

Fracture Prevention Treatments for Postmenopausal Women with Osteoporosis

This guide summarizes the effectiveness and safety of various treatments for preventing fractures among postmenopausal women with osteoporosis. It focuses on postmenopausal women because most of the clinical trials of treatment were conducted in this population. ■ This guide does not examine the effect of treatments on intermediate outcomes, such as bone mineral density or markers of bone turnover. ■ Treatments reviewed include bisphosphonates, selective estrogen receptor modulators (SERMs), hormonal medications, calcium, and vitamin D. The dose and price of drugs reviewed are listed on the back page.

Clinical Issue

Osteoporosis increases bone fragility and susceptibility to fracture. It occurs in aging individuals of both sexes but is more common in postmenopausal women. It also can result from secondary causes, such as treatment with glucocorticoids. Each year in the United States, about 1.5 million people experience a fracture related to osteoporosis. Of those with hip fractures, one in five die, and the same number end up in a nursing home within a year of the fracture.

The goal of treating osteoporosis is to prevent fractures and their associated disability. Candidates for treatment include individuals at high risk for fracture as defined by low bone density, history of prior fracture, significant secondary causes for developing osteoporosis, and risk factors for falls, such as difficulty with walking or balance. Selecting treatment requires careful consideration of the benefits, risks, and costs as well as the likelihood of adherence.

SOURCE The source material for this guide is a systematic review of 101 research publications about efficacy and 490 research publications about adverse events. The review, *Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis* (2007), was prepared by the Southern California Evidence-based Practice Center at RAND. The Agency for Healthcare Research and Quality (AHRQ) funded the systematic review and this guide. The guide was developed using feedback from clinicians who reviewed preliminary drafts.

Clinical Bottom Line

■ Some bisphosphonates (alendronate, risedronate, and zoledronic acid) and estrogen prevent hip and other nonvertebral fractures.

LEVEL OF CONFIDENCE: ● ● ●

■ Raloxifene, estrogen, teriparatide, and most bisphosphonates (alendronate, etidronate, ibandronate, risedronate, and zoledronic acid) prevent vertebral fractures.

LEVEL OF CONFIDENCE: ● ● ●

■ Calcitonin also prevents vertebral fractures.

LEVEL OF CONFIDENCE: ● ● ○

■ Raloxifene, tamoxifen, and estrogen increase the risk of thromboembolic events.

LEVEL OF CONFIDENCE: ● ● ●

■ It is unknown whether bisphosphonates work better to prevent fractures than any other osteoporosis treatments.

CONFIDENCE SCALE

The confidence ratings in this guide are derived from a systematic review of the literature. The level of confidence is based on the overall quantity and quality of clinical evidence.

HIGH ● ● ● There are consistent results from good quality studies. Further research is very unlikely to change the conclusions.

MEDIUM ● ● ○ Findings are supported, but further research could change the conclusions.

LOW ● ○ ○ There are very few studies, or existing studies are flawed.

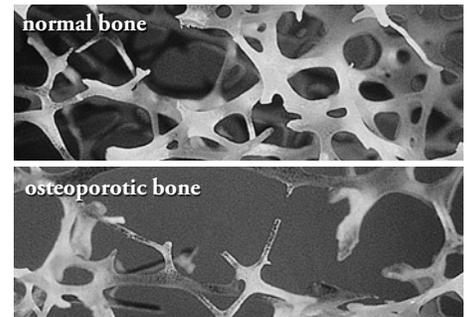


Treatment Approaches

Bone Mineral Density

The clinical definition of osteoporosis is based either on evidence of fracture or on the densitometric measurement of bone, bone mineral density (BMD). The most common BMD test is a DXA (dual-energy x-ray absorptiometry). BMD measurements are interpreted according to the number of standard deviations from the mean of a reference population of young adults. This is referred to as the T-score.

A negative value indicates a BMD measurement below the mean. A T-score lower than -2.5 is diagnostic of osteoporosis. If a postmenopausal woman has had a nontraumatic fracture (fragility fracture), she is considered to have osteoporosis regardless of her T-score.



Used with permission from the International Osteoporosis Foundation.

Bone Health

Many individuals, especially those at highest risk for osteoporotic fractures, do not obtain adequate calcium and vitamin D. While evidence is limited about the benefits of calcium and vitamin D supplements for fracture prevention, adequate calcium and vitamin D is essential to bone health.

The U.S. Surgeon General's report *Bone Health and Osteoporosis* (2004) recommends routine use of calcium and vitamin D supplements for postmenopausal women with inadequate dietary intake (see chart below). Daily calcium should not exceed 2,500 mg, and vitamin D should not exceed 2,000 IU daily for people without a documented vitamin D deficiency.

The report also encourages regular physical activity as a way to reduce falls by improving balance, strength, and endurance. Smoking and heavy alcohol use both increase the risk of fractures and should be discouraged.

Daily Recommendations for Calcium and Vitamin D		
Age	Calcium	Vitamin D
19–50	1,000 mg	200 I.U.
51–70	1,200 mg	400 I.U.
71 and over	1,200 mg	600 I.U.

Fracture Prevention Medications

Nonvertebral fragility fractures and vertebral compression fractures are commonly due to osteoporosis. Women who experience one fracture are more likely to have subsequent fractures.

The medications used for fracture prevention fall into three classes: bisphosphonates, selective estrogen receptor modulators (SERMs), and hormonal medications.

With the exception of teriparatide (recombinant parathyroid hormone), all these drugs work as antiresorptive agents, which inhibit osteoclastic activity. Teriparatide is an anabolic agent that stimulates new bone formation by activating osteoblasts.

Research shows that most of the drugs in each of the three classes reduce the risk of fracture among women who have osteoporosis. Most of the research looks at prevention of vertebral fractures. There is less research on nonvertebral sites. The evidence is summarized below.

Efficacy of Drugs¹ for Prevention of Osteoporotic Fractures

Drug (Brand)	Vertebral Fractures	Hip and Other Nonvertebral Fractures
BISPHOSPHONATES		
Alendronate (Fosamax®)	✓	✓
Etidronate (Didronel®)	✓	INSF
Ibandronate (Boniva®)	✓	INSF
Pamidronate ² (Aredia®)	INSF	INSF
Risedronate (Actonel®)	✓	✓
Zoledronic acid (Reclast®)	✓	✓
SERMs		
Raloxifene (Evista®)	✓	INSF
Tamoxifen ³ (Nolvadex®)	INSF	INSF
HORMONAL MEDICATIONS		
Calcitonin (Miacalcin®, Fortical®)	✓	INSF
Estrogen ⁴ (Premarin®, Prempro®, Premphase®)	✓	✓
Teriparatide (Forteo®)	✓	INSF ⁵ / ✓

¹ These drugs were evaluated in the systematic review.

² Trials focus primarily on transplant and cancer patients; few focus on postmenopausal women.

³ Based on a single study of women at increased risk of breast cancer with unknown bone mineral density.

⁴ The largest study of estrogen was the Women's Health Initiative, which included postmenopausal women with unknown bone mineral density.

⁵ Insufficient evidence for hip fracture prevention; effective for other nonvertebral fractures.

✓ = Effective for prevention of fractures with Level of Confidence: ●●● or ●●○.

INSF = Insufficient evidence.

SERMs = Selective estrogen receptor modulators.

Possible Harms of Treatment

Bisphosphonates

Gastrointestinal Problems

Gastrointestinal (GI) problems have been reported with all oral bisphosphonates. Mild upper GI symptoms include acid reflux, esophageal irritation, nausea, vomiting, and heartburn. Serious GI symptoms include esophageal and nonesophageal upper GI perforations, ulcers, and bleeds.

Adherence to dose instructions for oral medications can minimize the effects. These instructions include:

- Taking the pill on an empty stomach.
- Taking it with a large glass of water.
- Not eating or lying down for 30–60 minutes.

Atrial Fibrillation

There is concern that bisphosphonates, particularly zoledronic acid, may increase the risk of atrial fibrillation, but the current evidence is conflicting.

Musculoskeletal Pain

Severe musculoskeletal pain in people taking bisphosphonates is highlighted in a January 2008 Food and Drug Administration (FDA) alert. It may occur within days, months, or years after drug initiation and require discontinuation. These symptoms are in contrast to an acute response that may accompany initial exposure to bisphosphonates and resolve with continued use.

Osteonecrosis of the Jaw

This condition has been reported among patients taking bisphosphonates. The vast majority of cases occurred among people with cancer using intravenous bisphosphonates. A few cases occurred in women taking oral bisphosphonates for postmenopausal osteoporosis.

SERMs and Hormonal Medications

Stroke

- Estrogen increases the risk of stroke.

LEVEL OF CONFIDENCE: ● ● ●

Thromboembolic Events

- Raloxifene and tamoxifen increase the risk of pulmonary embolism.
- Raloxifene and estrogen increase the risk of venous thromboembolic events.

LEVEL OF CONFIDENCE: ● ● ●

LEVEL OF CONFIDENCE: ● ● ●

Breast Cancer

- Estrogen combined with progestin increases the risk of breast cancer.

LEVEL OF CONFIDENCE: ● ● ○

Gynecologic and Breast Problems

- Estrogen and tamoxifen increase the risk of gynecologic problems, such as endometrial bleeding.

LEVEL OF CONFIDENCE: ● ● ●

- Estrogen increases the odds of breast abnormalities other than cancer, including pain, tenderness, and fibrocystic changes.

LEVEL OF CONFIDENCE: ● ● ●

Osteosarcoma

Based on the results of animal studies with large doses of teriparatide, the FDA warns against prescribing it to those at increased risk for osteosarcoma, such as people with Paget's disease. The FDA also recommends against using teriparatide for longer than 2 years.

Selecting a Treatment Approach

Most of these drugs prevent fractures among postmenopausal women with osteoporosis. When selecting a treatment, consider these other factors.

Consider barriers to adherence and persistence, including mode of administration, dosing regimens, and cost.

- Weekly users of bisphosphonates have higher rates of adherence and persistence compared with daily users.
- Cost may be a barrier. Generics are not widely available. Intravenous drugs incur additional expense. Drugs, doses, and prices are listed on the back page. The Partnership for Prescription Assistance can also provide information on public and private assistance programs. Web site: www.pparx.org. Phone: (800) 477-2669.

Consider the risk of adverse events.

- GI problems can occur with oral bisphosphonates. Women who experience symptoms such as reflux or nausea may need to switch medications.
- Women with a history of serious GI disease, such as GI bleeds, should avoid bisphosphonates, except zoledronic acid.
- Avoid zoledronic acid for women at high risk for atrial fibrillation.

Consider supplementation.

- Adequate calcium and vitamin D intake is needed for normal bone homeostasis. Encourage women to take calcium supplements in divided doses and get adequate vitamin D.

Adherence

Treatment to prevent fractures is usually long term. Consider how well the woman will be able to take the medication as prescribed (adherence) and the possible barriers to continuing treatment (persistence).

- Rates of adherence and persistence with alendronate, etidronate, risedronate, raloxifene, estrogen, calcitonin, calcium, and vitamin D are low in women with osteoporosis.

LEVEL OF CONFIDENCE: ● ● ○

- Factors that affect adherence and persistence include side effects, absence of disease-related symptoms, comorbid conditions, ethnicity, socioeconomic status, and dosing regimens.

LEVEL OF CONFIDENCE: ● ● ○

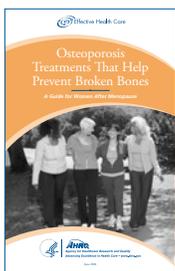
Still Unknown

- There is no research comparing exercise with other treatments for fracture prevention.
- We do not have enough data to determine if one class of drugs is superior to another for fracture prevention.
- We do not have enough data to determine if any of the bisphosphonates are more effective than the others for fracture prevention.

Resource for Patients

Osteoporosis Treatments That Help Prevent Broken Bones: A Guide for Women After Menopause is a

companion to this Clinician's Guide. It



can help women talk with their health care professional about treatment options. It provides information about the effectiveness of osteoporosis treatments for preventing fractures, side effects, and costs.

For More Information

For electronic copies of the consumer's guide, this clinician's guide, and the full systematic review, visit this Web site: www.effectivehealthcare.ahrq.gov

For free print copies call:

The AHRQ Publications Clearinghouse, (800) 358-9295

Consumer's Guide,
AHRQ Pub. No. 08-EHC008-2A

Clinician's Guide,
AHRQ Pub. No. 08-EHC008-3

For current osteoporosis screening recommendations, visit the U.S. Preventive Services Task Force Web site: www.ahrq.gov/clinic/uspstf/uspstoste.htm

AHRQ created the John M. Eisenberg Center at Oregon Health & Science University to make research useful for decisionmakers. This guide was prepared by David Hickam, M.D., Bruin Rugge, M.D., Theresa Bianco, Pharm. D., Sandra Robinson, M.S.P.H., Erin Davis, B.A., Martha Schechtel, R.N., and Valerie King, M.D., of the Eisenberg Center.

Treatments for Osteoporosis by Dose, Administration Route, and Price

Drug Name ¹	Brand Name	Dose ²	Route	Price per Month ³	
				Generic	Brand
BISPHOSPHONATES					
Alendronate	Fosamax®	10 mg daily	Oral	\$90	\$95
		70 mg once weekly	Oral	\$80	\$85
Etidronate ⁴	Didronel®	200 mg daily x14 days every 3 months	Oral	\$15	\$20
		400 mg daily x14 days every 3 months	Oral	\$30	\$35
Ibandronate	Boniva®	2.5 mg daily	Oral		\$100
		150 mg once monthly	Oral	NA	\$100
		3 mg every 3 months	IV		\$485 ⁵
Pamidronate ⁴	Aredia®	30 mg every 3 months	IV	\$35 ⁶	\$95 ⁶
Risedronate	Actonel®	5 mg daily	Oral		\$100
		35 mg once weekly	Oral		\$90
		75 mg daily for two days each month	Oral	NA	\$100
		150 mg once monthly	Oral		\$100
Zoledronic acid	Reclast®	5 mg once yearly	IV	NA	\$105 ⁷
SERMs					
Raloxifene	Evista®	60 mg daily	Oral	NA	\$100
Tamoxifen ⁴	Nolvadex®	20 mg daily	Oral	\$115	\$245
HORMONAL MEDICATIONS					
Calcitonin	Miacalcin®, Fortical®	100 IU every other day	SQ, IM	NA	\$425
		200 IU daily	IN		\$115
Estrogen ⁸	Premarin®	0.3 mg daily	Oral		\$35
		0.45 mg daily	Oral	NA	\$40
		0.625 mg daily	Oral		\$35
Estrogen plus medroxy-progesterone ⁸	Prempro®	0.3 mg / 1.5 mg daily	Oral		\$40
		0.45 mg / 1.5 mg daily	Oral	NA	\$50
		0.625 mg / 2.5 mg daily	Oral		\$40
		0.625 mg / 5 mg daily	Oral		\$40
	Premphase®	0.625 mg / 5 mg daily	Oral	NA	\$55
Teriparatide	Forteo®	20 mcg daily	SQ	NA	\$845
VITAMINS/MINERALS					
Calcium ⁴	Various	500 mg daily	Oral	\$3	Price
		1,000 mg daily	Oral	\$5	varies
		1,200 mg daily	Oral	\$6	
Vitamin D ⁴	Various	400 IU daily	Oral	\$1	Price
		800 IU daily	Oral	\$2	varies

¹ These drugs were evaluated in the systematic review.

² Doses are approved by the Food and Drug Administration (FDA) for treatment of osteoporosis unless otherwise noted.

³ Average Wholesale Price from *Red Book*, 2007. Price does not include administration-related costs.

⁴ Not FDA approved for prevention or treatment of osteoporosis. Doses are similar to those used in the research studies.

⁵ Price (\$1,455) averaged over 3 months.

⁶ Price (\$105, \$285) averaged over 3 months.

⁷ Price (\$1,250) averaged over 12 months.

⁸ Doses FDA approved for prevention of osteoporosis.

IV = intravenous, SQ = subcutaneous, IM = intramuscular, IN = intranasal, NA = not available as generic.