Management of osteoporosis

Effective ways to avoid debilitating fractures

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Alosa Health

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Activity Overview:

The goal of the educational program is to provide primary care clinicians with a review of the impact of osteoporosis and related fractures on their older patients, provide evidence-based practice recommendations for the screening and treatment of osteoporosis, and updates on the newest medications for osteoporosis.

The educational program has several components, which include:

- Written evidence report (print monograph)
- Summary document of top 4-5 key messages
- “Academic detailing” educational sessions in physicians’ offices with trained outreach educators (pharmacists, nurses, physicians) who present the material interactively
- Reference cards for easy access to key materials
- Patient education information (brochure/tear off sheets)

This program works to synthesize the current clinical information on this topic into accessible, non-commercial, evidence-based educational material, which is taught interactively to providers by specially-trained clinical educators.

Target Audience:

The educational program is designed for clinicians practicing internal medicine, primary care, family medicine, and geriatrics, and nurses and other health care professionals who deliver primary care.

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Review the burden of osteoporosis in older adults
- Apply screening recommendations to identify patients with osteopenia and osteoporosis

- Identify patients who should treated for osteoporosis
- Describe the non-pharmacologic interventions for low bone density
- Recognize the role of bisphosphonates as first-line treatment for osteoporosis
- Select appropriate treatment duration based on medication and patient factors

Disclosure Policy:

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Media used:

Printed educational material.

Instructions for Participation and Credit:

There are no fees to participate in this activity. To receive credit, participants must (1) read the statements on target audience, learning objectives, and disclosures, (2) study the educational activity, and (3) complete the post−test and activity evaluation. To receive *AMA PRA Category 1 Credit*™, or CNE nursing credit hours, participants must receive a minimum score of 70% on the post−test.

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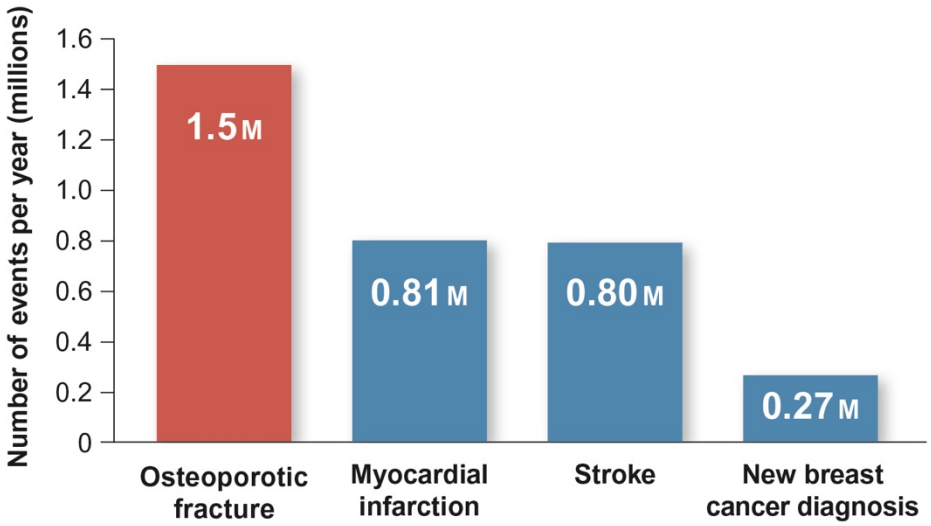
Introduction

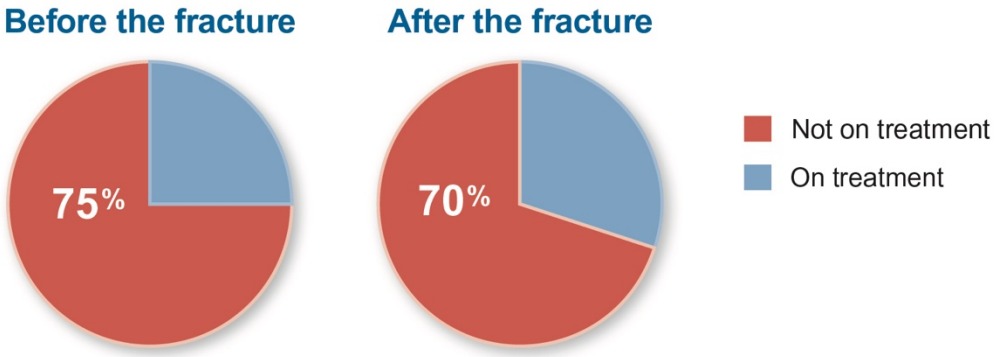
In 2017, an estimated 12% of women and men aged 50 years and older were estimated to have osteoporosis and another 43% with osteopenia or low bone mass.[1,2] Osteoporosis and osteopenia increase the risk of fractures which can lead to disability, institutionalization, morbidity, and mortality. Each year, more Americans experience an osteoporotic fracture than other common conditions, including myocardial infarction and stroke (Figure 1). The overall burden of disability and death from osteoporotic fractures exceeds that of breast or ovarian cancer.[3] Due to the aging U.S. population, the number of Americans with osteoporosis and osteopenia is expected to increase over the next 20 years, and the number of fractures is likely to double by 2040.[4]

Figure 1: Osteoporotic fracture is more common than other conditions in the U.S.[5–7]



Despite the high incidence of osteoporotic fractures and their associated morbidity and mortality, osteoporosis treatment to prevent fractures remains grossly underutilized. Among a population of 145,185 women who suffered an osteoporotic fracture, only 1 in 4 was prescribed a medication to reduce fracture risk before the fracture (Figure 2).

Figure 2: Treatment remains significantly underutilized in the highest risk patients[8]



Historically, appropriate screening for osteoporosis was lacking. In 2009, 48% of eligible women in Canadian primary care offices were not ordered for indicated screening for low bone mass.[9,10] For patients with a prior hip fracture, a clear indication for osteoporosis treatment, only 26-30% were on an appropriate therapy within 12 months of the fracture.[11,12] There are also disparities in osteoporosis screening and treatment for osteoporosis. Black patients are less likely to receive appropriate screening and treatment, while, Black patients with osteoporosis are more likely to have hip fractures than white patients with osteoporosis and have higher rates of mortality and debility following a fracture.[13,14]

Despite deficiencies in the screening and treatment of osteoporosis, early diagnosis and appropriate treatment are essential in preventing the morbidity and mortality associated with low bone mass and the primary care clinician is often the sole healthcare professional managing this disease. Here we provide an evidence review on appropriate diagnosis, monitoring, and treatment of patients with osteopenia and osteoporosis.

Definitions and diagnosis

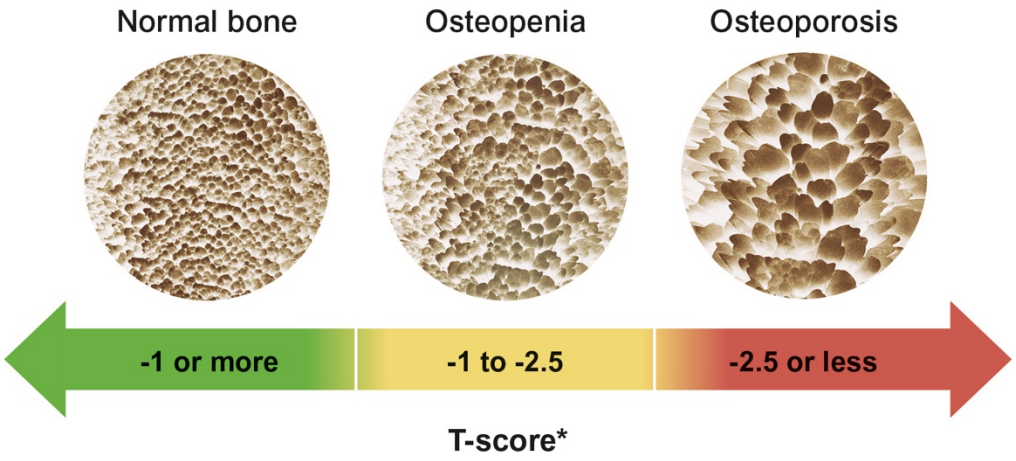
An international consensus development group in 1991 defined osteoporosis as “a disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and an increase in the fracture risk.”[15] Osteoporosis can be diagnosed radiographically and/or clinically.

Dual x-ray absorptiometry

Radiographically, dual X-ray absorptiometry (DXA) scans are used to measure the bone mineral density (BMD). Bone mineral density testing via DXA has been well established as a sensitive and specific indicator of fracture risk.[16,17] DXA has similar radiation exposure to a chest X-ray and less than a mammogram.[18] DXA can be performed at lumbar spine, hip, and forearm and the risk of fracture at any given skeletal site is best predicted by the DXA score at that bony site.[19–21]

DXA reports bone density values based on the number of standard deviations from the average bone density among age- and gender-matched individuals (Z-score) and among healthy young adults at peak bone mass (T-score). The T-score is the measure used to diagnose osteopenia and osteoporosis in postmenopausal women and men ≥50 years. As per criteria set by the World’s Health Organization in 1994, a T-score of -2.5 or less indicates osteoporosis, while a T-score between -1.0 and -2.5 indicates osteopenia. Figure 3 represents differences in trabecular bone (the porous and spongy bone found at the epiphyses of long bones and in vertebral bodies) among patients with normal bone, osteopenia, and osteoporosis. The Z-score, which compares a patient’s BMD to others of the same age and gender, can be used to diagnose osteoporosis in young adults.[22] T-scores are not used in adults <50 years because it is not clear if T-scores correlate with fracture risk in this population.[23]

Figure 3: Using the T-score to categorize bone health[24,25]



*A T-score compares the patient's bone density to that of a young healthy adult.

Clinically, diagnosis of osteoporosis can be made after a fragility fracture. Patients who sustain a hip or vertebra from trauma that is the equivalent to or less than falling from standing height have proven to be at high risk for major osteoporotic fractures, regardless of BMD. Similarly, a fragility fracture of the proximal humerus, pelvis, and, more controversially, of the wrist in conjunction with BMD in the osteopenia range may warrant a diagnosis of osteoporosis. Finally, osteoporosis can be diagnosed by elevated fracture risk, as determined by formal clinical risk factor assessments based on population-based cohort studies.

Fracture risk assessment tool (FRAX)

The most widely used clinical risk calculator is the FRAX Fracture Risk Assessment Tool (sheffield.ac.uk/FRAX/). FRAX was developed in 2008 based on nine population-based cohorts and has been validated against an additional 11 cohorts.[26] As of 2020 there were 71 models developed to provide risk assessment by country and racial group covering approximately 80% of the world population.[27] U.S. based FRAX models have been developed for Caucasian, Black, Hispanic and Asian patients.

FRAX is used to predict 10-year risk of major osteoporotic fracture and hip fracture in postmenopausal women and men aged 50 years or older who are not currently on osteoporosis treatment. A high fracture risk can be used to diagnose osteoporosis and to decide whether treatment is needed for those with osteopenia. Based on cost-benefit analyses, patients who have a FRAX score of ≥20% for major osteoporotic fracture or ≥3% for hip fracture in the next 10 years may be diagnosed with osteoporosis and should be offered treatment to reduce fracture risk.

In some situations, FRAX has been shown to underestimate the risk of osteoporotic fracture, specifically in patients with:[22,28]

- recent history of fracture (within 12 months)
- a history of more than one osteoporotic fracture

- increased fall risk, such as those with limited mobility
- type 1 and type 2 diabetes; long-standing diabetes increases fracture risk roughly equivalent to rheumatoid arthritis (RA), so clinicians can consider marking these patients as having RA to more accurately estimate fracture risk.[29]
- glucocorticoid doses >7.5 mg prednisone equivalent per day: For these patients, multiply the major osteoporotic fracture risk by 1.15 and the hip fracture risk by 1.2.[30,31]

Summary of diagnostic criteria

Based on the clinical and radiographic criteria outlined above, a diagnosis of osteoporosis is made in patients with any of the following:

- the presence of a fragility fracture of the hip or vertebra, regardless of BMD or fragility fracture of the proximal humerus, pelvis, or wrist with BMD in the osteopenia range,[28]
- bone mineral density 2.5 standard deviations below the young adult mean (T-Score ≤-2.5) at the lumbar spine, total hip, femoral neck, or distal 1/3 radius,[32] or
- elevated FRAX score of ≥20% for major osteoporotic fracture or ≥3% for hip fracture in the next 10 years.

For those without osteoporosis, a diagnosis of osteopenia is made when:

- bone mineral density is between 1.0-2.5 standard deviations below the young adult mean (T-score -1.1 to -2.4).[32]

NOTE: osteomalacia, a term often confused with osteoporosis, refers to a reduction in the mineralized component of bone rather than a reduction in the overall bone mass and architecture. Osteomalacia, which is most commonly caused by vitamin D deficiency, is often painful and symptomatic, compared with osteoporosis which is asymptomatic until a patient has a fracture. Osteoporosis may co-occur with osteomalacia.[33]

Epidemiology and risk factors

Clinical risk factors

The risk for developing osteoporosis is closely related to both age and sex. The risk of an osteoporotic fracture, at a given BMD, increases by 3 to 7 times between the ages of 45 and 85, approximately doubling with each decade of aging.[34,35] As patients get older, osteoporotic fractures are also increasingly likely to cause death or morbidity, including pain, decreased mobility, and loss of independence. In one trial of 758 patients receiving multidisciplinary care after a hip fracture, the one-year mortality increased from 2.1% in 60 to 69-year-old patients to 27.5% in patients over 90.[36]

Women are 3-7 times more likely than men to develop osteoporosis and are more likely to develop an osteoporotic fracture.[37,38] Men are, however, more likely to die following a hip fracture, although this may be confounded by the increased all-cause mortality among men.[39,40] Black women are less likely than white women to develop osteoporosis or to experience an osteoporotic fracture. However, black women with osteoporosis are more likely to have hip fractures and have increased debility and mortality following a fracture.[14,41] Other key risk factors and their relative impact on osteoporosis risk are summarized in Table 1.

Table 1: Summary of additional risk factors for the development of osteoporosis

Risk factor	Relative risk (RR)	Outcome captured
prior fracture[42]	1.86 (95% CI: 1.75-1.98)	any fracture
glucocorticoid use[43]	2.11 (95% CI: 1.12-3.96)	hip fracture
family history of maternal hip fracture[44]	2.0 (95% CI: 1.4-2.9) BMD adjusted 1.8 (95% CI: 1.2-2.7)	hip fracture
low body weight[45]	age adjusted: 1.93 (95% CI: 1.34-2.80) BMD adjusted: 0.98 (95% CI: 0.64-1.50)	hip fracture
smoking history[46]	1.29 (95% CI: 1.17-1.43) BMD adjusted: 1.13 (95% CI: 1.00-1.28)	osteoporotic fracture
heavy alcohol use[47]	1.39 (95% CI: 1.08-1.79)	hip fracture
rheumatoid arthritis[48]	all: 2.34 (95% CI: 2.05-2.63) no glucocorticoids: 1.15 (95% CI: 1.06-1.24)	all fractures
diabetes mellitus (type 1 and type 2)[29,49–51]	1.32 (95% CI: 1.19-1.46)	osteoporotic fracture

Pharmacologic risk factors

A variety of medications are also risk factors for the development of osteoporosis (Table 2, next page). Note that glucocorticoids are a significant risk factor and are included in table 1.

Table 2: Select medications implicated in fracture risk

Drug class	Relative Risk (RR) or Odds Ratio (OR)	Prevention recommendations[52]
anti-convulsant[53]	OR 2.2 (95% CI: 1.9-2.5)	calcium + vitamin D DXA screening If at risk for osteoporosis, use levetiracetam
benzodiazepines[54]	OR 1.25 (95% CI: 1.17-1.35)	DXA screening calcium + vitamin D
gonadotropin-releasing hormone (GnRH) agonists[55]	RR 1.45 (95% CI: 1.36-1.56)	calcium + vitamin D DXA screening
selective serotonin reuptake inhibitors (SSRIs)[56]	OR of fracture 1.69 (95% CI 1.51-1.90)	calcium + vitamin D
calcineurin inhibitors[52,57]	decreased BMD, controversial increased fracture risk	DXA pre- and post-transplant calcium + vitamin D osteoporosis treatment if T-Score ≤ 2.0
heparin/warfarin[52]	possibly increased fracture risk; fondaparinux or low molecular weight heparin (LMWH) preferred	LMWH or fondaparinux calcium + vitamin D
thiazolidinediones[58]	1.2-1.5 times increased fracture risk in women	Avoid in patients with osteoporosis calcium + vitamin D
aromatase inhibitors[59]	HR 1.38 (95% CI: 1.13-1.69)	DXA screening calcium + vitamin D osteoporosis treatment if T-score < -2.0 (some group < -1.0)

Proton pump inhibitors

Over the last 20 years, substantial research has been conducted evaluating the effects of proton pump inhibitors (PPIs) on osteoporosis and fracture risk. Numerous studies have found an association between PPI use and osteoporosis/fracture risk.[60–66] One suggested mechanism is that PPIs may reduce the intestinal absorption of calcium. An association between histamine receptor-2 blocking agents (e.g., famotidine) and osteoporosis has not been established and these medications may be safer for patients at risk for osteoporosis. Calcium citrate, in contrast to other calcium supplements, does not rely on an acidic gastric environment and may be preferred in patients on PPI therapy.[67]

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors

The **Canagliflozin Cardiovascular Assessment (CANVAS) Study**, published in 2017, reported on the cardiovascular effects of canagliflozin in patients with diabetes and high cardiovascular risk. After three

years of therapy, the incidence of fractures was significantly higher in patients randomized to receive canagliflozin vs. placebo (15.4 vs. 11.9 events/1,000 patient-years, p=0.02).[68] In patients receiving another SGLT-2 inhibitor, dapagliflozin, fractures were reported in 9.4% of patients compared to zero fractures in the placebo group.[69] Among patients with diabetes without pre-existing osteoporosis, canagliflozin was found to decrease the BMD compared to placebo, although the effect size was small (-1.2% [SE: -1.9 to -0.6%] change in total hip BMD). The difference was felt to be caused by changes in estrogen levels and decreases in body weight among those receiving canagliflozin.[70] The U.S. Food and Drug Administration (FDA) includes statements of a possible risk for fractures associated with canagliflozin and dapagliflozin in the medication's FDA label.[71,72] Despite these warnings, eight other randomized controlled trials of canagliflozin failed to show an increased fracture risk.[73] A 2016 metanalysis of 57 trials found no association between SGLT-2 inhibitors and fracture risk.[74] Another 2016 metanalysis of 38 randomized trials found no increased risk of fractures with dapagliflozin (HR 0.68; 95% CI: 0.37-1.25), canagliflozin (HR 1.15; 95% CI: 0.71-1.88) or empagliflozin (HR 0.93; 95% CI: 0.74-1.18).[75] In summary, there may be a small association between canagliflozin (and possibly dapagliflozin) and fracture risk. In general, because of the clear and profound benefit to this class of medication in patients with cardiovascular or renal disease, the fracture risk of SGLT-2 inhibitors should not prohibit the use of this class of agents. In patients with a high risk of fracture, empagliflozin may be a preferred agent.

Glucocorticoids

Glucocorticoids are the most common cause of secondary osteoporosis, with an estimated 2-5% annual incidence of vertebral fractures.[76,77] Glucocorticoids are thought to increase osteoclastogenesis and osteoclast activity while depressing osteoblastogenesis and osteoblast activity.[78] There is evidence that the risk of fracture is dose-dependent and that fracture risk decreases when the glucocorticoids are discontinued although may not return to pre-treatment risk levels.[79,80] Higher doses of inhaled glucocorticoids may also increase the fracture risk although most studies have been confounded by concurrent use of systemic steroids.[81,82] The risk of fracture in patients treated with glucocorticoids is a risk modifier independent of BMD and for this reason is included as a separate variable in the FRAX score. Daily doses of glucocorticoids in excess of 7.5 mg/day prednisone equivalent have been found to increase fracture risk beyond what is predicted by FRAX and adjustment for higher doses can be made to the FRAX risk scores (for doses >7.5 mg/day multiply the risk of major osteoporotic fracture by 1.15 and the risk of hip fracture by 1.2).[31,83]

The American College of Rheumatology provides recommendations for the management of osteoporosis risk associated with glucocorticoids.[84] According to these recommendations, the primary care clinician should have a high degree of suspicion for osteoporosis in patients treated with glucocorticoids and it is reasonable to begin screening for osteoporosis in both men and women at age 40. Cut-offs for initiation of therapy are similar to those for post-menopausal women with osteoporosis or fragility fractures but the cut-off for initiating therapy in *osteopenic* patients is set at a FRAX-calculated 10-year risk of ≥10% for major osteoporotic fracture and >1% for hip fracture risk as opposed to ≥20 or ≥3% respectively for patients not receiving glucocorticoids.

BOTTOM LINE: Osteoporosis is very common, especially in older adults. Osteoporotic fracture causes significant morbidity and mortality. Understanding risk factors such as age, comorbidities, lifestyle, and medications allows intervention to reduce the risk of fracture.

Screening for osteoporosis

The goal of screening for osteoporosis is to identify patients at high risk for fractures who might benefit from initiating treatment to reduce fracture risk. Screening methods include clinical assessment of risk factors and/or bone density testing. There is limited data on the appropriate age at which to begin screening of osteoporosis. Most guidelines suggest clinical risk factor assessment begin at a younger age than universal bone density testing. Universal DXA screening for post-menopausal women at age 65 has been recommended based on cost-effectiveness analysis; at this age, DXA screening results in both more cost-effective care[85] and less expensive care overall.[86] Similar findings were demonstrated for screening men with DXA between age 65 and 77.[87]

Evidence for screening

In the bisphosphonate era, there have been three large clinical trials evaluating the effect of screening for osteoporosis on the incidence of fractures.

The 2018 **SCOOP trial** enrolled 12,483 women living in the United Kingdom between the ages of 70 and 85.[88] Patients currently or previously on osteoporosis pharmacotherapy were excluded. Those randomized to screening had a FRAX score calculated and those above a U.K. specific fracture risk threshold were invited to undergo DXA testing. A mailer was sent to patient homes and to the patient's primary care clinician. Control group patients underwent standard care as defined by their healthcare professional. Over five years of follow up, fewer hip fractures occurred in the screening group compared to the usual care group (hazard ratio [HR] 0.72; 95% CI: 0.59-0.89). There was no difference in the risk of other types of osteoporotic fractures. The number needed to screen to avoid one hip fracture was approximately 111 women.

The 2018 **ROSE trial** enrolled 18,605 women in Denmark between the ages of 65 and 80.[89] Women with FRAX ≥15% in the screening arm were invited to a DXA scan via mailer to patient and primary care clinician. The control group received standard care as defined by the primary care clinician. Although there was no significant difference in fracture incidence between the screening and control group with intention-to-treat analysis, there was a reduction in fracture risk, particularly hip fracture risk, with per-protocol analyses.

The 2019 **SOS trial** enrolled 11,032 women between the ages of 65 and 90 in the Netherlands with at least one significant risk factor for osteoporosis.[90] The screening group underwent universal DXA whereas the usual care group received screening at the discretion of the clinician. There was no significant difference in the risk of fracture over a mean follow up of 3.7 years. Notably, in the screening group, only 69% of the participants who had an indication for treatment reported taking any medication for osteoporosis and this decreased to 46% after 36 months.

Universal screening for older adults

Universal DXA screening of post-menopausal women age 65 years or older is recommended by eight key U.S. guideline writing bodies, the American Association of Clinical Endocrinologist (AACE)/American College of Endocrinology (ACE)[91], Bone Health and Osteoporosis Foundation (BHOF)[28,92], International Society for Clinical Densitometry (ISCD)[22], U.S. Preventative Services Task Force (USPSTF)[93], American College of Family Physicians (AAFP)[94], American College of Preventative Medicine (ACPM)[95], American College of Obstetrics and Gynecology (ACOG)[96], and North American Menopause Society (NAMS).[97].

Several guideline writing groups additionally recommend universal screening of men aged ≥70. This recommendation is based on population data suggesting that the prevalence of osteoporosis in 70-year-old men is similar to that in 65-year-old women.[98]

Risked based screening for younger adults

In addition to universal screening, clinical guidelines also agree that younger adults over age 50 should undergo DXA screening if they have elevated risk of osteoporotic fracture. While recommendations for how to assess risk are not standardized, many experts suggest the use of a formalized risk assessment calculator to identify a patient's 10-year risk of osteoporotic fracture. Results from such formal risk scores can then be used to identify patients at sufficiently high risk of fracture to warrant DXA testing.

Our recommendation, consistent with recommendations by the USPSTF, is to perform DXA screening in women aged 50-64 years and men aged 50-69 years based on results of a FRAX score risk assessment. Specifically, this population should undergo a DXA if their 10-year risk of a major osteoporotic fracture is >8.4%, which is the risk for a 65-year-old woman without additional clinical risk factors.

Screening intervals

Population based registries demonstrate that after an initial BMD test, the time to the development of osteoporosis (if not already present) is strongly related to the initial T-score. One such study tracked how long it took for approximately 10% of patients with osteopenia to progress to osteoporosis stratified according to initial T-Score (see table 3).[99,100]

Table 3: Selected guideline for recommended DXA screening intervals

Initial T-Score	Interval to re-screen	Number of years to 10% develop osteoporosis (95% CI)[99]
> -1.5	10 to 15 years	16.5 (13.6-20.2)
-1.5 to -2.0	3 to 5 years	4.6 (4.1-5.1)
< -2.0	1 to 2 years	1.0 (0.8-1.1)

Screening should be repeated sooner if any new clinical risk factors for osteoporosis develop or if a patient sustains an incident fracture.

Logistic considerations for screening

The DXA is not a very expensive test, but cost may serve as a barrier for many patients if the test is not covered by insurance. DXA scanning is covered by Medicare for:

- women ≥65 years of age
- women deemed by clinician to be estrogen-deficient or at increased risk of osteoporosis
- men and women with vertebral abnormalities suggestive of osteopenia, osteoporosis or fracture
- men and women on glucocorticoids at doses equivalent or greater than 5 mg of prednisone per day for >90 days

- men and women with primary hyperparathyroidism
- men and women being monitored while on FDA-approved osteoporosis therapy

DXA testing is covered every two years for screening or more frequently for patients on chronic glucocorticoids.

The International Society of Clinical Densitometry recommends preferentially using scores obtained at the lumbar spine, total hip, and femoral neck for diagnosis of osteoporosis although the distal 1/3 radius can be used if the quality of measures at the hip or spine are unsatisfactory (e.g., scoliosis at the spine, bilateral hip replacement). Additional radiology testing such as quantitative ultrasound, CT scans, and trabecular bone scans are less clinically established and are not recommended for clinical use by non-specialized primary care physicians.

BOTTOM LINE: Clinicians should universally screen all women aged 65 and over and men aged 70 and over using a DXA. Younger adults over age 50 with risk factors should be screened with a DXA if they have a FRAX score of ≥8.4% major osteoporotic fracture in the next 10 years. Reassess annually for new risk factors or periodically rescreen using DXA based on T-score.

Non-pharmacologic risk reduction strategies

Calcium and vitamin D

Appropriate bone mineralization and architecture is mediated by homeostatic mechanisms of the kidneys, bones, and parathyroid glands. As serum calcium is used to form the calcium hydroxyapatite that is the principal component of mineralized bone, it has long been suspected that adequate body stores of calcium are necessary for normal bone strength. A negative calcium imbalance, from low calcium intake, malabsorption, vitamin D deficiency (which impairs calcium absorption), and hypercalciuria, results in upregulation of parathyroid hormone (PTH), which increases osteoclast-mediated bone destruction and demineralization.

As a result, adequate dietary intake of calcium is recommended to maintain bone health. Based on physiological calcium-balance studies, the National Academy of Medicine (formerly the Institute of Medicine) recommends at least 1,000 mg of calcium intake per day for women 19-50 years old and men 19 to 70 years old and at least1,200 mg of calcium intake per day for women >50 years old and men >70 years old.[101]

Because Vitamin D is necessary for adequate gastrointestinal calcium absorption, adequate intake of Vitamin D has also been suggested to protect bone health. The National Academy of Medicine (NAM) recommended at least 600 international units (IU) of vitamin D daily for men and women <70 years old and at least 800 IU daily for adults >70 years old, with a goal of maintaining serum 25-hydroxyvitamin D (25OHD) ≥20 ng/mL. Some experts recommend a higher 25OHD target of 30 ng/mL for patients with osteoporosis. This is supported by the finding that PTH levels begin to increase after serum 25OHD levels drop below 30 ng/mL.[102] Furthermore, there is some evidence that a goal serum 25OHD level of >30 ng/mL may improve treatment response to bisphosphonate and avoid treatment failure, including BMD loss and fractures.[103]

Efficacy data supporting supplementation

For adults who do not get the recommended doses of calcium and vitamin D from natural sources, supplementation has been recommended. However, there is conflicting data from multiple randomized clinical trials on the efficacy of vitamin D and calcium supplementation in preventing osteoporosis and fractures.

A 1992 trial of 3,270 institutionalized ambulatory elderly women (mean age 84) randomized to calcium and vitamin D supplementation versus placebo for 18 months found a significant increase in femoral neck bone mineral density and a significant decrease in the incidence of hip (43% reduction, p=0.043) and non-vertebral (32% reduction, p=0.015) fractures.[104] A subsequent 1997 randomized trial among healthy, women and men without osteoporosis (T-Score > -2) found that calcium and vitamin D supplementation was associated with a lower risk of first fracture (RR 0.50; 95% CI: 0.2-0.9).[105]

Subsequent trials, however, have questioned the generalizability of these conclusions. A 2006 trial among Women's Health Initiative enrollees found that among 36,282 women 50-79 years of age with or without osteoporosis (mean hip T-Score = -0.65) supplementation with calcium and vitamin D increased bone mineral density but did not reduce the incidence of fractures.[106] However, baseline calcium intake in this study population was already >1,000 mg of calcium per day, and a "adherent" patients (those who took >80% of the supplement doses) were found to have a 29% reduction in hip fracture in a secondary pre-protocol analysis. An open-label randomized trial of calcium and vitamin D supplementation in women with or without osteoporosis over 70 years of age did not find a reduction in fracture risk.[107] Finally, even among those with pre-existing osteoporotic fractures, vitamin D and calcium supplementation was not found to be effective as secondary prevention of new fractures in a study of mainly female patients over age 70 in the U.K.[108]

These conflicting trial results prompted the Cochrane Review to conduct a meta-analysis in 2014 which found that, among 49,853 older women and men (with or without existing osteoporosis), treatment with vitamin D and calcium reduced the incidence of hip fractures (RR 0.84; 95% CI: 0.74-0.96).[109] Subgroup analysis found that the risk reduction was greatest in institutionalized rather than community dwelling patients. In contrast to the conclusions of the Cochrane Review, a subsequent meta-analysis published in JAMA in 2017 found that supplementation with vitamin D and calcium had no effect on fracture risk in community dwelling older adults (with or without existing osteoporosis).[110]

Based on these analyses we conclude that there is poor quality evidence that combined supplementation with calcium and vitamin D may modestly reduce the risk of fracture in older men and women and that the risk reduction is probably highest in institutionalized patients (nursing homes, rehabilitation facilities, long-term care facilities).

Vitamin D supplementation alone

Observational studies have found an association between low levels of serum vitamin D and fracture risk. A 2017 meta-analysis found that the relative risk of hip fracture was 1.58 (95% CI: 1.41-1.77) for those with serum vitamin D level <60 nMol/L compared to those with levels >60 nMol/L. However, large randomized controlled trials comparing vitamin D supplementation alone (without calcium) and placebo have found inconsistent results, with most finding no effect on incident fracture risk.[111–114] In the largest randomized controlled trial of 25,871 generally healthy participants across the U.S. (the **VITAL trial**), vitamin D supplementation at a dose of 2,000 IU daily did not reduce fracture risk over five years, even in those with lower baseline levels of vitamin D.[115] Furthermore, large bolus dosing may be harmful as one

high quality randomized controlled study actually found an increased risk of both falls and fractures with vitamin D supplementation dosed as 500,000 IU bolus annually, compared to placebo.[116] Overall, vitamin D supplementation alone (without calcium) has not been shown to reduce fracture incidence in the general population. Although there is very limited data in patients with very low vitamin D levels, these patients are at high risk for osteomalacia and fractures.[117] The NAM identified a serum level of <12 ng/mL as placing a patient at significant risk for low bone density and that a level >20 ng/mL is adequate for 97.5% of individuals.[101]While we do not recommend routine screening for vitamin D levels, we would encourage vitamin D testing in patients with osteoporosis and osteopenia as it would be important to supplement these patients with very low vitamin D levels. For patients with osteoporosis and at risk for fractures, it is also pertinent to ensure adequate calcium and vitamin D intake.

Safety of calcium and vitamin D supplementation

Gastrointestinal (GI) side effects, including constipation, bloating, and gas, are common with calcium supplementation. While calcium supplementation can increase the risk of nephrolithiasis, it is important to note that dietary (as opposed to supplemental) calcium actually reduces the risk by binding oxalate in the GI tract. Between 2010-2021, 10 meta-analyses have investigated whether calcium supplementation increases cardiovascular risk, with four finding a significant risk.[118–127] In 2016, the American Society for Preventative Cardiology and the National Osteoporosis Foundation concluded that calcium intake of <2,000 mg/day is not associated with a risk of cardiovascular and/or cerebrovascular disease or mortality.[128] The NAM also recommends limiting total calcium intake to <2,000 mg/day.[101]

The primary concern with vitamin D intoxication is hypercalcemia, which generally does not occur with supplemental doses of <10,000 IU/day or at serum 25OHD levels of <150 ng/mL.[101] The NAM recommends <4,000 IU/day of vitamin D and to avoid 25OHD levels above 50-60 ng/mL, as all-cause mortality may be higher beyond this level.[101]

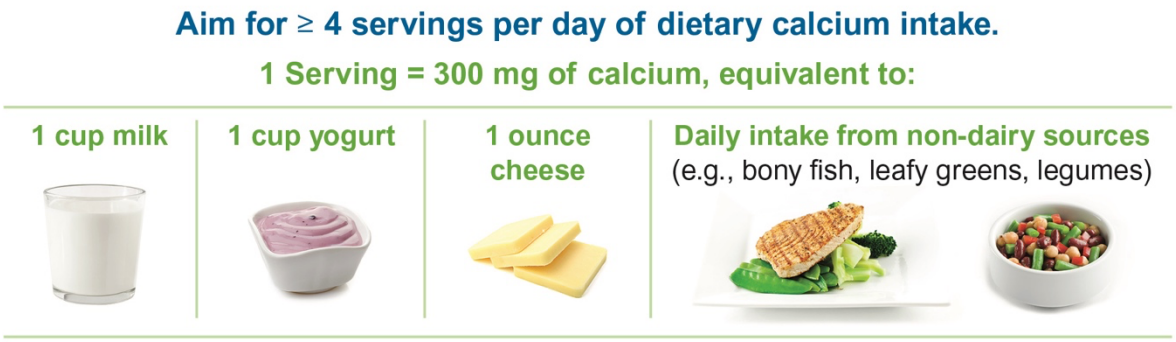
Recommendations for those without established osteoporosis and osteopenia

For the general population, we do not recommend routine testing of vitamin D levels. We recommend adequate dietary calcium and vitamin D intake but do not recommend the use of dietary supplements unless multiple risk factors for osteoporosis (see epidemiology and risk factors) are present.

Recommendations for those with osteoporosis and osteopenia

Patients with diagnosed osteoporosis or osteopenia identified by DXA screening should be encouraged to meet the recommended daily doses of calcium (1,200 mg) and vitamin D (800 IU). Because calcium supplementation can be associated with side effects, dietary intake is preferred, with use of supplementation only as needed for patients without adequate dietary calcium intake.

Figure 4: Examples of calcium servings



If patients do not consume 4 servings per day of calcium, they should supplement as follows:

- ≥3 servings: no supplementation needed
- 1-2 servings: 500-600 mg per day
- 0 servings: 500-600 mg twice a day

The type of calcium supplementation depends on a patient's medical history and preferences. Calcium citrate does not require gastric acid for absorption and is best for patients on acid blocking therapy such as a proton pump inhibitor.[129] Calcium carbonate is more widely available and is effective if taken with meals. Calcium supplementation should be limited to 600 mg at a time. Note that these quantities refer to elemental calcium and strengths may vary by calcium salt.

For vitamin D, we recommend supplementation as needed to reach a serum 25OHD goal of 30-50 ng/mL for optimal bone health.

Preventing falls

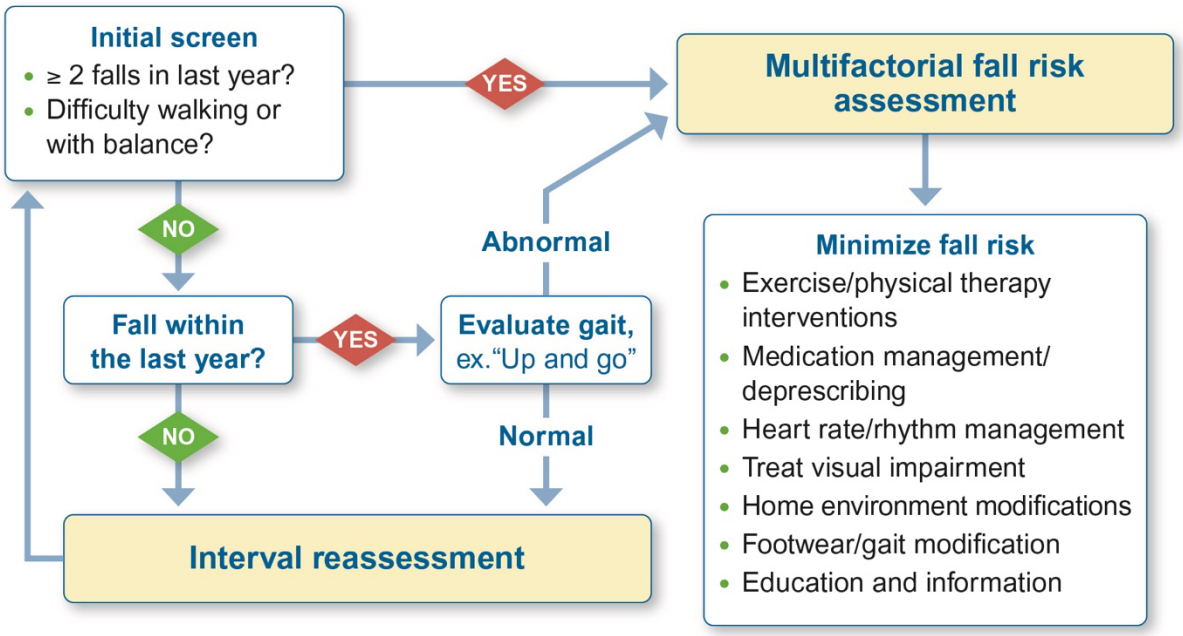
Although low bone density is a risk factor for fractures, an inciting traumatic event is often required for bone fractures and falls are a common mechanism for osteoporotic fractures. Reducing the incidence of falls is a key intervention in preventing morbidity and mortality from osteoporosis and osteopenia.

Among community dwelling older adults approximately 50% of falls result in injury, 4-6% result in a fracture, and fall related injuries account for 5.3% of all hospitalizations in older adults. Complications from falls are the leading cause of death from injury among both men and women over 65.[130] The estimated yearly medical costs attributable to fall related injuries is 50 billion U.S. dollars; $2.8 billion are spent yearly in the state of Pennsylvania alone.[131,132]

Screening for fall risk

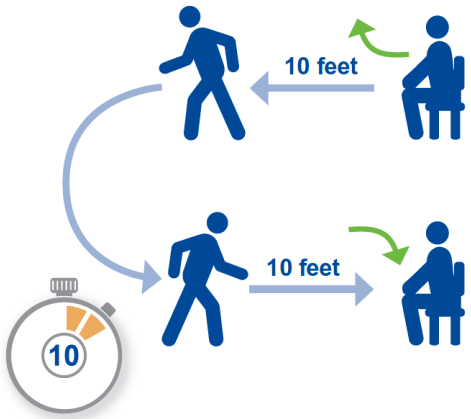
As described below, multifactorial fall risk reduction interventions have been shown to be effective in high-risk individuals. Effective screening for fall risk can allow for the targeted allocation of aggressive fall risk reduction resources. There are limited data on the most effective means for fall risk screening; however, a fall risk assessment is a required component of the Welcome to Medicare primary care visit. The CDC recommends a stepwise approach to fall screening as detailed in Figure 5 (next page).

Figure 5: An approach to minimizing fall risk



Timed up and go test

Figure 6: The Timed Up and Go Test (TUG)



Instructions

- Ask the patient to sit in a standard chair.
- Tape a line on the floor 10 feet away.
- Tell the patient to *"Stand up from the chair, walk at your normal pace to the line on the floor, turn, walk back to the chair, and sit down again."*
- Repeat 3 times and average trials 2 and 3.
- Average time > 12 seconds suggests high risk.

In addition, the TUG test may reveal several characteristic gait patterns.

The mean time to complete the Timed Up and Go test is 9.4 seconds (8.9-9.9) for adults at least 60 years of age.[133] Scores greater than 12 seconds are associated with decreased mobility and elevated fall risk.[134–136]

Mitigating fall risk

Comprehensive fall prevention programs are an effective mechanism for reducing the incidence of falls. A 1994 randomized trial of multifactorial interventions (including medication review, exercise programs and behavioral instructions) among 301 community dwelling adults over 70 years old found that the incidence ratio of falls for those enrolled in the program was 0.76 (95% CI: 0.58-0.98), after adjusting for age, sex, baseline fall risk factors, and number of prior falls.[137] Another 2004 randomized trial of 310 community dwelling adults over 70 years old also found a 31% reduction in fall occurrences compared to controls (RR 0.69; 95% CI: 0.50-0.96) for those enrolled in a 7-week multifactorial fall prevention program focused on limb strength and balance, home environment adaptation, vision checks, and high-risk medication reviews, compared to controls.[138]

A meta-analysis of 40 randomized controlled trials of fall risk interventions found that multifactorial interventions (such as those described in the above two trials) reduced fractures by an adjusted risk ratio of 0.82 (95% CI: 0.72-0.94). Exercise programs alone were also effective with adjusted risk ratio of 0.86 (95% CI: 0.75-0.99). Isolated home environment interventions and education only programs were not associated with a significant reduction in fall risk, although they are important elements of multifactorial programs.[139] A 2012 Cochrane review found similar benefits for fall risk reduction programs.[140]

Table 4: Practical advice for patients to reduce falls risk

Risk factors for falls	Treatment options
Poor gait, strength, balance	Refer to physical therapy and/or to an evidence-based exercise or fall prevention program
Medications that can increase fall risk (e.g., benzodiazepines, anticholinergics, antipsychotics)	Optimize medications by stopping, switching, or reducing dose of these drugs whenever possible
Home hazards (e.g., throw rugs, uneven floors)	Connect patients with an occupational therapist to evaluate home safety and provide recommendations. This may be reimbursable by Medicare.
Orthostatic hypotension	• Stop, switch, or reduce the dose of contributing medications. • Establish an appropriate blood pressure goal. • Encourage adequate hydration. • Recommend compression stockings.
Visual impairment	• Refer to ophthalmologist/optometrist to determine whether the patient might benefit from cataract surgery. • Educate about depth perception and single vs. multifocal lenses.
Feet/footwear issues	• Teach about shoe fit, traction, insoles, and heel height. • Refer to a podiatrist.

Evidence-based programs assist patients with reducing fall risk. Healthy steps programs improve strength and balance in older adults. Home based assessments of common fall hazards can improve safety within the home to reduce fall and fracture risk. The CDC program, Stopping Elderly Accidents, Deaths & Injuries (STEADI), provides a host of links and resources for patients and caregivers. See

CDC.gov/STEADI. Local resources at Area Agencies on Aging and other health and wellness centers may also be available.

Alcohol and tobacco use

Heavy alcohol and tobacco use are known contributors to overall morbidity and mortality. They have also been shown to increase the risk of osteoporosis and/or fractures. Daily drinking greater than 2 standard drinks for women and four standard drinks for men is associated with an increased fracture risk.[141] Smoking increases the risk of hip fracture by about 80% and is associated with decreased bone mineral density in post-menopausal women.[46,142] As a result, reducing risk of fracture is just one of several health benefits that can be achieved by reducing heavy alcohol consumption and quitting smoking.

Exercise

Physical activity is a critical component of a healthy lifestyle for older adults and has been shown to reduce the risk of osteoporosis. A meta-analysis of 10 randomized trials found that targeted, unsupervised exercise interventions increased bone mineral density and that this effect was more pronounced in patients with underlying osteopenia/osteoporosis than for those with normal bone density.[143] Among 101 post-menopausal women with T-score < -1.0 randomized to high-intensity and impact training versus low intensity based programs, high-intensity, high-impact exercise was found to be superior to low intensity programs in improving bone mineral density (lumbar spine BMD +2.9%, $p<0.001$).[144] A 2011 Cochrane Review of 43 randomized trials of exercise interventions found that exercise interventions were associated with higher bone mineral density and that non-weight bearing resistance training was most effective for hip/pelvis BMD whereas combination weight bearing (impact exercise) and resistance training as opposed to one or the other in isolation was most effective for lumbar spine BMD. There was no impact of these interventions on the risk of fracture.[145] Another meta-analysis comparing resistance only exercise to combined programs that include impact (i.e., weight-bearing) exercise found that combined training is more effective in preserving bone mineral density that resistance training alone.[146] On the bases of these data, combined resistance and weight-bearing exercise is recommended for all women and men at risk for the development of osteoporosis.

BOTTOM LINE: Patients with osteoporosis or osteopenia should have adequate calcium and vitamin D intake, with supplementation if needed. Prevent falls through evidence-based interventions and home assessments to remove common hazards. Exercise, limiting alcohol intake, and stopping smoking also contribute to improved bone health.

Pharmacotherapy

Fortunately, several classes of medications have emerged with robust evidence of safety and effectiveness in terms of preventing osteoporotic fractures. There is overwhelming evidence that the benefits of these treatments outweigh risks among a broad range of patients, including some patients with osteopenia alone.

Based on the available evidence and aligned with clinical guidelines, we recommend pharmacotherapy be offered for patients with:

- any history of osteoporotic fractures of the hip or spine regardless of bone density, or history of a fracture at the proximal humerus, pelvis, and wrist with concurrent osteopenia
- radiographic osteoporosis as defined by a T-score below -2.5 at the lumbar spine, total hip, femoral neck, or distal 1/3 radius
- osteopenia with a FRAX defined 10-year hip fracture risk ≥3% or major osteoporotic fracture risk ≥20%.
- women ≥65 years old with osteopenia (bisphosphonates only)

See below for a summary of evidence for each of these recommendations.

History of osteoporotic fractures

The risk of subsequent fractures after an initial osteoporotic fracture is high. A 2004 metanalysis of 11 cohort studies also found a relative risk of fracture of 1.86 (95% CI: 1.75-1.98) for patients with a fracture history compared to those without a fracture history. This risk was slightly lower but still significantly elevated even after adjustment for bone mineral density (RR 1.77; 95% CI: 1.64-1.91).[147]

The first randomized trial investigating osteoporosis pharmacotherapy as secondary prevention after an incident hip fracture (without regard to bone mineral density) was published in 2007. In the **Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Recurrent Fracture (HORIZON) trial** patients with a recent hip fracture (regardless of bone mineral density) were randomly assigned to yearly zoledronic acid infusion vs. placebo and monitored for a median of 1.9 years. The HR for any subsequent fractures was 0.65 (95% CI: 0.50-0.84) and mortality was significantly lower in the treatment group (HR 0.72; 95% CI: 0.56-0.93).[148]

Radiographic osteoporosis

The risk of a hip fracture increases with decreasing bone mineral density. The relative risk of a hip fracture increases by 2.07 (95% CI: 1.91-2.24) with each standard deviation decrease in bone mineral density.[17] The majority of phase III trials of osteoporotic pharmacotherapy use bone mineral density as inclusion criteria, with multiple safe and effective therapies among this group.

Osteopenia with a FRAX defined 10-year hip fracture risk ≥3% or major osteoporotic fracture risk ≥20%

Cost-effectiveness analysis studies have identified a FRAX hip fracture 10-year risk of 3% as the cutoff at which bisphosphonates become cost-effective with a threshold of $60,000 per quality-adjusted life-year gained under the assumption of $600/year drug costs with a fracture risk reduction of 35%.[149] Furthermore, a systematic review of prior cost-effectiveness studies found that assigning treatment thresholds on the bases of fracture risk by FRAX score is likely more cost-effective than using strict T-score-based cutoffs.[150]

Older women with osteopenia

There are no current guideline writing bodies that endorse providing pharmacologic therapy on the basis of osteopenia alone, except for some patients on long-standing glucocorticoids and aromatase inhibitors.

Recent trial results, however, offer compelling evidence in support of the inclusion of osteopenic women aged ≥65 years to those offered pharmacologic therapy for primary prevention of osteoporotic fractures.

In a subgroup analysis of the four phase III trials on risedronate restricted to post-menopausal women with osteopenia (T-Score -1 to -2.5) without pre-existing fractures, researchers found a 73% risk reduction (HR 0.27; 95% CI: 0.09-0.83) on the combined outcome of vertebral and non-vertebral fractures. The number of post-menopausal osteopenic women needed to treat to prevent one fragility fracture was 21. There were no statistically significant adverse events identified in the treatment vs. control groups.[151] Similar results were found in a sub-group analysis of alendronate therapy, although those with pre-existing fractures were not excluded; the HR for vertebral fractures was 0.40 (95% CI: 0.19-0.76).[152]

The sole randomized trial of osteoporosis pharmacotherapy designed with osteopenic women as the primary inclusion group was published in 2018. The trial randomized 2,000 women ≥65 years with T-score -1 to -2.5 to receive intravenous zoledronic acid or placebo for 18 months. The primary outcome of fragility fracture was significantly less frequent in the treatment group vs. placebo (HR 0.63; 95% CI: 0.50-0.79) with a number needed to treat to prevent a fracture in one woman of 15. There was no increased incidence of adverse events in the treatment group.[153] The treatment effect of zoledronic acid remains statistically significant at both high and low pre-treatment fracture risk (based on FRAX score).[154] On the bases of these studies, therapy with bisphosphonates for post-menopausal women ≥65 years with osteopenia alone may be clinically effective and should be offered to such women. There is limited data on the cost-effectiveness of such interventions.

Pharmacologic classes

The classes of medications used to treat osteoporosis work by two main mechanisms. Anti-resorptive therapies, including bisphosphonates and denosumab, block osteoclast activity that promotes bone resorption. Anabolic agents, including teriparatide and abaloparatide, promote osteoblast activity (i.e., bone formation). Romosozumab, which was recently approved by the FDA in 2019, works by both reducing bone resorption and promoting bone formation.

In most cases, due to a combination of cost, tolerability, and safety, bisphosphonates are recommended as first-line therapy for fracture reduction in osteoporosis. In select patients at very high risk of fracture, including those with vertebral fracture(s), multiple fractures, and very low BMD (T-score <-3.0), referral to Endocrinology/Rheumatology should be considered to treat with anabolic agents first, prior to use of anti-resorptive agents like bisphosphonates. Randomized controlled studies have shown that starting with anabolic agents prior to anti-resorptive therapies result in greater gains in BMD than treating with anabolic medications following use of anti-resorptive therapies.[155]

Bisphosphonates

Bisphosphonates exert their anti-fracture effect via binding to calcium hydroxyapatite particularly at sites of active bone remodeling. Bisphosphonate molecules that are not incorporated into bone are excreted via the urine. Within the bone, bisphosphonates work primarily by inhibiting the activity of osteoclasts and also stimulate the differentiation and longevity of osteoblasts.[156]

Role in treatment

The first bisphosphonate was approved by the FDA to treat osteoporosis in 1995. Since then, robust evidence of safety has made bisphosphonates the first-line treatment for most patients with osteoporosis. Currently, 4 bisphosphonates are available in the US, including 3 oral formulation and 1 intravenous formulation dosed annually (Table 5).

Oral bisphosphonates can cause dangerous pill esophagitis. As a result, patients prescribed oral bisphosphonates should be able to sit upright or stand for 30 minutes following ingestion. Intravenous options are preferred in patients with gastroesophageal reflux disease (GERD) or other esophageal diseases, malabsorption (e.g., bariatric surgery, celiac disease), or if adherence is a concern. Oral bisphosphonates vary based on their dosing frequency ranging from daily to monthly. Patient preference for weekly or monthly oral option vs. a yearly infusion may drive selection. Because ibandronate has not been shown to reduce the risk of hip fracture, generally other oral bisphosphonates (alendronate or risedronate) are preferred for initial therapy. Bisphosphonates should not be prescribed in patients with hypocalcemia or creatinine clearance < 35 mL/min.

Table 5: Bisphosphonate treatment options

				Prevents fracture	
Medication	**Route**	**Dose**	**Frequency**	**Vertebral**	**Hip**
alendronate (Fosamax, generics)	oral	10 mg 70 mg	daily weekly	√	√
ibandronate (Boniva, generics)	Oral IV	150 mg 3 mg	monthly 3 months	√	
risedronate (Actonel, generics)	oral	5 mg 35 mg 150 mg	daily weekly monthly	√	√
zoledronic acid (Reclast, generic)	IV	5 mg	yearly	√	√

Efficacy

There have been few head-to-head randomized trials comparing bisphosphonates. A 2005 randomized trial (**Fosamax Actonel Comparison Trial (FACT)**) comparing alendronate to risedronate among postmenopausal women >40 with T-score < -2.0 found that alendronate had greater increases in BMD (3.4% vs. 2.1% p<0.001) at the hip after one year of therapy; similar results (4.6% [alendronate] vs. 2.5% [risedronate]; p<0.001) were found after two years of therapy.[157,158]

In another trial comparing zoledronic acid to weekly oral bisphosphonate in postmenopausal women with T-score <2.0 zoledronic acid was associated with lower levels of bone turnover markers and the majority of surveyed patients expressed a preference for a yearly infusion versus weekly oral therapy.[159] Network meta-analyses incorporating head-to-head and placebo-controlled trials have also demonstrated that zoledronic acid is likely superior to oral bisphosphonates in terms of fracture risk reduction. A 2011 meta-

analysis of eight randomized trials found a 79% probability that zoledronic acid was superior to oral bisphosphonates in the prevention of vertebral fractures.[160] A 2017 network meta-analysis of 24 randomized controlled trials found that zoledronic acid had the lowest odds ratio (was most effective) for the prevention of vertebral fractures.[161] Table 6 shows the results of a 2019 network meta-analysis comparing efficacy of selected bisphosphonates in postmenopausal women.

Table 6: Summary of bisphosphonate efficacy[162]

Drug	RR vs. placebo (95% CI)	
	Vertebral fracture	Hip fracture
Ibandronate	0.67 (0.48-0.93)	0.62 (0.29-1.36)
Alendronate	0.57 (0.45-0.71)	0.61 (0.42-0.90)
Risedronate	0.61 (0.48-0.78)	0.73 (0.58-0.92)
Zoledronate	0.38 (0.25-0.58)	0.60 (0.45-0.81)

Bisphosphonates have also been shown to reduce fractures in men, although there is much less data. A trial of 1,199 men with osteoporosis treated with zoledronic acid vs placebo for two years demonstrated a 67% reduction in vertebral fractures (RR 0.33; 95% CI: 0.16-0.70).[163] Alendronate was studied in at least two randomized trials among men with osteoporosis. Alendronate significantly reduced the risk of vertebral fractures but not non-vertebral fractures.[164,165] A 2009 randomized controlled trial enrolled 316 men with osteoporosis to risedronate vs placebo over two years. The incidence of new vertebral fractures was significantly lower in the risedronate group (relative risk reduction 61%, p=0.0026).[165]

Safety

Upper Gastrointestinal Symptoms: Bisphosphonates are generally safe and well-tolerated. Oral bisphosphonates are associated with symptoms of upper GI irritation. In a 12-week exploratory study of alendronate vs. placebo in postmenopausal women, a similar rate of upper GI symptoms were reported in the treatment and control group (22.7% treatment vs. 20.4% placebo). However, serious upper GI symptoms and symptoms that led to study discontinuation were more frequent in the alendronate group (20.3% vs. 12.9%).[166] A 1996 analysis of post-marketing adverse event reporting data for alendronate found that among 470,000 patients undergoing treatment, there were 199 reported adverse effects to the esophagus, 51 of which were classified as serious or severe. The most common events were ulcers, esophagitis, erosive esophagitis, dysphagia and odynophagia. Endoscopic evaluation of a selection of these patients suggests the etiology of symptoms is from prolonged contact with the medication as evidenced by well-circumscribed lesions with surrounding normal tissue. To avoid GI symptoms, oral bisphosphonates should be taken in the morning with a full glass of water (6-8 oz) and patients should not lie flat for at least 30 minutes following administration.[167]

Osteonecrosis of the jaw: Osteonecrosis of the jaw refers to development of exposed bone in the maxillofacial region that does not heal within eight weeks.[168] Osteonecrosis of the jaw was initially noted in patients undergoing radiation therapy to the jaw or mouth.[169] The first cases of osteonecrosis of the jaw in association with bisphosphonate use were reported in 2004 among patients treated with IV bisphosphonates.[170] A 2013 meta-analysis of 12 studies with 2,652 cases and 1,571,997 controls found an odds ratio for osteonecrosis of the jaw associated with bisphosphonate use of 2.32 (95% CI: 1.38-3.91).[171]

The risk of osteonecrosis is substantially higher for patients receiving intravenous zoledronic acid to treat a malignancy, which requires much higher doses than treatment of osteoporosis (monthly vs. yearly). A 2008 review of 78 cases of osteonecrosis of the jaw found that only 5% of were in patients receiving bisphosphonates for osteoporosis as opposed to malignancy.[172] The risk is thought to be higher for IV than for oral bisphosphonates.[173] The risk appears to increase with duration of therapy although given low case numbers this association does not meet statistical significance.[174] The overall incidence of osteonecrosis is very low. For the treatment of osteoporosis, the incidence of osteonecrosis of the jaw is between 1-69 per 100,000 person-years for oral bisphosphonates, 0-90 for IV bisphosphonates and 0-30 for denosumab.[175] These findings led the FDA to include updated labeling indicating the risk of osteonecrosis with IV and oral bisphosphonates.

Approximately 50% of cases of osteonecrosis of the jaw occur following dental procedures (namely tooth extractions),[176] some dental providers have proposed prophylactic interventions before or after dental procedures for patients receiving bisphosphonates. The American Association of Oral and Maxillofacial Surgeons (AAOMS) guidance on medication related osteonecrosis of the jaw recommends:[177]

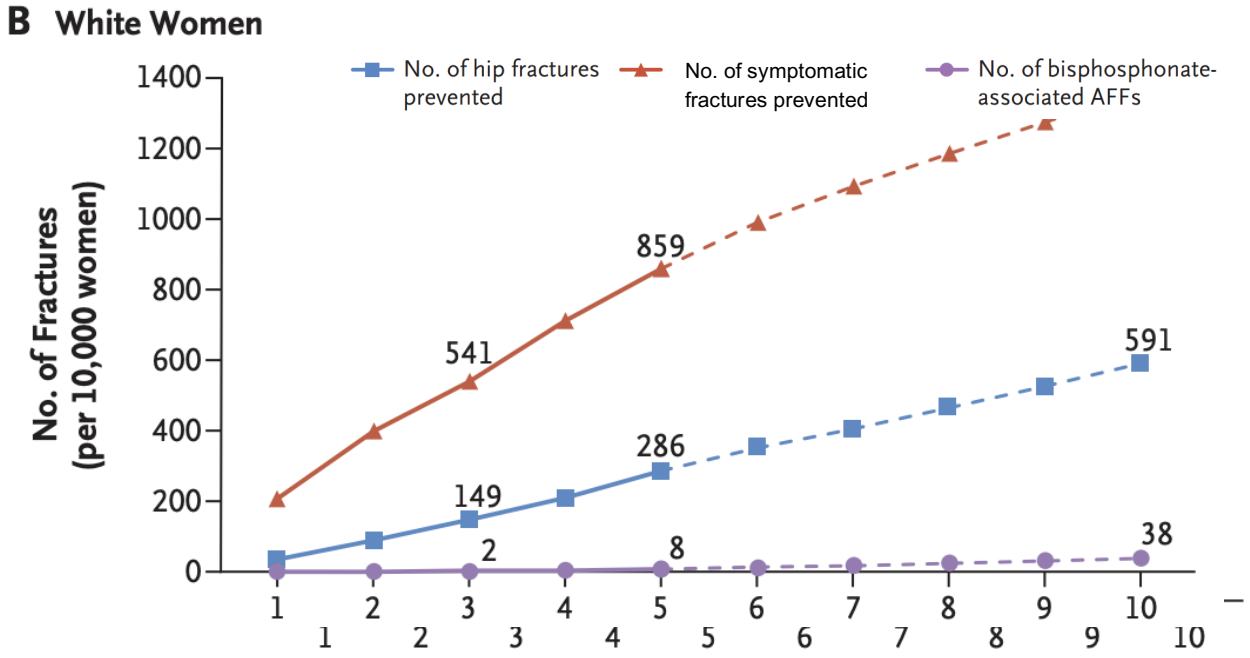
- dental screening and interventions prior to initiation of anti-resorptive therapies (supported by retrospective studies compared to patients who were not screened).
- a drug holiday for high-risk patients (>4 years of therapy, concomitant steroid use, or smoking history) 2-month pre-procedure and 3-month post-procedure. Very limited data to support or refute a “drug-holiday” with dental procedures for patients who are not high risk.

In the 2011 updates on osteoporosis treatment recommendations, the American Dental Association’s Council on Scientific Affairs declared “the benefit provided by anti-resorptive therapy outweighs the low risk of developing osteonecrosis of the jaw”.[178]

Atypical Femur Fracture: Initial reports of sub-trochanteric femur fractures occurring with minimal to no trauma in patients on bisphosphonate therapy were published in 2005-2007.[179,180] These fractures have subsequently become known as atypical femur fractures (AFF). A meta-analysis of 11 cohort and case-control studies found a significant association between bisphosphonate use and the risk of AFF (adjusted OR 1.70; 95% CI: 1.22-2.37).[181] Following at least five years of bisphosphonate therapy, the incidence of AFF was 130 cases per 100,000 person-years according to a 2011 case-control study whereas the incidence is between 3.2-50 per 100,000 person years for patients with a shorter duration of therapy.[182,183] There is limited to no data comparing the incidence of AFF in patients receiving bisphosphonates for malignant vs. non-malignant indications. The risk of AFF rises with increasing duration of bisphosphonates use and decreases by 70% with each successive year after discontinuation.[184] In 2010, the FDA released updates to the *warnings and precautions* sections of the label for all bisphosphonate drugs indicating a risk of atypical femur fracture.[185]

Despite the well-established risk of AFF, risk-benefit analysis weighs heavily in favor of bisphosphonate use for appropriate durations of therapy. For average-risk white postmenopausal women taking bisphosphonates for five years, there are 1,363 clinical fractures and 591 hip fractures prevented compared to only 38 cases of atypical femur fractures. There appears to be a higher risk for atypical femur fracture among women of Asian descent potentially related to differences in drug metabolism, pelvic/hip morphology, and drug adherence.[186–188]

Figure 7: Fractures prevented and AFF in white women[189]



Atrial fibrillation: In the phase III randomized trials of alendronate (**FIT Trial**)[190] and zoledronic acid (**HORIZON-Pivotal Fracture Trail**)[191], there was an association between trial drug and the incidence of serious atrial fibrillation. In the FIT trial, alendronate was associated with a 51% increase (HR 1.51; 95% CI: 0.97-2.40) in the development of serious atrial fibrillation (defined as requiring hospitalization or judged to be life-threatening); however, there was no association with all atrial fibrillation events, including less severe episodes of atrial fibrillation. In the HORIZON-Pivotal Fracture trial, similar results were found. Serious atrial fibrillation occurred in 1.3% receiving zoledronic acid and 0.5% receiving placebo ($p<0.001$). Again, there was no significant association for overall atrial fibrillation events. Potential physiologic mechanisms for this association include alterations in cardiomyocyte calcium homeostasis, increased cardiac fibrosis and acute phase inflammatory reactions.[192] Other studies involving both IV and oral bisphosphonates, however have not reproduced these findings.[193–196] A 2010 and 2021 meta-analysis of clinical trials did not find an association between bisphosphonates and atrial fibrillation.[197,198] In 2008 the FDA provided a review of clinical safety data and found that there was no clear association between bisphosphonate use and atrial fibrillation.[199]

Acute phase reaction: Intravenous bisphosphonates can be associated with a transient acute phase reaction characterized by fevers, myalgias and arthralgias (1 in 3 patients for zoledronic acid) usually limited to 24 to 72 hours and becoming less frequent and severe with subsequent infusions (31.6% after dose 1, 6.6% after dose 2, 2.8% after dose 3).[191,200] Acetaminophen or ibuprofen every 6 hours for 3 days post-infusion can reduce the flu-like symptoms by about 50%.[201]

Transient hypocalcemia: Transient hypocalcemia can occur with bisphosphonate therapy and may be more marked in patients receiving IV formulations. Clinical factors associated with the development of symptomatic hypocalcemia include hypovitaminosis D, secondary hyperparathyroidism, kidney disease and other causes of impaired calcium homeostasis.[202,203]

Ocular inflammation: Uveitis, conjunctivitis, episcleritis, scleritis, ocular pain, and photophobia have been reported in both IV and oral bisphosphonates. The mechanism of action of this effect is unknown and appears to be idiosyncratic. As of 2004 there were 550 suspected cases reported to the World Health Organization drug monitoring database.[204]

Monitoring therapy

To assess treatment response for patients on bisphosphonates, a baseline and repeat DXA scan after 1-2 years of treatment should be performed. Monitoring with DXA can help with identifying drug failure and has been shown to improve medication adherence and decrease fracture risk.[205] DXA scans should be performed at the same facility to allow for comparison.

Sustaining 2 or more fractures or BMD loss of >4% is considered drug failure. Importantly, stable BMD after 1-2 years does not indicate treatment failure, and patients should be counseled about the expected results. In cases of treatment failure, adherence should be assessed, secondary osteoporosis work-up performed, and change in therapy should be considered.

Duration of therapy

The optimal duration of therapy of bisphosphonates has been a topic of substantial research given the significant media attention paid to the rare complications (particularly atypical femur fracture and osteonecrosis of the jaw) and the clinical data suggesting that duration of therapy may increase these risks. The **Fracture Intervention Trial Long-term Extension (FLEX) trial** randomized postmenopausal women who had completed five years of alendronate therapy to five additional years of therapy vs. placebo.[206] Compared to those who continued alendronate, patients receiving a placebo had a decline in BMD (although on average BMD remained higher than prior to initiating treatment), but no increased risk of fracture. A subsequent post-hoc analysis found that for those with a post-treatment T-score ≤ -2.5 at the femoral neck, continued treatment with alendronate for a total of 10 years significantly reduced the risk of non-vertebral fracture.[207] Women with a history of vertebral fracture at the end of the five years of alendronate were also more likely to benefit from continued alendronate therapy for a full 10 years.[208] In summary, this study has been used to support a time-limited treatment of 5 years except in cases of elevated fracture risk.

A 2014 extension of a randomized controlled trial of zoledronic acid therapy randomized 1,233 postmenopausal women who had completed three years of zoledronic acid to an additional three years versus placebo.[209] Continuation of zoledronic acid was associated with a reduced incidence of fractures only among patients with T-score ≤ -2.5 at the total hip after the three initial years of therapy and among patients with an incident vertebral fracture during the initial three years of therapy.

On the bases of these studies, we recommend repeat BMD testing following five years of oral bisphosphonate therapy, or after three years of zoledronic acid, with continued therapy for an additional five or three years for those with T-score ≤ -2.5 at the hip, incident vertebral fractures, or those with new or substantial clinical risk factors for fracture (e.g., ongoing or new glucocorticoid use). Please see Figure 10 on page 29 for further details.

After completion of bisphosphonate treatment, DXA should be monitored every 2-3 years. Based on expert opinion, a Task Force of the American Society for Bone and Mineral Research recommends restarting treatment if BMD decreases, T-score falls back into the osteoporosis range, or an incident fracture occurs.[210]

Denosumab

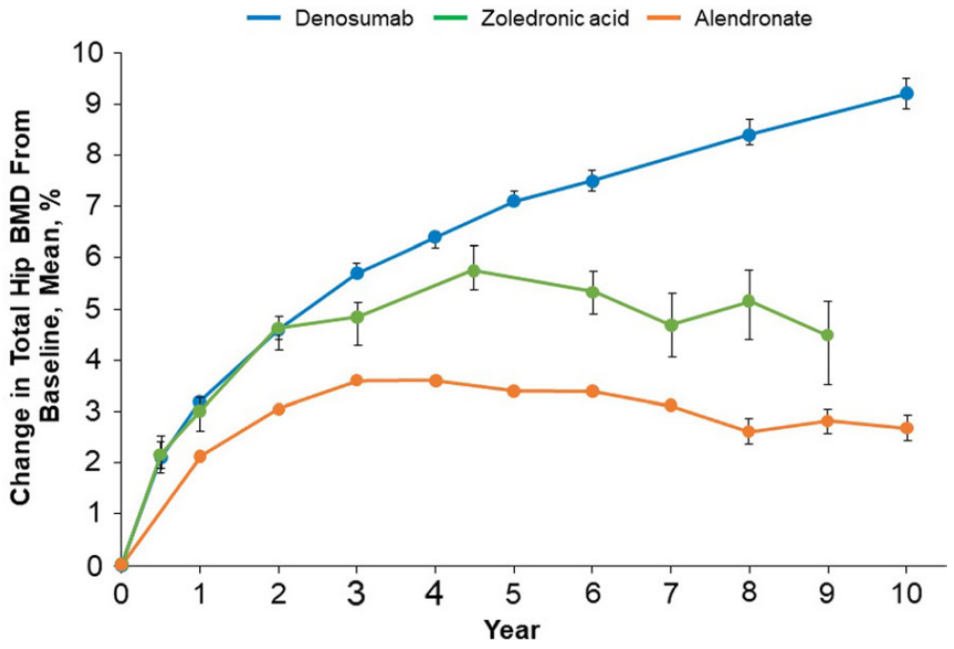
A fully human monoclonal antibody, denosumab targets the receptor activator of NF-κB ligand (RANKL) blocking the interaction between RANKL and RANK on osteoclast cells, preventing their maturation and triggering apoptosis. Denosumab (Prolia) is a subcutaneous injection of 60 mg administered every six months. This may be administered by a clinician or via home injections, and thus can be covered by a patient's medical or pharmacy benefit.

Efficacy

The **Fracture Reduction Evaluation of Denosumab in Osteoporosis (FREEDOM) trial**, published in 2009, randomized 7,868 postmenopausal women aged 60-90 years with T-score ≤-2.5 and > -4.0 to denosumab or placebo. After three years of therapy, the primary endpoint of new vertebral fractures was significantly lower in the treatment group (RR 0.32; 95% CI: 0.26-0.41). The secondary endpoints of non-vertebral fractures (RR 0.80; 95% CI: 0.67-0.95) and hip fractures (RR 0.60; 95% CI: 0.37-0.97) were also significantly lower in the treatment group.[211]

Although there have been no trials comparing denosumab vs. bisphosphonates for treatment of osteoporosis, denosumab does seem to provide an increase in BMD, compared to either oral or IV bisphosphonates (Figure 8).

Figure 8: Denosumab has greater improvement in BMD that oral or IV bisphosphonates[212]



Adverse effects

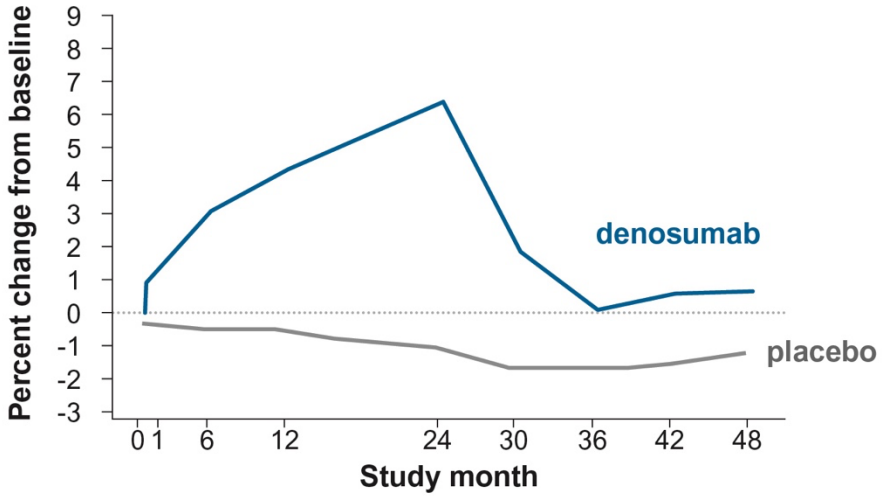
The **FREEDOM trial** had significantly more cases of severe cellulitis (0.3% vs <0.1%), eczema (3.0% vs 1.7%), and flatulence (2.2% vs 1.4%) in the treatment group. There were no cases of osteonecrosis of the jaw.[211] An extension study showed that the rate of adverse events was stable throughout the ten years

and similar to that observed during the initial three years of treatment. There was one case of atypical femoral fracture and 13 cases of osteonecrosis of the jaw.[213] Patients who have low creatinine clearance (i.e., < 30 mL/min) are at risk for hypocalcemia. Similar to bisphosphonates, osteonecrosis of the jaw and atypical femur fractures are rare complications.

Discontinuation and bone loss: Denosumab discontinuation causes a rebound in osteoclast activity that results in a rapid reduction BMD. A 2008 trial of 412 postmenopausal women with T-score -1.8 to -4 randomized patients to 24 months of denosumab therapy or placebo (or open-label alendronate) followed by discontinuation for one year. Upon discontinuation of denosumab, BMD decreased to near pre-treatment levels (although patients randomized to placebo had a larger total decrease in BMD by 36 months). When denosumab was resumed, BMD increased back to near pre-discontinuation levels within 12 months. Discontinuation of denosumab resulted in a more profound decrease in BMD compared to discontinuation of alendronate.[214] These decreases in BMD may increase the risk of fracture, although evidence is limited. One study found an increased risk of fracture for patients who had missed a dose of denosumab compared to patients who received all doses with the increased risk occurring during the missed dose interval.[215]

Among the 256 patients enrolled in the FREEDOM trial who discontinued denosumab after 24 months of therapy, BMD decreased to near but slightly above pre-treatment levels. The denosumab group did, however, maintain higher BMD after discontinuation of therapy than the group initially randomized to placebo.[216]

Figure 9: After denosumab discontinuation BMD rapidly decreases[216]



Initiation of a bisphosphonate after denosumab discontinuation may help to preserve the BMD gained from denosumab therapy. In a single arm trial among 23 post-menopausal women treated for about 2.4 years of denosumab, providing a single infusion of zoledronic acid six months after discontinuation of denosumab maintained the BMD gains of denosumab therapy for at least 2.5 years.[217] A second study utilizing alendronate therapy following discontinuation of 1-year of denosumab therapy in postmenopausal women also found that most women maintained gains in BMD.[218]

However, the evidence for using bisphosphonates to protect BMD gains after denosumab discontinuation is mixed. In a small case series of six women who were treated in the FREEDOM trial, a single dose of

zoledronic acid did not fully prevent BMD loss after discontinuation of denosumab. The authors hypothesized that bone turnover may still be suppressed 6 months post-denosumab, limiting the uptake of bisphosphonates at that time, and that administrating IV bisphosphonate when bone turnover markers increase may be more effective.[219] Subsequently, a randomized controlled trial tried different timing of zoledronic acid administration (6 or 9 months after last denosumab dose or when bone turnover markers increased) in patients who were treated with denosumab for a mean duration of 4.6 years.[220] In all arms, treatment with zoledronic acid did not prevent BMD loss in these patients discontinuing denosumab. One difference may be that these patients had been treated with denosumab longer (mean duration of 4.6 years). There is some suggestion that preserving bone density gains with bisphosphonates may be more effective in patients who were on denosumab for <3 years.

Duration of therapy

Denosumab continues to improve bone mineral density and sustains fracture risk reduction after 10 years of treatment. Patients enrolled in the initial 3-year FREEDOM trial were able to continue denosumab therapy for an additional seven years.[213] A total of 4,550 patients were enrolled and 2,626 completed the full extension study. The risk of fracture remained low throughout the 10 years and was similar to the incidence during the initial three years of the trial. BMD continued to increase each year through the entire 10 years of the trial. Relative to baseline BMD, three years of therapy was associated with a 10% increase in BMD and ten years of therapy with an increase of 21.7%.

Not all patients will want to continue denosumab indefinitely. Transitioning to a bisphosphonate after stopping denosumab may help prevent the dramatic bone density losses and increase in fracture risk when denosumab is discontinued. Recommendations on how best to bridge denosumab with bisphosphonates continues to evolve. In general, bisphosphonate therapy is started around the time a dose of denosumab would be due (about six months). Either IV zoledronic acid or oral bisphosphonates have been used. The European Calcified Tissue Society recommends at least 1 to 2 years of bisphosphonate therapy for patients receiving 2.5 years or less of denosumab treatment. Patients on denosumab for longer than 2.5 years should transition to IV zoledronic acid with monitoring of bone turnover markers. Such a plan may best be managed by an endocrinologist or rheumatologist.

Anabolic agents

Compared to anti-resorptive therapies (i.e., bisphosphonates, RANKL inhibitors), anabolic agents are more effective at increasing bone mineral density and reducing fracture risk.[221–223] There are two parathyroid hormone based therapies available: teriparatide (Forteo; parathyroid hormone analog [PTH 1-34]) and abaloparatide (Tymlos; parathyroid hormone related peptide analog [PTHrP 1-34]). Compared to placebo, teriparatide treatment for 18 months reduced risk of vertebral fractures by 65% (RR 0.35; 95% CI: 0.19-0.50) and increased lumbar spine BMD by 13%.[224] The risk of hip fracture was also lower in the treatment group.[225] Abaloparatide treatment for 18 months decreased risk of vertebral fractures by 86% compared with placebo (RR 0.14; 95% CI: 0.05-0.39) in high-risk postmenopausal women with a T-score ≤ -2.5 and pre-existing vertebral fractures, low trauma non-vertebral fractures alone, or T-score < -3.0 alone.[226] As these are parathyroid hormone analogs, precautions include patients with hypercalcemia, primary hyperparathyroidism, hypercalciuria, and urolithiasis.

Initial studies of parathyroid hormone analogs in rats suggested an increased risk of osteosarcoma. Previously, there was a black box warning to that effect for both teriparatide and abaloparatide and a lifetime limit of 2 years of therapy. Human data has not borne out this osteosarcoma concern.[227] Among

75,247 patients in the FDA-mandated FORTEO registry, there were no cases of osteosarcoma.[228] In a survey of Medicare claims data, there were no cases of osteosarcoma identified among 153,000 patients on teriparatide.[229] Finally, another 15-year surveillance study found that the incidence of osteosarcoma associated with teriparatide use was similar to background incidence rate at approximately 2.5 cases per million per year in U.S. adults.[230] Given these findings, the black box warning has been removed from both teriparatide and abaloparatide; however, due to lack of data, lifetime use of abaloparatide remains limited to 2 years. It is still advised to avoid using parathyroid hormone analogs in patients at risk for osteosarcoma, including patients with open epiphyses, Paget's disease, bone metastases, history of skeletal malignancies, and prior radiation therapy involving the skeleton.

The increase in BMD was durable for two years following treatment discontinuation when patients were started on a bisphosphonate at the completion of abaloparatide therapy.[231] Treatment with parathyroid hormone analogs, therefore should be followed by bisphosphonate or other anti-resorptive agent to maintain gains in BMD.

Romosozumab (Evenity), is a sclerostin inhibitor that is both an anabolic and anti-resorptive agent. It is administered as a monthly injection for 12 months. Treatment for one year reduced the risk of new vertebral fracture by 73% compared to the placebo group (RR 0.27; 95% CI: 0.16-0.47) in 7,180 post-menopausal women with T-score of -2.5 to -3.5. Twelve months of romosozumab was followed by 12 months of denosumab therapy. At the end of 24 months, those treated with romosozumab had a lower cumulative risk of fracture (RR 0.25; 95% CI: 0.16-0.40).[232] Increases in bone mineral density and decreases in fracture risk were maintained for three total years (1 year of romosozumab and 2 years of denosumab) in an extension trial.[233]

Romosozumab has also been compared to alendronate and has been found to reduce the risk of vertebral fractures (RR 0.63; 95% CI: 0.47-0.85) and clinical fractures (HR 0.72; 95% CI: 0.54-0.96) more than alendronate.[234] The most common side effect in these two clinical trials was a generally mild injection site reaction. Other side effects can include orthostatic hypotension with initial dose, dizziness, and leg cramps. Although there were no concerns for cardiovascular events in the clinical trial against placebo, there were more adjudicated serious cardiovascular events with romosozumab compared to alendronate, though not statistically significant (2.5% vs. 1.9%; OR 1.31; 95% CI: 0.85-2.00). A black box warning states that patients should not start romosozumab if they have had a myocardial infarction or stroke in the past year. A few cases of osteonecrosis of the jaw and atypical femoral fractures have also been reported with romosozumab.

Anabolic agents are indicated in cases of very high fracture risk, including:

- multiple fragility fractures, especially vertebral fractures
- T-Score < -3
- other failed osteoporosis therapies
- multiple clinical risk factors particularly the use of long-term, high dose glucocorticoids.

Typically, patients using anabolic therapies are managed by osteoporosis specialists. Prospective trials have demonstrated that if anabolic agents are started first before anti-resorptive therapies, there is a greater effect on BMD, whereas when anti-resorptive treatment proceeds anabolic use, there is a reduced impact on BMD.[235]

Other agents

The Women's Health Initiative (WHI) randomized trial found that hormone replacement therapy (HRT) increased bone density and reduced fractures. However, the WHI also found an increased incidence of coronary heart disease (HR 1.29; 95% CI: 1.02-1.63), breast cancer (HR 1.26; 95% CI: 1.00-1.59), stroke (HR 1.41; 95% CI: 1.07-1.85), and pulmonary embolism (HR 2.13; 95% CI: 1.39-3.25) with HRT compared to placebo. As a result of the other risks, use of HRT for osteoporosis has declined substantially. Absolute excess risks per 10,000 person-years were 7 for coronary heart disease, 8 for strokes, 8 for invasive breast cancer and 9 for pulmonary embolisms. In comparison absolute risk reductions per 10,000 person-years were 5 fewer hip fractures. The health risks of estrogen exceeded the benefits in healthy post-menopausal women.[236] The risk of adverse effects from HRT appears to be lower in younger women.[237] As a result, the Endocrine Society recommends HRT treatment/prevention of osteoporosis for a subset of women at low risk of adverse effects (i.e., those under age 60 or fewer than 10 years since the onset of menopause) who are not considered to be appropriate for non-estrogen therapies for osteoporosis.[238,239]

Raloxifene is a selective estrogen receptor modulator that is FDA-approved for prevention and treatment of osteoporosis. Although raloxifene has been shown to reduce vertebral fractures, it has not been shown to reduce non-vertebral or hip fractures.[240] There is a rapid decline in BMD to pre-treatment levels when raloxifene is discontinued.[241] Similar to HRT, risks include venous thromboembolism and fatal stroke in women with cardiovascular risk factors (HR 1.49; 95% CI: 1.00-2.24). However, in contrast to HRT, it reduces risk of invasive breast cancer.[242] Raloxifene may be suitable for postmenopausal women with low bone density at the spine, personal and/or family history of breast cancer, and low venous thromboembolism risk.[243]

Calcitonin, administered as 200 IU intranasal spray once daily or 100 IU subcutaneous/intramuscular injection daily, is no longer routinely used due to concerns about efficacy and safety.[244] In 2013, the FDA reviewed the use of calcitonin due to concern of increased cancer risk, although there was no significant increased risk of cancer in a meta-analysis of 21 randomized controlled trials.[245]

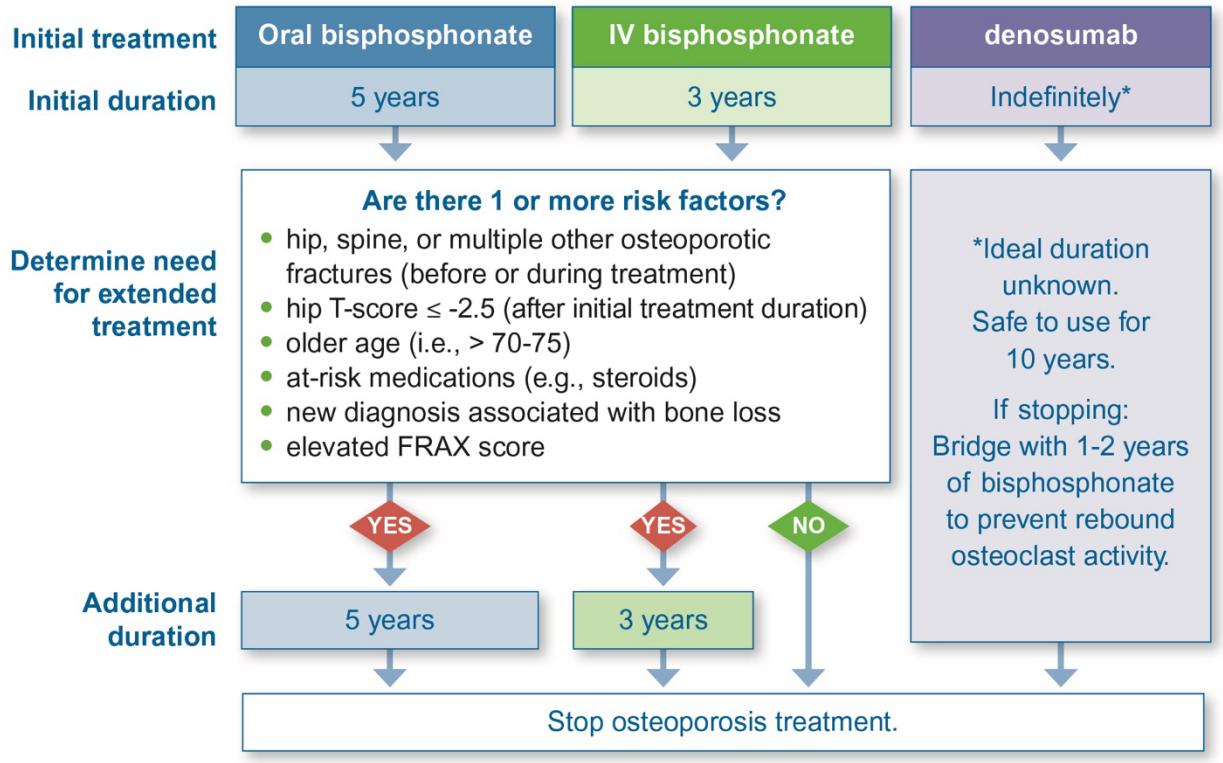
Summary of pharmacologic treatment recommendations

For primary care clinicians, bisphosphonates, either administered orally or intravenously, will be the most commonly prescribed medication for osteopenia/osteoporosis. Alendronate and risedronate are oral bisphosphonates that are effective in reducing vertebral, hip, and non-vertebral fractures and are generally well-tolerated. For patients with esophageal disorders, malabsorption issues, compliance concerns, or have gastrointestinal side effects with oral bisphosphonates, IV zoledronic acid should be used. The flu-like symptoms of zoledronic acid can be mitigated by treatment with acetaminophen. Most patients can be treated with 5 years of oral bisphosphonates or 3 years of IV bisphosphonates, but high-risk patients, including those with hip T-score $\leq$ -2.5 after the initial treatment course or those with history of vertebral fractures, should continue treatment for a total of 10 years with oral bisphosphonates or 6 years with IV bisphosphonates.

For patients who are intolerant to or have failed therapy with bisphosphonates, denosumab is an option. However, due to rebound bone loss and potentially increased risk of fracture with discontinuation, denosumab must be continued indefinitely. Patients discontinuing denosumab should be transitioned to 1-2 years of bisphosphonate treatment. Overall, the risks of osteonecrosis of the jaw and atypical femur fractures with bisphosphonates and denosumab are extremely low and the benefits of fracture prevention far outweigh these risks.

Referral to Endocrinology/Rheumatology should be considered for patients at very high risk of fracture who are receptive to more advanced therapies, such as anabolic agents. These patients include those with vertebral fracture, multiple fractures, very low BMD (T-score <-3.0), and drug failure. Furthermore, osteoporotic patients with CKD IIIB, IV, and V, for which bisphosphonates are contraindicated, should be managed by Endocrinology/Rheumatology or Nephrology.

Figure 10: treatment duration recommendations based on fracture risk[28,207,246]



BOTTOM LINE: Bisphosphonates are the first-line osteoporosis treatment for most patients given as either the IV or oral forms. Denosumab is effective for preventing fracture but can lead to rapid bone loss with discontinuation. Anabolic agents, such as teriparatide and abaloparatide, and romosozumab are reserved for the highest risk patients, are prescribed for limited durations, and generally used by osteoporosis specialists.

Putting it all together

Osteoporosis is a common medical condition in older adults that leads to significant morbidity and mortality. Primary care clinicians play a significant role in the identification and treatment of osteoporosis.

- **Screen for osteoporosis with a DXA scan:** all women ≥ _65 years old, men ≥ _70 years old, and select patients ≥ _50 years old at elevated risk for a fracture.
- **Bisphosphonates are the first-line treatment** for most patients with osteoporosis and osteopenia.
- Treatment should last at least **5 years for oral bisphosphonates or 3 years for intravenous bisphosphonates,** with longer treatment for those with the highest fracture risk.
- In patients with osteoporosis, **ensure adequate intake of calcium and vitamin D,** recommend exercise, and counsel about the risks of tobacco and alcohol.
- **Assess fall risk,** and refer to evidence-based fall prevention programs.

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