Sentara® Health Plans

SENTARA HEALTH PLANS CLINICAL PRACTICE GUIDELINE:

OSTEOPOROSIS

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Guideline History

Date Approved	08/00
Date Revised	08/08, 04/02, 11/05, 12/05, 01/06, 01/08, 03/08, 03/10, 03/14,11/15, 03/16, 3/18, 3/20, 05/22, 05/24
Date Reviewed	09/26
Next Review Date	09/28

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ACOG
The American College of Obstetricians and Gynecologists

CLINICAL PRACTICE GUIDELINE

NUMBER 1

REPLACES PRACTICE BULLETIN NUMBER 129, SEPTEMBER 2012

Osteoporosis Prevention, Screening, and Diagnosis

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

PURPOSE: To provide updated evidence-based recommendations for the prevention, screening, and diagnosis of postmenopausal osteoporosis.

TARGET POPULATION: Postmenopausal patients without identified risk factors for fracture, low bone mineral density, or secondary osteoporosis related to medication or a medical condition.

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 the 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 on the basis of standardized inclusion and exclusion criteria. Included studies underwent quality assessment, and a modified GRADE (Grading of Recommendations, Assessment, Development and Evaluations) evidence-to-decision framework was applied to interpret and translate the evidence into recommendation statements.

RECOMMENDATIONS: This Clinical Practice Guideline includes updated recommendations on the role of exercise, calcium, and vitamin D in osteoporosis prevention; osteoporosis screening and diagnosis; rescreening intervals; and interventions to prevent falls. 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. According to 2010 U.S. Census data for the total population (noninstitutionalized and institutionalized), an estimated 8.2 million women aged 50 years and older were diagnosed with osteoporosis (compared with 2 million men), and an additional 27.3 million women had low bone mass (2). Approximately 71% of osteoporotic fractures in people aged 50 years and older occur in women (3). The purpose of this Clinical Practice Guideline is to provide updated, evidence-based recommendations for the prevention, screening, and diagnosis of postmenopausal osteoporosis.

The American College of Obstetricians and Gynecologists (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. When describing research findings, this document uses the gender terminology reported by the investigators. 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.

Summary of Recommendations

Prevention

ACOG recommends routine aerobic physical activity (moderate-to-high impact) and weight bearing-exercises (muscle strengthening or exercise against resistance) to maintain bone health and prevent bone loss. **(STRONG RECOMMENDATION, MODERATE-QUALITY EVIDENCE)**

Counsel patients to consume the recommended daily allowance of dietary calcium and vitamin D for bone health and general health. **(GOOD PRACTICE POINT)**

Screening and Diagnosis

ACOG recommends screening for osteoporosis in postmenopausal patients 65 years and older with BMD testing to prevent osteoporotic fractures. **(STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE)**

ACOG recommends screening for osteoporosis with BMD testing to prevent osteoporotic fractures in postmenopausal patients younger than 65 years who are at increased risk of osteoporosis, as determined by a formal clinical risk assessment tool. **(STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE)**

ACOG suggests repeat osteoporosis screening in postmenopausal patients with initial BMD test results near treatment thresholds or with significant changes in risk factors; for most patients, repeat BMD testing should be performed no sooner than 2 years after initial screening. **(CONDITIONAL RECOMMENDATION, LOW-QUALITY EVIDENCE)**

Fall Prevention

Assess risk of falls in postmenopausal patients with low BMD or osteoporosis. Fall-prevention strategies for those at increased risk include weight-bearing and muscle-strengthening exercises as well as individualized multifactorial interventions (eg, vision assessment and treatment, balance training, and environmental assessment and modification). **(GOOD PRACTICE POINT)**

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.

GOOD PRACTICE POINT

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

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

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 the Cochrane Library, Cochrane Collaboration Registry of Controlled Trials, EMBASE, PubMed, and MEDLINE. Parameters for the search included human-only studies published in English. Several U.S. Preventive Services Task Force (USPSTF) systematic reviews served as the evidence base for the clinical recommendations on osteoporosis screening, calcium and vitamin D supplementation for fracture prevention, and interventions to prevent falls (5-7). In these instances, the literature search was limited to the end date of the USPSTF search until 2018. If a USPSTF systematic review was not available, 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 liter-ature search. A final supplemental literature search was performed in February 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) on the basis of 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 (8); be published in English; and include participants who identified as female or women, were postmenopausal, and did not have risk factors for fracture, low BMD, or secondary osteoporosis related 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 lim-ited 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 and Manuscript Development

A modified GRADE (Grading of Recommendations, Assessment, Development and Evaluations) evidence-to-decision framework was applied to interpret and translate the evidence into draft recommendation statements, which were classified by strength and evidence quality (9, 10). 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 (11). 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 Com-mittee on Clinical Practice Guidelines and other internal review bodies before continuing to publication.

CLINICAL OVERVIEW

Epidemiology

In the United States, the prevalence of osteoporotic fracture varies by race, with the highest rates reported among White and Hispanic populations, followed by Native American, Asian, and Black populations (12) (when describing research findings, this document uses the race-ethnicity terminology reported by the investigators). In the United States, one in two women older than 50 years will experience an osteoporotic fracture (13). However, only 24% of women aged 60 and older receive osteoporosis treatment during the first year after a fracture (14).

Health inequities have been identified at each step in osteoporosis care, including screening, dual energy X-ray absorptiometry (DXA) testing after fracture, treatment initiation, and outcomes after fracture. Studies of DXA screening rates among postmenopausal women show that Black women are less likely to be screened for osteoporosis compared with women in other racial and ethnic groups (15-19). Black women (relative risk [RR] 0.66; 95% CI 0.50-0.88) and Hispanic women (RR 0.58; 95% CI 0.39-0.87) are less likely than White women to undergo DXA testing after hip fracture (17). In a study of 1,000 women 60 years and older who received care at a primary care practice, African American women received fewer prescriptions for osteoporosis treatment after diagnosis than Caucasian women (79.6% vs 89.2%, P<.05) (19). In a secondary analysis of data from the Reasons

for Geographic and Racial Differences in Stroke (REGARDS) study, women with osteoporosis who self-identified as African American were less likely to receive therapy than women who identified as Caucasian (20). 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 (21). 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 their White counterparts (22).

Although these studies did not investigate the underlying causes of the observed patient-level differences in osteoporosis screening, treatment, and outcomes, racial inequities in health care reflect racism and discrimination at the structural, institutional, and individual levels (23-27). 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 (23, 25). Individual practitioner-level factors, including implicit biases, also contribute to health inequities (23, 25). For example, in the case of osteoporosis, several studies showed that racial disparities in screening and treatment rates persisted even after accounting for insurance status and socioeconomic factors, suggesting that health practitioner bias may have influenced clinical decision making (17-19). It also is important to consider the social factors that affect health care access and health outcomes (24). 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) (19), 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 (23, 24). 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 ensure quality care for all patients.

Bone Physiology

Although changes in bone mass and microarchitecture are well characterized, other aspects of bone quality are not as well understood. Bone mass is usually stable in healthy premenopausal individuals. As estrogen levels decline around menopause, bone resorption by osteoclasts increases and exceeds the ability to form new bone by osteoblasts. This leads to bone loss and loss of microarchitecture of both trabecular and cortical bone, which increases the risk of fracture. Bone mass may begin to decrease before menopause, with an accelerated phase of bone loss during the menopausal transition (28). Age also affects bone quality, such that a woman aged 80 years has a much higher risk of fracture compared with a woman aged 50 years with the same BMD (29).

Risk Factors

There are a variety of genetic and lifestyle factors, medications, and medical conditions that contribute to the development of osteoporosis (Box 1) (30-33). Low BMD and a history of fragility fracture are significant pre-dictors of future fractures (34). Postmenopausal women who experience an osteoporotic vertebral fracture are at significantly increased risk of a subsequent vertebral fracture within the next year, and this risk remains elevated over time if the fracture is untreated (35).

Bone Mineral Density Measurement and Classification

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 or a Z-score. The World Health Organization defines osteoporosis as a BMD T-score of less than or equal to -2.5 standard deviations. (Table 1) (36).

The T-score is the basis for diagnosing osteoporosis in the postmenopausal population. It is calculated by comparing an individual's BMD measurements at the hip or spine with the peak mean BMD in a healthy, young-adult reference population and is expressed as the number of standard deviations from the mean BMD. The International Society for Clinical Densitometry recommends using "a uniform Caucasian (non-race adjusted) female normative database for women of all ethnic groups" and data from the Third National Health and Nutrition Examination Survey (NHANES III) for this reference standard (37, 38). Some research suggests that T-scores may have different predictive value in different racial and ethnic groups. In a study that pooled deidentified data from the Women's Health Initiative, the World Health Organization T-score classification underestimated the risk of major osteoporotic fracture in all racial and ethnic groups, with the degree of underestimation varying between groups, and the largest underestimation occurring in African American women (39). The authors of another study that used a Chinese American reference standard to recalculate the T-scores of 4,039 postmenopausal Chinese American women found that a large percentage of women who had been diagnosed with osteoporosis using NHANES III reference standards were reclassified as having osteopenia (40). The source of these variations is not clearly understood, and more research is

Box 1. Common Risk Factors for Osteoporosis

- Increasing age
- Parental history of hip or spine fracture
- BMI less than 20 kg/m^2 or body weight less than 127 lb
- Smoking
- Excessive alcohol use (ie, more than three drinks per day)
- Conditions, diseases, and medications associated with secondary osteoporosis:*
  - AIDS and HIV, anorexia nervosa, diabetes mellitus (type 1 and type 2), diminished ovarian reserve, gastric bypass, hyperparathyroidism, hypocalcemia, premature menopause (induced, surgical, or spontaneous), primary ovarian insufficiency, renal impairment, rheumatoid arthritis, Turner's syndrome, vitamin D deficiency
  - Antiepileptic drugs (eg, phenytoin, carbamazepine, primidone, and phenobarbital), antiretroviral drugs, aromatase inhibitors, chemotherapy, DMPA, glucocorticoids, gonadotropin-releasing hormone agonists, gonadotropin-releasing hormone antagonists), heparin

Abbreviations: AIDS, acquired immunodeficiency syndrome: BMI, body mass index: DMPA. depot medroxyprogesterone acetate: HIV, human immunodeficiency virus.

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

Data from Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, 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;26:1-46. 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.

needed in this area to explore the observed differences and to clarify the implications for clinical practice.

A Z-score is expressed as the number of standard deviations between an individual's BMD and the mean BMD of a reference population of the same sex, age, and ethnicity (37). It is useful for identifying premenopausal individuals who may be at risk of secondary osteoporosis (ie, osteoporosis caused by a medical condition or a medication) for whom further evaluation might be needed. For premenopausal individuals, a Z-score of -2.0 or lower is considered "below the expected range for age" (37). As with T-scores, further research is needed to explore and address nonbiologic contributors to Z-score differences based on race and ethnicity.

CLINICAL RECOMMENDATIONS AND EVIDENCE SUMMARY

Prevention Strategies

Physical Activity

AGOG recommends routine aerobic physical activity (moderate-to-high impact) and weight-bearing exercises (muscle strengthening or exercise against resistance) to maintain bone health and prevent bone loss. (STRONG RECOMMENDATION, MODERATE-QUALITY EVIDENCE)

Table 1. World Health Organization Bone Densitometry Criteria for Diagnosing Osteoporosis

Category	T-Score*
Normal	-1.0 or greater
Low bone mass (osteopenia)	Between -1.0 and-2.5
Osteoporosis	-2.5 or less

*T-score is the number of standard deviation units above or below the mean average bone mineral density value for a healthy young adult.

Data from World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: report of a WHO study group. WHO Technical Report Series 843. WHO; 1994. Accessed May 18, 2021. https://apps.who.int/iris/bitstream/handle/10665/39142/WHO_TRS_843_eng.pdf

Physical activity provides a number of benefits throughout the lifespan, and the Centers for Disease Control and Prevention recommends that all adults engage in at least 150 to 300 minutes per week of moderate-intensity activity or 75 minutes to 150 minutes per week of vigorous-intensity aerobic physical activity (or a combi-nation of both) (41). Physical activity early in life stimu-lates bone remodeling, which leads to increased bone density and contributes to higher peak bone mass. Although the ideal physical activity for strengthening bone has not been established, resistance and high-impact or weight-bearing exercises (eg, free weights or resistance bands, jogging, stepping, and jumping rope) appear to show the most benefit (42, 43). One meta-analysis of studies conducted in premenopausal women found that jumping exercises significantly increased BMD in the femoral neck and trochanter (42). A subsequent review of 12 systematic reviews of studies that included populations ranging from girls to postmenopausal women showed that combined impact exercise proto-cols, such as high-impact exercise with resistance train-ing, appeared to preserve or improve BMD or both throughout the lifespan (43). Some studies also have found that in addition to improving balance and helping to prevent falls, tai chi training in postmenopausal women may have a beneficial effect on BMD and bone turnover markers, which is thought to be related to its weight-shifting movements (44, 45).

Because menopause can be a time of significant reduction in bone density, it is critical that perimenopausal and postmenopausal patients are intentional in their approach to exercise. In a systematic review of 43 RCTs with 4,320 postmenopausal women aged 45-70 years, the authors reported a small, but statistically significant increase in femoral neck BMD associated with the use of non-weight-bearing, high-force exercises such as progressive resistance strength training and a slight increase in spinal BMD with the use of combination exercise programs (46). These results are consistent with findings from more recent, higher-quality meta-analyses that examined the effect of different types of exercise and found that combined resistance training programs (ie, resistance and high-impact or weight-bearing exercise) among postmenopausal women increased femoral neck and lumbar spine BMD when compared with resistance alone (47) and preserved BMD at the lumbar spine, femoral neck, total hip, and total body when compared with baseline values (48). A systematic review of 15 studies in postmenopausal and older women (aged 65 years or older) demonstrated mixed results with multicomponent training (49). Because the interventions were heterogeneous and included various combinations of exercises (ie, low-impact and high-impact aerobic, resistance, strength training, and weight-bearing), it was unclear which type of multicomponent training program was the most effective; however, many of the included studies demonstrated an overall positive effect on bone mass (49). The amount of exercise performed also may influence the effects on BMD. In an RCT of 379 postmenopausal women, those who participated in a 300-minute weekly regimen of high-intensity aerobic exercise compared with 150 minutes weekly had a statistically significant higher BMD at the end of 12 months, with the effects remaining at 12-month follow-up (50).

Studies have attempted to determine the best types of exercise to improve bone health in older postmenopausal women. The LIFTMOR RCT found that high-intensity resistance and impact training in postmenopausal women older than 58 years with osteopenia was associated with improvement in lumbar spine and femoral neck BMD without an increased risk of fracture, which is one of the concerns about high-intensity exercise in older women (51, 52). Older postmenopausal women who cannot do 150 minutes per week of moderate-intensity activity or bone-strengthening exercises (eg, because of mobility issues or chronic diseases) should be as physically active as their conditions allow. There is some evidence that walking programs alone may improve BMD of the hip (53). In addition, because of the minimal risk and other beneficial general health effects of physical activity, sedentary women can be encouraged to perform brisk walking in a safe environment as a means of improving bone health.

Whole-body vibration training, which uses a machine with a vibrating platform, also has been suggested as a possible way to improve muscle strength, balance, motility, and BMD in older women. Several high-quality systematic reviews (54-56) and a more recent RCT (57) showed a positive effect of whole-body vibration for postmenopausal women. However, the adequate level of vibratory stimulation to reduce BMD decline is not clear, and further study is needed before a recommendation can be made about this intervention.

In a small RCT of postmenopausal women with osteopenia who were taking calcium and vitamin D supplementation, those who participated in a 6-month regimen of three-times-weekly high-impact exercise had a significant increase in BMD at the spine and femoral neck compared with those who participated in strength training or no exercise (58). In a more recent small RCT of postmenopausal women who took calcium and vitamin D supplements, twice-weekly combined high-impact and high-resistance training was associated with greater improvement in BMD at the femoral neck compared with fast walking three to five times per week; however, T-score differences at the lumbar spine were not statistically significant (59).

Vitamin D and Calcium

Counsel patients to consume the recommended daily allowance of dietary calcium and vitamin D for bone health and general health. (GOOD PRACTICE POINT)

The USPSTF has issued guidelines on the use of vitamin D and calcium supplementation for fracture prevention in community-dwelling adults (ie, not living in a nursing home or institution) who do not have vitamin D deficiency, osteoporosis, or a history of fracture (60). For community-dwelling, postmenopausal women, the USPSTF recommends against supplementation with 400 international units or less of vitamin D and 1,000 mg or less of calcium to prevent fractures because adequate evidence indicates that supplementation has no effect on fracture incidence (6, 60). The USPSTF found that there is insufficient evidence on whether supplementation with higher doses of vitamin D and calcium, alone or combined, prevents fracture in community-dwelling postmenopausal individuals (ie, a USPSTF "I statement") (60). For premenopausal individuals, the USPSTF has concluded that the evidence is insufficient to recommend for or against supplementation with calcium and vitamin D, alone or combined, for primary prevention of osteoporotic fracture (ie, an "I statement").

The USPSTF recommendations are based on a systematic review of 11 RCTs that included a total of 51,419 community-dwelling adults without vitamin D deficiency, osteoporosis, or prior fracture (6). There was no difference in hip fracture risk with vitamin D supplementation alone (three RCTs, 5,496 participants; absolute risk difference [ARD], -0.01%; 95% CI -0.80% to 0.78%). Supplementation with vitamin D and calcium together had no effect on the risk of total fractures (one RCT, 36,282 participants; ARD -0.35%; 95% CI -1.02% to 0.31%) or hip fracture (two RCTs, 36,727 participants; ARD not reported). Supplementation with vitamin D and calcium was associated with an increased risk of kidney stones (three RCTs, 39,213 participants; ARD, 0.33%; 95% CI 0.06%-0.60%). Only two trials studied calcium supplementation alone, and neither reported a significant difference in fractures at any site.

Although calcium and vitamin D supplementation do not appear to be effective for prevention of osteoporotic fractures in average-risk individuals, a diet that includes the Institute of Medicine (now known as the National Academy of Medicine) recommended daily allowance (RDA) of calcium and vitamin D is important for bone health and general health. 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 (61). For vitamin D, the RDA is 600 international units per day to age 70 years and 800 international units thereafter (61). 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 (61). Although severe and prolonged vitamin D deficiency can cause bone mineralization diseases such as osteomalacia in adults, the USPSTF has concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults (62). Similarly, the Endocrine Society advises that there is insufficient evidence to recommend screening individuals who are not at risk of vitamin D deficiency (63).

Screening and Diagnosis

Evaluation for osteoporosis involves clinical examination (medical history, physical examination, height measurement), risk assessment with a formal risk assessment tool, and BMD testing (as indicated by age or risk assessment tool results). Diagnostic criteria are pre-sented in Box 2.

Box 2. Diagnostic Criteria for Postmenopausal Osteoporosis

Any one of the following criteria is consistent with a diagnosis of postmenopausal osteoporosis:

- 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 toolt

*Hip (femoral neck) and lumbar spine measurements by DXA provide the most accurate and precise measurements of BMD. When one or both these sites cannot be evaluated (eg, in the case of bilateral hip replacements, lumbar spine surgery, or both}, BMD 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, Pelak 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 2020:26:1-46. 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

Clinical Evaluation

Clinical evaluation for osteoporosis includes medical history, physical examination, and measurement of changes in height. Medical history should assess for significant risk factors and conditions, diseases, and medications associated with secondary osteoporosis (Box **1**). An unexplained fragility fracture is diagnostic of osteoporosis even with normal or absent BMD test results (Box 2) (32).

Height loss can be an indicator of an asymptomatic vertebral fracture (30). In an analysis of a cohort of postmenopausal women who underwent serial height measurements, a change of greater than 0.8 inches (2 cm) during 1-3 years appeared to be the optimal threshold for evaluation for vertebral fracture (64). The National Osteoporosis Foundation recommends that patients who have lost 1.5 inches (4 cm) or more from their peak height at age 20 years or 0.8 inches (2 cm) or more from a previously documented measurement should undergo vertebral imaging (30). Vertebral compression fractures can be diagnosed on X-ray or by vertebral fracture assessment at the time of DXA, when available. Assessment can be performed using either lateral thoracic and spine X-ray or lateral vertebral fracture assessment, which is available on most DXA machines.

Height loss also may indicate an increased risk of nonvertebral fracture (65). In a cohort study of 3,124 postmenopausal women aged 65 years and older, height loss of greater than 2 inches (5 cm) was associated with a significantly increased risk of hip fracture (hazard ratio [HR], 1.50; 95% CI 1.06-2.12] and nonspine fracture (HR, 1.48; 95% CI 1.20-1.83), even after adjustment for BMD and vertebral fracture incidence (65).

Risk Assessment Tools

The USPSTF review of some of the most common validated osteoporosis risk assessment tools (Osteoporosis Risk Assessment Instrument, Osteoporosis Index of Risk, the Osteoporosis Self-Assessment Tool, the Simple Calculated Osteoporosis Risk Estimation, and the Fracture Risk Assessment Tool [FRAX]) showed that they performed comparably and had moderate predictive ability for osteoporosis, with individual or pooled area under the curve (AUC) values ranging from 0.58 to 0.82 (5, 31). (An AUC of 0.5 indicates no discrimination; 0.7 or greater, acceptable discrimination; and 1.0, perfect discrimination.)

FRAX, one of the most widely used tools, is a computer-based algorithm that can be applied with or without a femoral neck BMD score to estimate the 10-year risk of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture) in adults 40 years and older. FRAX can be used to help assess the need for BMD testing in postmenopausal patients younger than 65 years with potential risk factors or to determine the need to initiate pharmacotherapy in a patient with a T-score between -1.0 and - 2.5.

Risk calculations are based on multiple clinical risk factors, including sex, age, height, weight, previous fracture, parental history of hip fracture, use of steroids, smoking and alcohol intake, rheumatoid arthritis, and other secondary causes of bone loss (66, 67). FRAX is based on country-specific epidemiologic data, and the U.S. FRAX tool has separate calculators for Caucasian, Black, Asian, and Hispanic racial and ethnic groups (66). FRAX's accuracy in identifying major osteoporosis fracture risk without input of femoral neck BMD T-score was similar to the other common risk assessment tools evaluated, with a pooled AUC of 0.66 (95% CI 0.63-0.69). When including the hip BMD T-score, FRAX's pooled AUC for predicting future major osteoporotic fracture in women was 0.70 (95% CI 0.68-0.71) (5).

The FRAX tool has several important limitations. The degree of each potential risk factor alters overall fracture risk, but FRAX scoring does not allow input of specific amounts, dosage, or duration for alcohol intake, corticosteroid use, or smoking or for the number of prior fractures. Spine BMD is not incorporated into the model, nor is a history of recent falls, both of which increase the risk of osteoporotic fracture. The fracture risk score may be underestimated in individuals with these risk factors (68). FRAX has separate calculators to adjust for differences in T-score-related fracture risk that have been observed between racial and ethnic groups, but the basis for these differences is poorly understood. The role of systemic racism and social determinants of health as contributing factors merits further study to address racial and ethnic inequities in bone health.

Bone Mineral Density Testing

AGOG recommends screening for osteoporosis in postmenopausal patients 65 years and older with BMD testing to prevent osteoporotic fractures.

(STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE)

In addition to ACOG, several other major osteoporosis guideline groups recommend screening for osteoporosis with DXA in all postmenopausal women who are 65 years and older (30, 31, 69, 70). Hip (femoral neck) and lumbar spine measurements by DXA provide the most accurate and precise measurements of BMD. When one or both of these sites cannot be evaluated (eg in the case of bilateral hip replacements, lumbar spine surgery, or both), BMD measurement at the forearm (distal one third of the radius) can be used for diagnosis (30, 32). In a postmenopausal patient, a BMD T-score of -2.5 or less establishes a diagnosis of osteoporosis (Table 1) (36). A T-score between -1.0 and -2.5 indicates low bone density (or osteopenia) (36). For patients with T-scores between -1.0 and - 2.5, the use of a risk assessment tool such as FRAX can help determine the need for pharmacologic therapy.

ACOG recommends screening for osteoporosis with BMD testing to prevent osteoporotic fractures in postmenopausal patients younger than 65 years who are at increased risk of osteoporosis, as determined by a formal clinical risk assessment tool. **(STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE)**

Screening for osteoporosis with DXA also is recommended in postmenopausal women younger than 65 years who are at elevated risk (30, 31, 69, 70). Formal, validated risk assessment tools should be used to estimate frac-ture risk in patients younger than 65 years to determine whether DXA testing would be useful. The USPSTF suggests assessing risk factors (Box 1) and applying a clinical assessment tool like FRAX to patients with at least one risk factor (31). The USPSTF recommends BMD testing for postmenopausal women younger than 65 years who have a 10-year FRAX calculated risk of major osteoporotic fracture of greater than 8.4%, which is equal to the risk of a 65-year-old White woman without major risk factors for osteoporosis (31).

Screening Intervals

Most major osteoporosis screening guidelines do not provide guidance on the role or timing of retesting in patients with normal bone density and low fracture risk. The North American Menopause Society notes that for individuals who are not receiving osteoporosis treatment, repeat screening before 2-5 years from initial testing is not necessary (69). The USPSTF screening guidelines also do not include a recommendation regarding the need for repeat testing or appropriate screening intervals, but note that limited good-quality evidence shows no benefit to repeating BMD testing earlier than 4-8 years after an initial normal BMD test result (5, 31). The USPSTF evidence review included modeling studies that sug-gested that the optimal screening interval varies primarily based on BMD and age (71, 72). One modeling study used data from 4,957 women 67 years or older who were monitored for up to 15 years to estimate the time for 10% of women to develop osteoporosis before having a hip or clinical vertebral fracture: approximately 15 years for those with initial normal bone density (T-score -1.00 or higher) or mild osteopenia (T-score -1.01 to -1.49), 5 years for initial moderate osteopenia (T score -1.50 to -1.99), and 1 year for initial advanced osteopenia (T-score -2.00 to - 2.49) (71). In another modeling study, 4,068 postmenopausal women in the Women's Health Initiative BMD cohort were monitored for up to 11.2 years (72). The authors estimated that the time for 1% of women without baseline osteoporosis to have a hip or clinical vertebral fracture was 12.8 years for women aged 50-54 years and 7.6 years for women aged 60-64 years. A more recent analysis of data from 9,304 participants in the Women's Health Initiative Bone Density Substudy who were monitored for a mean of 12.4 years showed that repeat BMD testing 3 years after a baseline BMD test was not associated with improved prediction of subsequent hip or major osteoporotic fracture beyond the baseline BMD test alone, leading the authors to conclude that 3-year repeat BMD testing should not routinely be performed (73).

ACOG suggests repeat osteoporosis screening in postmenopausal patients with initial BMD test results near treatment thresholds or with significant changes in risk factors; for most patients, repeat BMD testing should be performed no sooner than 2 years after initial screening. **(CONDITIONAL RECOMMENDATION, LOW-QUALITY EVIDENCE)**

Evidence suggests that the individuals who are most likely to benefit from a shorter interval between BMD screenings include those with a low baseline BMD or a BMD near treatment thresholds and those with medical conditions or who use medications that place them at risk of accelerated bone loss (71). For follow-up of patients with risks for fracture or low BMD, the American College of Radiology recommends a 2-year monitoring interval based on the expected rate of change of bone mineralization. In patients at risk of substantial short-term decreases in demineralization, such as those receiving glucocorticoid therapy, 1-year follow up is recommended (74). Serial bone density measurements should be performed at the lumbar spine, total hip, or femoral neck. Because of differences between types of DXA machines and the need for consistent calibration, patients ideally should have follow-up measurements on the same DXA device as their prior measurement (32, 37, 74).

Lifestyle and Environmental Modifications to Prevent Falls

Assess risk of falls in postmenopausal patients with low BMD or osteoporosis. Fall-prevention strategies for those at increased risk include weight-bearing and muscle-strengthening exercises as well as individualized multifactorial interventions (eg, vision assessment and treatment, balance training, and environmental assessment and modification). **(GOOD PRACTICE POINT)**

Postmenopausal patients with osteoporosis or low BMD are at increased risk of fractures, which often occur in older adults as a result of trips, slips, or falls. Based on indirect evidence from fall-prevention studies among older community-dwelling adults, strategies that identify and address important risk factors for falls are likely also beneficial for individuals at increased risk of fall-related osteoporotic fracture. Important risk factors for falls include older age; history of falls; impairments in mobility, gait, and balance; environmental factors (eg, loose throw rugs, low-level lighting); medical conditions (eg, anxiety, depression, vitamin D deficiency, kyphosis, orthostatic hypotension, poor vision, history of stroke); and

medications that cause sedation (30, 32, 75). Referral to or consultation with a specialist in fall prevention, such as a physical therapist or occupational therapist, can be considered to provide further risk assessment and targeted interventions tor patients at increased risk of falls.

The USPSTF recommends exercise interventions tor community-dwelling adults 65 years or older who are at increased risk of falls (75). The systematic review that informed the USPSTF guidelines found that a variety of exercise interventions were associated with a statistically significant reduction in fall incidence (RR 0.89; 95% CI 0.81-0.97) and injurious falls (incidence rate ratio 0.81; 95% CI 0.73-0.90) among community-dwelling adults 65 years or older (7). Although it was unclear which specific types of exercises were the most beneficial, the most common exercises studied included those that targeted gait, balance, and functional training (17 trials); flexibility (eight trials); and endurance training (five trials) (7).

The USPSTF systematic review found that multifactorial interventions were associated with a small but statistically significant reduction in the incidence of falls (incidence rate ratio 0.79; 95% CI 0.68-0.91) among community-dwelling adults 65 years and older, but did not decrease the incidence of fall-related morbidity or mortality (7). Multifactorial interventions that were evaluated included assessment tor modifiable risk factors tor falls followed by initiation of targeted interventions, such as group or individual exercise, cognitive-behavioral therapy, nutritional therapy, education, medication management, urinary incontinence management, environmental changes, physical or occupational therapy, and other services or referrals tailored to address other identified risk factors (75).

Expert guidelines on osteoporosis management recommend multifactorial interventions for fall prevention, including risk assessment, exercise, vision assessment, balance training, and environmental assessment and modification (30, 32, 76). For individuals at increased risk of falls, the National Osteoporosis Foundation recommends consideration of multifactorial interventions, including tai chi and other exercises programs, home safety assessment and appropriate modification, removal of psychotropic medications, and correction of visual impairment (30). The American Association of Clin-ical Endocrinologists recommends similar multifactorial tall-prevention strategies, particularly exercises for bal-ance and increased trunk muscle strength, such as walk-ing, jogging, tai chi, stair climbing, weight training, and other activities with resistance (32). European guidelines on osteoporosis management also recommend fall risk assessment, regular weight-bearing exercise that is tailored to the individual, and interventions to address modifiable risk factors for those at increased risk (76).

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APPENDICES

Supplemental Digital Content

A. Literature search strategy: http://links.lVVvV.com/AOG/C371
B. PRISMA diagram: http://links.lVVvV.com/ AOG/C372
C. Evidence tables: http://links.lww.com/AOG/C373

CONFLICT OF INTEREST STATEMENT

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Published online on August 19, 2021.

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Osteoporosis Prevention, Screening, and Diagnosis. Clinical Practice Guideline No. 1. American College of Obstetricians and Gynecologists. Obstet Gynecol 2021;138:494-506.

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ACOG
The American College of Obstetricians and Gynecologists

CLINICAL PRACTICE GUIDELINE

Number 2

REPLACES PRACTICE BULLETIN NUMBER 129, SEPTEMBER 2012

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 preven-tion, 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 meth-odology 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 ex-tracted (study design, sample size, details of interven-tions, 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, thought-ful, 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 Afri-can 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 signifi-cantly 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 out-comes 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 osteopo-rosis 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. (GOOO PRACTICE POINTJ

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 indica-tions (ie, new risk factors for bone loss, surgery, or a signif-icant change in medical therapy) (26, 29). All breast cancer patients and survivors should be counseled regarding life-style and nutritional modification&--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 t
- 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/GI-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, Pelak 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 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 toolt

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.

1For 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/ic:2019-00221.

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-

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[11] 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[11]
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].

[1]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.

[1]Wu CH, Hung WC, Chang IL, Tsai TT, Chang VF, 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.

‡[1]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/druglnfo.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, Waclawski-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, Andriana 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).

ttAvailable 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, Andriana 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.))

HLiu 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-QUALITYEVIDENCE)**

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 poten-tial 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 func-tion (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 bi-sphosphonates 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); how-ever, 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 com-pared 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 non-vertebral 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 sus-tained 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 bisphospho-nates, 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 unwill-ing 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. **(COND1T1ONAL 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 hor-mone 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, intrana-sal 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 Abalopara-tide 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 frac-ture (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 break-down. 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, second-ary osteoporosis, or use of medications that can cause bone loss (24). Expert guidelines also recommend eval-uation of renal function and serum calcium and vitamin D levels every 1-2 years during osteoporosis pharmaco-therapy (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). Assess-ment 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 stud-ies of osteoporosis pharmacotherapy have included calcium and vitamin D supplementation in both the inter-vention and control groups. However, these groups as well as the American Association of Clinical Endocrinol-ogists 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 reduc-tion 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 system-atic review of 23 RCTs on the effect of various phytoes-trogens on BMD in perimenopausal and postmenopausal women concluded that soy isoflavones probably increase BMD (93). However, the systematic review included stud-ies 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 pep-tide (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.Q1 ±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.l\NW.com/AOG/C609
B. PRISMA diagram: http://links.lww.com/ AOG/C610
C. Evidence tables: http://links.lww.com/AOG/C611

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Published online on March 24, 2022.

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Management of Postmenopausal Osteoporosis. Clinical Practice Guideline No. 2. American College of Obstetricians and Gynecologists. Obstet Gynecol 2021;139:698-717.

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