD (98). A randomized placebo-controlled trial that included 131 postmenopausal women with T-scores of -1 or lower found that supplementation with specific collagen peptide (ie, small proteins that may accumulate in bone) was associated with a statistically significant improvement in BMD T-score at 12 months (spine: intervention group 0.1 ± 0.6 vs control group -0.03 ± 0.18, analysis of covariance $P=.3$; femoral neck: intervention group 0.09 ± 0.24 vs control group -0.01 ± 0.19, analysis of covariance P=.003) (99).

Lifestyle Interventions

Osteoporosis management should include patient counseling about fall prevention and exercise (11, 24, 25). Fractures often occur in older adults because of trips, slips, or falls, which underscores the importance of including fall-prevention strategies (such as vision assessment and treatment, balance training, and environmental assessment and modification) as part of osteoporosis management. Routine aerobic physical activity (moderate-to-high impact) and weight-bearing exercises (muscle strengthening or exercise against resistance) are also recommended to prevent falls, maintain bone health, and prevent bone loss (3). Patients also should be counseled about other lifestyle changes to help improve bone

Box 4. Suggested Indications for Subspecialist* Referral for Osteoporosis Management

- T-score less than −3.0
- New fragility fracture
- Normal bone mineral density and fragility fracture
- Recurrent fractures or progressive bone loss despite osteoporosis treatment
- Osteoporosis that is unusual or not responding to treatment
- Endocrine or metabolic causes of secondary osteoporosis (eg, hyperthyroidism, hyperparathyroidism, hypercalciuria, or elevated prolactin)
- Comorbidities that complicate treatment (eg, chronic kidney disease, low glomerular filtration rate, or malabsorption syndromes)

*An endocrinologist or other osteoporosis specialist.

Data from Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, 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(suppl 1):1-46. doi: 10.4158/GL-2020-0524SUPPL.

and overall health, such as smoking cessation and reduction of alcohol intake (11, 24, 25, 100). For more information, see ACOG Clinical Practice Guideline 1, *Osteoporosis Prevention, Screening, and Diagnosis* (3).

Referral

Expert guidelines on osteoporosis management suggest referral to an endocrinologist or other osteoporosis specialist for patients who meet any of the criteria in Box 4 (24). Patients hospitalized with a fragility fracture should have consultation with a fracture liaison team or referral to a bone specialist (24). Referral to a fracture liaison team has been associated with an increased rate of BMD screening and initiation of pharmacologic treatment, and limited evidence suggests a decrease in fracture recurrence (101).

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APPENDICES

Supplemental Digital Content

A. Literature search strategy: http://links.lww.com/AOG/C609
B. PRISMA diagram: http://links.lww.com/AOG/C610
C. Evidence tables: http://links.lww.com/AOG/C611

CONFLICT OF INTEREST STATEMENT

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