

# Treatment To Prevent Osteoporotic Fractures: An Update

## Focus of Research for Clinicians

As an update to the 2007 report, a systematic review of 567 clinical studies published between January 2005 and March 2011 examined the comparative effectiveness and safety of treatments to prevent fractures in people with low bone density (including osteoporosis). The full report, listing all studies, is available at [www.effectivehealthcare.ahrq.gov/lbd.cfm](http://www.effectivehealthcare.ahrq.gov/lbd.cfm). This summary, based on the full report of research evidence, is provided to inform discussions of options with patients and to assist in decisionmaking along with consideration of a patient's values and preferences. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

## Background

Approximately 52 million people in the United States are affected by osteoporosis or low bone density. Osteoporosis, a severe form of low bone density especially common in postmenopausal women, is a systemic skeletal disease characterized by decreasing bone mass and microarchitectural deterioration of bone tissue and consequential increases in susceptibility to fracture. Clinical diagnosis of osteoporosis may be based on the results of bone mineral density (BMD) measurement with dual energy x-ray absorptiometry (DXA).<sup>1</sup>

Risk factors for osteoporotic fracture include (but are not limited to): increasing age, female sex, postmenopause for women, hypogonadism or premature ovarian failure, ethnic background (higher for whites), low body weight, previous fracture, previous vertebral fracture due to minimal trauma, parental history of hip fracture, rheumatoid arthritis, low BMD, current smoking, higher alcohol intake (three or more drinks per day), vitamin D deficiency, low calcium intake, hyperkyphosis, falling, and immobilization. Risk is also increased with the chronic use of certain medications, including glucocorticoids, anticoagulants, anticonvulsants, aromatase inhibitors, cancer chemotherapeutic drugs, and gonadotropin-releasing hormone agonists.

<sup>1</sup> BMD is classified according to T-score, the number of standard deviations above or below the mean BMD for healthy adults, as determined by DXA. A T-score of -2.5 or less is classified as osteoporosis; between -2.5 and -1.0 is considered low bone density (osteopenia); and -1 or greater is considered normal.

Risk scores that combine clinical risk factors with BMD testing results have been developed to better predict a patient's risk of osteoporotic fracture. One such tool is the Fracture Risk Assessment Tool (FRAX®) developed by the World Health Organization. FRAX is a set of race- and nation-specific algorithms that take into account a patient's individual risk factors to estimate the absolute 10-year risk of major osteoporotic fractures.

Interventions to prevent osteoporotic fracture include pharmacologic agents, dietary and supplemental vitamin D and calcium, and weight-bearing exercise. These interventions have been studied and used (with less frequency) in patients with osteopenia (T-score between -2.5 and -1.0). Pharmacologic agents investigated in the systematic review include bisphosphonates, teriparatide (a peptide hormone), estrogen in the form of menopausal hormone therapy (MHT), the selective estrogen receptor modulator raloxifene, and the biological agent denosumab.

These pharmacologic agents are antiresorptive, with the exception of teriparatide, which is anabolic. There were no new findings about calcitonin in this updated report.

## Conclusion

The ability of medications to decrease fracture risk is most strongly established for postmenopausal women with osteoporosis (BMD scores in the osteoporosis range and/or pre-existing fractures). Bisphosphonates, denosumab, raloxifene, and teriparatide reduce vertebral fracture risk, but only alendronate, risedronate, zoledronic acid, and denosumab reduce hip fracture risk. Raloxifene does not reduce the risk of hip or other nonvertebral fractures. Limited evidence supports a potential benefit of vitamin D and calcium (alone or in combination) in lowering fracture risk. Studies to date are inadequate to provide estimates of the benefits or harms from exercise. Most osteoporosis interventions have possible adverse effects, which should be taken into account in decisionmaking. Dosing frequency appears to affect adherence and persistence, with weekly doses having improved adherence over daily regimens. Limited evidence suggests treatment extended beyond 5 years can provide additional reductions in vertebral fracture risk (measured at 10 years). For nonvertebral fractures, post-hoc analysis found reduction in risk only for women who had osteoporosis or prevalent vertebral fractures at 5 years. Monitoring BMD during therapy does not fully reflect treatment benefits, as patients with BMD losses during anti-resorptive therapy may still experience reduced fracture risk.

## Clinical Bottom Line

### Benefits

#### Pharmacologic Agents

- Alendronate, risedronate, zoledronic acid, and denosumab reduce the risk of hip and other nonvertebral fractures in postmenopausal women with osteoporosis. ●●●
- Bisphosphonates (alendronate, risedronate, zoledronic acid, and ibandronate), denosumab, teriparatide, and raloxifene reduce the risk of vertebral fractures in postmenopausal women with osteoporosis. ●●●
- Teriparatide reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis. ●●○
- Regarding the need for calcium with bisphosphonates, the combination of alendronate and calcium significantly decreased the risk for any type of clinical fracture when compared with alendronate alone. ●○○
- Reduced risk of other fracture types and risk reduction in subpopulations is achieved by fewer medications and supported by varied strengths of evidence. (See Tables 1 and 2 for details.)

#### Exercise and Dietary Supplementation

- The evidence is insufficient to estimate benefits from exercise, or to identify the specific duration, intensity, and type of exercise program that will decrease fracture risk. ○○○
- Vitamin D (>800 units taken orally) taken in combination with calcium may reduce fracture risk in people who are institutionalized. ●●○ However, evidence is lacking for clear benefit of vitamin D when taken alone for the general population.
- Studies show no difference between calcium alone and placebo in reducing the risk for vertebral and nonvertebral fractures. ●●○
  - However, calcium significantly reduced hip fracture risk in one pooled analysis and overall fracture risk in another pooled analysis.
- No difference was found between calcium alone and vitamin D alone in reducing risk for vertebral, or hip, or other nonvertebral fractures. ●●●

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### Benefits (Continued)

#### Menopausal Hormone Therapy (MHT)

- In studies of postmenopausal women in general, MHT\* reduces the risk of vertebral, hip, and other nonvertebral fractures ●●●; however, in postmenopausal women with established osteoporosis, MHT does not reduce fracture risk significantly ●●○.
- No differences in comparative effectiveness for fracture prevention have been shown between bisphosphonates and MHT (estrogen). ●●○
- No differences in fracture incidence have been shown in comparisons of MHT with either raloxifene or vitamin D. ●○○

\* The Women's Health Initiative reported serious adverse effects associated with MHT, such that routine use of MHT in postmenopausal women is now discouraged.

### Monitoring, Adherence, and Persistence

- The evidence to date has not clarified the value of BMD monitoring to assess treatment effectiveness. According to indirect evidence, even patients who continue to lose BMD during therapy experience statistically and clinically significant reductions in fracture risk. ●●●
- One large randomized controlled trial (RCT) showed that after 5 years of initial alendronate therapy, an additional 5 years of therapy continued to reduce vertebral fracture risk. Continued reduction in nonvertebral fracture risk was found at 10 years (in a post-hoc analysis) only in women who had osteoporosis (T-score < -2.5) or prevalent vertebral fractures after the first 5 years of treatment. ●●○
- Decreased adherence to bisphosphonates is associated with an increased risk of fracture (vertebral, nonvertebral, or both). ●●○
- Although RCTs examining bisphosphonates report high levels of adherence (majority >90%), those with raloxifene reported adherence rates of 65 to 70 percent. ●●○
  - Observational studies (perhaps more indicative of the experience in practice) of patients taking bisphosphonates in combination with calcium and vitamin D show that in many patients adherence and persistence with the treatment regimen are poor. ●●●

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## Clinical Bottom Line (Continued)

### Monitoring, Adherence, and Persistence (Continued)

- Observational studies show that adherence to therapy with bisphosphonates is improved with weekly regimens when compared with daily regimens. ●●●
  - Evidence is lacking to evaluate comparative adherence to monthly versus weekly regimens.
- Observational studies show that other factors affecting adherence and persistence include, but are not limited to, dosing frequency, side effects of medications, comorbid conditions, knowledge about osteoporosis, and medication cost. Age, previous history of fracture, and concomitant medication use do not appear to affect adherence or persistence. ●●○

BMD = bone mineral density; MHT = menopausal hormone therapy; RCT = randomized controlled trial

#### Strength of Evidence Scale

- High: ●●● There are consistent results from good-quality studies. Further research is very unlikely to change the conclusions.  
 Moderate: ●●○ Findings are supported, but further research could change the conclusions.  
 Low: ●○○ There are very few studies, or existing studies are flawed.  
 Insufficient: ○○○ Research is either unavailable or does not permit estimation of a treatment effect.

## Table 1: Effectiveness of Medications To Prevent Fracture Risk

The table below lists whether or not the following medications reduce the risk of the listed fracture types for postmenopausal women with osteoporosis.

| Medication      |                 | Vertebral | Nonvertebral  | Hip           | Wrist         |
|-----------------|-----------------|-----------|---------------|---------------|---------------|
| Bisphosphonates | Alendronate     | ☑ ●●●     | ☑ ●●●         | ☑ ●●●         | ☑ ●○○         |
|                 | Risedronate     | ☑ ●●●     | ☑ ●●●         | ☑ ●●●         | ☑ ●○○*        |
|                 | Zoledronic acid | ☑ ●●●     | ☑ ●●●         | ☑ ●●●         | Not specified |
|                 | Ibandronate     | ☑ ●●●     | Not specified | Not specified | Not specified |
| Denosumab       |                 | ☑ ●●●     | ☑ ●●●         | ☑ ●●●         | Not specified |
| Teriparatide    |                 | ☑ ●●●     | ☑ ●●○         | Not specified | Not specified |
| Raloxifene      |                 | ☑ ●●●     | ☒ ●●●         | ☒ ●●●         | ☒ ●●●         |

☑ = reduced fracture risk; ☒ = did NOT reduce fracture risk  
 \*Risedronate-mediated reduction in wrist fracture did not reach the conventional level of statistical significance.

## Additional Information

- Fracture risk reduction is greatest in women with established osteoporosis and/or prevalent fractures, and reduction of fracture risk from treatment is not dependent on patient age (i.e., older individuals are as likely to benefit from treatment as younger individuals). ●●●
- Women with established osteoporosis benefit more from treatment than do postmenopausal women with osteopenia and without prevalent fractures.
- Most authorities no longer consider calcitonin to be an appropriate treatment for osteoporosis, yet it is still widely prescribed. Evidence supports the conclusion that it is not effective in postmenopausal women with osteoporosis.

**Table 2: Effectiveness in Subpopulations**

| Patient Population   | Pharmacotherapies                                     |  |            |
|--|---|--|------------|
| <b>Medications that reduce <i>overall</i> fracture risk in the given patient populations:</b>                        |   |  |            |
| Patients with high risk for fracture (including postmenopausal women with osteoporosis)                              | Alendronate<br>Denosumab<br>Ibandronate<br>Raloxifene | Risedronate<br>Teriparatide<br>Zoledronic acid | ●●●        |
| Patients treated with glucocorticoids  | Alendronate<br>Risedronate                            | Teriparatide                                   | ●●○ to ●●● |
| Patients with a higher risk of falling (e.g., patients with hemiplegia, Alzheimer’s disease, or Parkinson’s disease) | Alendronate<br>Risedronate                            | Vitamin D                                      | ●●○        |
| Transplant recipients and patients treated chronically with corticosteroids  | Inconclusive support for any agents                   |  | ○○○        |
| <b>Medications that reduce <i>fragility</i> fracture risk in the given patient populations:</b>                      |   |  |            |
| Postmenopausal women with osteopenia who do not have prevalent vertebral fractures                                   | Risedronate   |  | ●○○ to ●●○ |

**Table 3: Adverse Effects With Rated Findings**

| Medication   |                                | Adverse Effect  | Magnitude of Association (From Pooled Analysis of Clinical Data) <sup>a</sup>  |     |
|--|--------------------------------|---|--|-----|
| Bisphosphonates                                      | Bisphosphonates (class)        | Possible association with atypical subtrochanteric fractures of the femur   | Not available—but the risk for this type of fracture is low. (Data are inconsistent, but the U.S. Food and Drug Administration has issued a boxed warning about this possible adverse effect.) | ●○○ |
|  | Alendronate                    | Mild upper GI events <sup>b</sup>   | OR = 1.08, 95% CI: 1.01 to 1.15  | ●●● |
|  |                                | Hypocalcemia  | 9/301 treatment vs. 0/207 placebo  | ●●○ |
|  | Zoledronic acid                | Hypocalcemia  | OR = 7.22, 95% CI: 1.81 to 42.7  | ●●○ |
| Intravenous forms of zoledronic acid and ibandronate | Osteonecrosis of the jaw (ONJ) | Less than one case per 100,000 person-years of exposure. (Nearly all cases of ONJ are reported in people being treated for cancer.) | ●●●  |     |

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**Table 3: Adverse Effects With Rated Findings (Continued)**

| Medication  | Adverse Effect                         | Magnitude of Association (From Pooled Analysis of Clinical Data) <sup>a</sup>  |     |
|---|--|--|-----|
| Raloxifene  | Pulmonary embolism                     | OR = 5.27, 95% CI: 1.29 to 46.4  | ●●● |
|   | Thromboembolic events                  | OR = 1.63, 95% CI: 1.36 to 1.98  | ●●● |
|   | Myalgias, cramps, and limb pain        | OR = 1.53, 95% CI: 1.29 to 1.81  | ●●● |
|   | Hot flashes                            | OR = 1.58, 95% CI: 1.35 to 1.84  | ●●● |
| Menopausal hormone therapy: estrogen and estrogen-progestin combination | Cerebrovascular accidents <sup>c</sup> | Estrogen: OR = 1.34, 95% CI: 1.07 to 1.68<br>Combination: OR = 1.28, 95% CI: 1.05 to 1.57  | ●●● |
|   | Thromboembolic events <sup>c</sup>     | Estrogen: OR = 1.36, 95% CI: 1.01 to 1.86<br>Combination: OR = 2.27, 95% CI: 1.72 to 3.02  | ●●● |
|   | Breast cancer                          | Estrogen: In the WHI, <sup>d</sup> this hormone was associated with reduced incidence of breast cancer in women with hysterectomy when compared with placebo (HR = 0.77, 95% CI: 0.62 to 0.95), but subgroup analysis noted that risk reduction was concentrated in women without benign breast disease or a family history of breast cancer. No risk reduction was seen in women at high risk for breast cancer.<br><br>Combination: In the WHI, <sup>e</sup> estrogen-progestin was associated with more occurrences of invasive breast cancer than with placebo (HR = 1.25, 95% CI: 1.07 to 1.46), tumors more likely to have lymph node metastases (HR = 1.78, 95% CI: 1.23 to 1.58), and more breast cancer-related deaths (HR = 1.96, 95% CI: 1.00 to 4.04). |     |
| Teriparatide  | Hypercalcemia                          | OR = 12.9, 95% CI: 10.49 to 16.0   | ●●○ |
|   | Headaches                              | OR = 1.44, 95% CI: 1.24 to 1.67  | ●●○ |
| Denosumab   | Mild upper GI events <sup>b</sup>      | OR = 2.13, 95% CI: 1.11 to 4.4   | ●●○ |
|   | Rash                                   | OR = 2.01, 95% CI: 1.5 to 2.73   | ●●● |
|   | Infection                              | OR = 1.28, 95% CI: 1.02 to 1.60  | ●●● |

<sup>a</sup> 95% CI = 95 percent confidence interval; HR = hazard ratio (in cancer research, a measure of how often a particular event happens in one group compared with how often it happens in another group over time); OR = odds ratio (the odds of the condition developing in those taking the listed medications compared with the odds in patients receiving placebo treatment); RR = relative risk (the incidence of the conditions in those taking the listed medications compared with the incidence in patients receiving placebo treatment); WHI = Women's Health Initiative

<sup>b</sup> Mild upper GI events = conditions involving the upper gastrointestinal tract such as acid reflux, esophageal irritation, nausea, vomiting, and heartburn.

<sup>c</sup> These findings are from the original 2007 report. Note: The WHI reported adverse effects associated with menopausal hormone therapy, including venous thromboembolic events, stroke, and a variable effect on breast cancer.

<sup>d</sup> Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol* 2012 Mar 6 [Epub ahead of print]. PMID: 22401913.

<sup>e</sup> Chlebowski RT, Anderson GL, Gass M, et al; WHI Investigators. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA* 2010 Oct 20;304(15):1684-92. PMID: 20959578.

## Table 4: Additional Possible Adverse Effects

The following are additional possible adverse effects listed by the U.S. Food and Drug Administration (FDA) that were not findings of the report.

| Medications                                      | Adverse Effect(s)   |
|--|---|
| <b>Alendronate, risedronate, and ibandronate</b> | <ul style="list-style-type: none"> <li>■ Musculoskeletal pain</li> <li>■ Hypocalcemia</li> <li>■ Osteonecrosis of the jaw</li> <li>■ Severe irritation of upper gastrointestinal mucosa</li> </ul>  |
| <b>Zoledronic acid</b>                           | <ul style="list-style-type: none"> <li>■ Severe musculoskeletal pain</li> <li>■ Renal toxicity and acute renal failure</li> </ul>   |
| <b>Denosumab</b>                                 | <ul style="list-style-type: none"> <li>■ Hypocalcemia</li> <li>■ Osteonecrosis of the jaw</li> </ul>  |
| <b>Teriparatide</b>                              | <ul style="list-style-type: none"> <li>■ Increased risk of bone cancer</li> </ul>   |
| <b>Vitamin D</b>                                 | <ul style="list-style-type: none"> <li>■ Signs of toxicity: nausea, vomiting, anorexia, polyuria, constipation, weakness, and weight loss</li> <li>■ Excess vitamin D can cause irreversible kidney damage and renal failure</li> <li>■ By raising blood levels of calcium, excessive vitamin D can cause dementia, memory loss, and arrhythmias</li> </ul> |

## Gaps in Knowledge

- Evidence is insufficient to evaluate potential associations between bisphosphonate use and either esophageal cancer or atrial fibrillation. However, an FDA safety review notes that a relationship between zoledronic acid and atrial fibrillation is still an area of active surveillance, though an association remains unproven.
- Much less evidence is available about the efficacy for the antifracture effects of currently available osteoporosis therapies for patients with osteopenia, as most studies focused on patients with established osteoporosis.
- Studies comparing exercise with medications are lacking. Additionally, there are no RCTs examining the specific duration, intensity, and type of exercise program required to decrease fracture risk.
- Evidence regarding the effectiveness of therapies to prevent or treat osteoporosis in men is lacking.
- Studies have not directly compared the antifracture effectiveness of longer durations of treatment among the various therapies. Thus, it is unclear how long patients should remain on therapy. The benefits and harms of drug holidays are also unclear.
- Data are insufficient to determine the comparative effectiveness among individual bisphosphonates or between bisphosphonates and calcium, raloxifene, or teriparatide.
- No RCTs tested combinations of osteoporosis therapies or sequential use of osteoporosis therapies in relation to fracture outcomes.
- No studies have examined explicitly the benefits and adverse effects associated with the popular practice of BMD monitoring during the course of therapy.
- This review did not assess quality-of-life issues.



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## What To Discuss With Your Patients

- The serious health consequences associated with low bone density and fracture
- The potential benefits and adverse effects associated with treatment options
- The specific instructions for how to take certain medicines such as bisphosphonates and the impact this might have on the patient's lifestyle
- The importance of treatment adherence and how that affects fracture risk reduction
- Risk factors for low bone density and fracture, including conditions and medications in the elderly that might predispose them to falls
- Approaches to avoiding falls, such as addressing hazards in the home, wearing appropriate footwear, and installing night lights
- The specific side effects the patient might encounter, and when the patient should inform you should these occur

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## Resource for Patients

*Reducing the Risk of Bone Fracture, A Review of the Research for Adults With Low Bone Density* is a free



companion to this clinician research summary. It provides:

- Information about treatment options
- Current evidence regarding effectiveness and side effects
- Questions for patients to ask their doctor

*Healthy Bones: A Decision Aid for Women After Menopause*, an online tool for postmenopausal women, is also available at [www.effectivehealthcare.ahrq.gov/lbddecisionaid.cfm](http://www.effectivehealthcare.ahrq.gov/lbddecisionaid.cfm). It provides:

- A tool to help a woman calculate her risk of breaking a bone
- Detailed information about medicines to prevent fractures
- Questions for patients to ask their doctor

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## Ordering Information

For electronic copies of *Reducing the Risk of Bone Fracture, A Review of the Research for Adults With Low Bone Density*, this clinician research summary, and the full systematic review, visit [www.effectivehealthcare.ahrq.gov/lbd.cfm](http://www.effectivehealthcare.ahrq.gov/lbd.cfm). To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

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## Source

The information in this summary is based on *Treatments To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis: An Update to the 2007 Report*, Comparative Effectiveness Review No. 53, prepared by the Southern California Evidence-based Practice Center, a Rand Health Center, under Contract No. HHS-290-2007-10062-I for the Agency for Healthcare Research and Quality, March 2012. Available at [www.effectivehealthcare.ahrq.gov/lbd.cfm](http://www.effectivehealthcare.ahrq.gov/lbd.cfm). This summary was prepared by the John M. Eisenberg Center for Clinical Decisions and Communications Science at Baylor College of Medicine, Houston, TX.