Keeping old bones from breaking: 
The diagnosis, prevention, and treatment 
of osteoporosis

Balanced data about medications
www.RxFacts.org

Copyright © 2010 by The Alosa Foundation. All rights reserved.
# Table of contents

Introduction........................................................................................................................ 5
Burden of osteoporosis....................................................................................................... 5
Pathophysiology and risk factors for osteoporosis......................................................... 6
Diagnosis of osteoporosis................................................................................................. 7
Recommendations for all patients.................................................................................. 10
When are osteoporosis medications needed?............................................................... 15
Pharmacotherapy: postmenopausal women ................................................................. 17
Steroid-induced osteoporosis......................................................................................... 26
Osteoporosis in men .................................................................................................... 28
Intravenous bisphosphonates after hip fracture........................................................... 30
Adherence and persistence ......................................................................................... 30
Monitoring response to therapy ................................................................................ 32
Adverse effects of bisphosphonates............................................................................ 32
FDA safety alert with proton pump inhibitors............................................................ 37
Other medications....................................................................................................... 38
Costs............................................................................................................................ 38
Putting it all together................................................................................................. 40
Appendix 1. The FRAX algorithm .............................................................................. 41
Appendix 1. The FRAX algorithm (cont’d) ............................................................... 42
Appendix 2. Estimating dietary calcium intake – the calcium calculator .............. 43
References.................................................................................................................... 44
**Introduction**

Osteoporosis is generally a silent disease until a fracture occurs. Fractures are common: about half of all Caucasian women have an osteoporotic fracture in their lifetime, and so about 1 in 5 men.\(^1\) Osteoporosis is less common in African-Americans, but those with osteoporosis have the same fracture risk as Caucasians. Although men have fewer osteoporotic fractures than women, those that do have a higher risk of post-fracture mortality.\(^2\)

Osteoporosis can often be diagnosed and treated before a fracture occurs. However, many patients do not receive information about osteoporosis or appropriate testing to make the diagnosis. In addition, many patients who are diagnosed or have an osteoporosis-associated fracture do not receive treatment even though there is good evidence that proper care can reduce the risk of a first and subsequent fracture.\(^3\) Failure to diagnose and manage osteoporosis imposes an enormous clinical, personal, and economic burden on patients and the healthcare system.

The primary care clinician plays a critical role in identifying and managing osteoporosis. This document summarizes the current medical literature and offers practical strategies for addressing this common problem.

**Burden of osteoporosis**

At least 10 million people in the United States are affected by osteoporosis, and it is the most important cause of most fractures in the elderly. The most common osteoporotic fractures are those of the vertebrae (spine), proximal femur (hip) and distal forearm (wrist).

**Table 1. Burden of osteoporosis in the U.S.**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>
| **Osteoporosis**\(^3, 4\) | • 8 million women  
                          | • 2 million men                                                |
| **Low bone density (osteopenia) of the hip**\(^3, 4\) | • 34 million people                                           |
| **Osteoporotic fracture**\(^5\) | • 1.5 million people annually  
                          | • 430,000 hospital admissions, 2.5 million medical office visits, and about 180,000 nursing home admissions annually in the U.S.\(^1\)  
                          | • over $17 billion in healthcare costs per year\(^6\)         |

Hip fractures result in mortality rates of approximately 20% within 1 year,\(^1\) and are associated with a 2.5-fold increased risk of future fractures.\(^7\) About 20% of patients who fracture their hip require long-term nursing home care, and only 40% of patients regain
their pre-fracture level of independence.\textsuperscript{1} An increased mortality rate is also seen after vertebral fractures, which cause significant complications including back pain, height loss, and kyphosis. Postural changes associated with kyphosis may limit activity. Wrist fractures are less disabling but can meaningfully decrease quality of life.\textsuperscript{3}

Hip fractures comprise 14\% of first-time osteoprotic fractures and 72\% of fracture costs.\textsuperscript{6} The number of hip fractures and associated costs are expected to triple by 2040 due to the aging population.\textsuperscript{3}

### Pathophysiology and risk factors for osteoporosis

Peak bone mass in adults is reached by age 18-25 years, and is determined largely by genetic factors, with additional contributions from nutrition, physical activity and health status during growth. An imbalance between bone resorption and bone formation occurs with menopause and advancing age, leading to a reduction in bone mineral density (BMD) and abnormal skeletal architecture (osteoporosis). This causes reduced bone strength and an increased risk of fracture from minimal trauma.

The three major non-modifiable risk factors for osteoporosis are age, female gender, and white race. Other risk factors are shown in Table 2.\textsuperscript{3,8,9}
Table 2. Risk factors for osteoporosis and/or fractures

<table>
<thead>
<tr>
<th>Lifestyle and diet</th>
<th>Medical conditions</th>
<th>Medications</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>low calcium intake</td>
<td>COPD</td>
<td>systemic corticosteroid therapy of ≥ 5 mg per day prednisone or equivalent for ≥ 3 months</td>
<td>early onset of menopause (&lt; age 45)</td>
</tr>
<tr>
<td>excessive alcohol intake (3 or more drinks per day)</td>
<td>Cushing’s disease</td>
<td>anticonvulsants</td>
<td>family history of osteoporosis</td>
</tr>
<tr>
<td>immobilization</td>
<td>diabetes</td>
<td>aromatase inhibitors</td>
<td>failure to reach peak bone mass in young adulthood</td>
</tr>
<tr>
<td>body mass index &lt; 20 kg/m²</td>
<td>hyperparathyroidism</td>
<td>cyclosporine A</td>
<td>Prior fractures (risk for 2nd fracture)</td>
</tr>
<tr>
<td>smoking</td>
<td>hyperthyroidism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vitamin D deficiency</td>
<td>hypogonadism</td>
<td>depo-medroxyprogesterone</td>
<td></td>
</tr>
<tr>
<td>inadequate exercise</td>
<td>lupus</td>
<td>gonadotropin releasing hormone agonists</td>
<td></td>
</tr>
<tr>
<td>high caffeine intake</td>
<td>malabsorption syndromes, especially celiac disease</td>
<td>proton pump inhibitors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>renal failure</td>
<td>pioglitazone, rosiglitazone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rheumatoid arthritis</td>
<td>tacrolimus</td>
<td></td>
</tr>
</tbody>
</table>

Many osteoporosis-related fractures result from falls, so risk factors for falls are an important determinant of fracture risk. For a discussion of falls risk factors, see pages 8-12 of the iDIS evidence document on preventing falls and enhancing mobility at www.RxFacts.org.

**Diagnosis of osteoporosis**

**Bone mineral density**

Osteoporosis may present with fragility fracture (defined as a fracture occurring from a force equivalent to a fall from standing height or less). The diagnosis of osteoporosis is based either on evidence of fragility fracture or on the measurement of bone mineral density (BMD).4

The most common BMD test is dual-energy x-ray absorptiometry (DXA or DEXA) of the total hip, femoral neck, and lumbar spine, using the lowest of the 3 BMD scores for
diagnosis. BMD measurements are expressed in absolute terms of grams per square centimeter scanned (g/cm²) and as a relationship to two norms: 

- compared to “young normal” adults of the same sex (T-score) or
- compared to the expected BMD for the patient’s age and sex (Z-score).

The difference between the patient’s score and the norm is expressed in standard deviations (SD) above or below the mean. A negative value indicates a BMD measurement below the mean. Osteoporosis is defined according to T-scores as shown in the table below.

### Table 3. Diagnosis by BMD T-scores

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal bone mass</td>
<td>≥ -1.0</td>
</tr>
<tr>
<td>Osteopenia (low bone mass)</td>
<td>between -1.0 and -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>≤ -2.5</td>
</tr>
</tbody>
</table>

A patient who has had a fragility fracture is considered to have osteoporosis regardless of the T-score.

### Indications for BMD testing

Clinical guidelines suggest measurement of bone density prior to considering medications for osteoporosis in most patients. Testing is recommended in the following groups:

- women age 65 and older and men age 70 and older, regardless of clinical risk factors
- younger postmenopausal women and men 50 – 69 with a high risk factor profile
- women in the peri-menopausal period with risk factors such as low body weight (BMI < 21 kg/m²), prior low-trauma fracture, or high risk medication (see below)
- adults who have a fracture after age 50
- adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids in a daily dose ≥ 5 mg prednisone or equivalent for ≥ 3 months) that can cause low bone mass
- a patient being treated for osteoporosis, to monitor treatment effect
- postmenopausal women discontinuing estrogen

Medicare covers BMD testing for many patients age 65 and older, including those who:

- are estrogen-deficient women at risk for osteoporosis
- have vertebral abnormalities
- have primary hyperparathyroidism
- are receiving, or planning to receive, long-term glucocorticoid therapy in a daily dose ≥ 5 mg prednisone or equivalent for ≥ 3 months
- are being monitored to assess the response to osteoporosis medication.
Estimate fracture risk algorithm (FRAX)\textsuperscript{3}

A World Health Organization (WHO) fracture risk algorithm (FRAX) calculates the 10-year probabilities of hip and major osteoporotic fractures (defined as vertebral, hip, forearm or proximal humerus fracture). The U.S.-adapted algorithm is available at http://RxFacts.org/FRAX.php for Hispanic, Black, Caucasian, and Asian people. The FRAX tool can be used to guide initiation of treatment (see page 15).

FRAX is intended for use in postmenopausal women and men aged ≥ 50 years. It is not intended for use in younger adults or children, and has not been validated in patients currently or previously treated with medications for osteoporosis. In the absence of femoral neck BMD, total hip BMD may be substituted. Use of BMD from non-hip sites in the algorithm is not recommended. A reproduction of the input screen from the FRAX website is shown below.

Figure 1. The FRAX risk calculator

<table>
<thead>
<tr>
<th>Please answer the questions below to calculate the ten year probability of fracture with BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country:</strong> US (Caucasian)</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
</tr>
<tr>
<td>1. Age (between 40-90 years) or Date of birth</td>
</tr>
<tr>
<td>2. Sex</td>
</tr>
<tr>
<td>3. Weight (kg)</td>
</tr>
<tr>
<td>4. Height (cm)</td>
</tr>
<tr>
<td>5. Previous fracture</td>
</tr>
<tr>
<td>6. Parent fractured hip</td>
</tr>
<tr>
<td>7. Current smoking</td>
</tr>
<tr>
<td>8. Glucorticoids</td>
</tr>
<tr>
<td>9. Rheumatoid arthritis</td>
</tr>
<tr>
<td>10. Secondary osteoporosis</td>
</tr>
<tr>
<td>11. Alcohol (3 or more units per day)</td>
</tr>
<tr>
<td>12. Femoral neck BMD (gm/cm\textsuperscript{2})*</td>
</tr>
</tbody>
</table>

*In patients without a BMD test, the field should be left blank

Hardcopy charts of fracture risk are available at http://RxFacts.org/FRAX_charts.php

Examples of these charts for 60 and 80 year old Caucasian and Black women are provided in Appendix 1.
**Vitamin D**

Vitamin D deficiency is very common but underdiagnosed.\textsuperscript{10-12} Patients at particular risk for vitamin D deficiency include the elderly, institutionalized or housebound patients, the chronically ill, those with limited sun exposure, malabsorption syndromes (e.g., celiac disease) or chronic renal insufficiency, dark-skinned people, and women who are veiled.\textsuperscript{3} Heavy use of sunscreen to reduce the risk of skin cancer can also lead to vitamin D deficiency,\textsuperscript{10, 13} as sunscreen can reduce the synthesis of Vitamin D by more than 90%.\textsuperscript{10} A serum 25-hydroxy vitamin D level [25(OH)D] should be obtained in patients at risk of vitamin D deficiency, in obese individuals and in those with low bone density.\textsuperscript{9}

**Other tests**

In patients in whom a specific cause of osteoporosis is suspected (see Table 2), a few specific blood and urine studies are useful. These may include thyroid function tests, antigliadin antibodies, anti-human-transglutaminase antibodies (anti-hTg), serum parathyroid hormone, serum creatinine, and testosterone levels in men. Check the serum calcium; a low value can be informative (but assess the serum albumin as well to evaluate whether protein binding is a factor). However, a normal value does not necessarily reflect whole body calcium status; normal parathyroid hormone function can increase calcium resorption from bone and regulate falls in serum calcium. A 24-hour urine calcium of less than 50 mg suggests either insufficient intake or poor absorption.\textsuperscript{9} The utility of bone turnover markers for diagnosing osteoporosis in routine care has not been established.

**Recommendations for all patients**

**Calcium and Vitamin D**

**Calcium and fracture risk reduction**

A meta-analysis of 29 trials (N=63,897, 92% women) that administered calcium alone or with vitamin D to prevent fractures and bone loss in people aged ≥ 50 years found:\textsuperscript{14}

- Treatment with calcium was associated with a 12% risk reduction in fractures of all types (relative risk 0.88; 95% CI, 0.83-0.95) compared to placebo or other control. Addition of vitamin D did not provide additional risk reduction compared to calcium alone.
- The treatment effect was greater with calcium doses of 1,200 mg or more, compared to doses less than 1,200 mg (risk reduction, 20% vs. 6% respectively; p=0.006).
Recommendations for calcium intake

Lifelong adequate calcium intake is necessary to attain peak bone mass and maintain bone health. Providing adequate daily calcium is a safe and inexpensive way to help reduce fracture risk.

All patients over 50 should have a daily intake of elemental calcium of at least 1,200 mg per day, including supplements if necessary. Men and women aged 50 and older typically consume only about 600 to 700 mg per day of calcium in their diets. Increasing dietary calcium is the first-line approach, but is difficult for most patients to accomplish, so calcium supplements should be used when an adequate dietary intake cannot be achieved. Daily calcium intake in excess of 1,200-1,500 mg per day have limited benefit and may increase the risk of developing kidney stones or cardiovascular disease.

A simple and easy to use dietary calcium calculator is available at http://www.myoptumhealth.com/portal/ManageMyHealth/Calcium+Calculator. A reproduction of the input screen, instructions for use, and an example calculation are shown in Appendix 2. Some examples of the calcium content of common foods are as follows:

• 8 oz. glass of milk (fat-free, low fat, or whole): 300 mg
• 1 oz cheddar cheese: 200 mg
• 2 oz American cheese: 350 mg
• 8 oz calcium-fortified orange juice: 300 mg

Calcium absorption and dosing

• Calcium intake and intestinal absorption decrease with age.
• For optimal absorption, a single dose of calcium supplement should contain no more than 500 mg of elemental calcium, so divided doses will often be needed.
• Calcium carbonate is the least expensive preparation, requires acid for absorption because the acid dissolves the calcium tablet, and should be taken with meals.
• Calcium citrate is more expensive, but does not require acid for absorption, and does not need to be taken with meals. It is preferred in patients on acid-suppressive therapies.
• The absorption of many medications (e.g. levothyroxine, fluoroquinolones, tetracycline, phenytoin, ACE-Inhibitors, iron, and bisphosphonates) can be significantly decreased when given with calcium. These medications should be taken several hours before or after calcium supplements.

Vitamin D and fracture risk reduction

Low serum 25(OH)D levels are associated with higher fracture risk. Two recent meta-analyses have produced conflicting results. A recent Cochrane review of vitamin D to prevent fractures in men over 65 years and postmenopausal women found:

• Vitamin D alone did not significantly reduce the risk of hip, non-vertebral, vertebral, or any new fracture compared to placebo or no treatment.
• **Vitamin D alone** did not significantly reduce the risk of hip, non-vertebral, vertebral, or any new fracture compared to calcium alone.

• **Vitamin D with calcium** reduced hip fractures by 16% compared to placebo or no treatment (relative risk, 0.84; 95% CI, 0.73 to 0.96). There were non-significant reductions in vertebral fractures (relative risk, 0.91; 95% CI, 0.75 to 1.11) and in non-vertebral fractures (relative risk 0.95; 95% CI, 0.90 to 1.00).

• **Vitamin D with calcium** was not significantly better than calcium alone in reducing the risk of hip fracture (relative risk, 0.83; 95% CI 0.61-1.12), non-vertebral fracture (relative risk, 0.96; 95% CI, 0.79 to 1.16), or vertebral fracture (relative risk, 0.14; 95% CI 0.01-2.77).

A second meta-analysis examined the efficacy of vitamin D (with or without calcium) in preventing non-vertebral and hip fractures in patients ≥ 65 compared to calcium or placebo. For doses > 400 IU daily, results were as follows:

• Vitamin D reduced the risk of non-vertebral fractures by 20% (relative risk, 0.80; 95% CI, 0.72-0.89).

• Vitamin D reduced the risk of hip fractures by 18% (relative risk, 0.82; 95% CI, 0.69-0.97).

The risk reductions with vitamin D at doses > 400 IU daily were independent of additional calcium supplementation.

**High-dose vitamin D and falls/fracture risk**

A recent randomized, placebo-controlled trial examined the effect of high-dose vitamin D on fractures and falls. The trial enrolled 2,256 community-dwelling women, aged 70 years or older, at high risk of fracture. The patients were randomly assigned to receive once-yearly vitamin D3 (500,000 units) or placebo for 3-5 years.

Surprisingly, women assigned to the vitamin D group had a 15% increased risk of falls compared to women in the placebo group (relative risk, 1.15; 95% CI, 1.02 to 1.30) and a 26% increased risk of fracture (relative risk, 1.26; 95% CI, 1.00-1.59).

These results do not alter the importance of adequate vitamin D intake and correcting vitamin D deficiency. However, the administration of yearly super-high-dose vitamin D may be hazardous.

**Calcitriol and fracture risk reduction**

Calcitriol (Rocaltrol) supplements have not been shown to reduce the risk for osteoporotic fractures, and they are not FDA-approved for treatment of osteoporosis.

**Vitamin D metabolism**

Endogenous vitamin D3 (cholecalciferol) is derived from sunlight exposure and diet. Vitamin D2 (ergocalciferol) is produced by UVB irradiation of the plant steroid ergosterol. Both vitamin D3 and vitamin D2 are metabolized in the liver to 25-hydroxy vitamin D. 25(OH)D undergoes a second hydroxylation in the kidneys to 1,25-dihydroxy-
vitamin D3 (calcitriol), which is the active form of vitamin D. Calcitriol increases renal absorption of calcium and intestinal absorption of calcium and phosphorus.

**Vitamin D and diet**

Cholecalciferol is found in small quantities in some foods such as fatty fish, liver, egg yolks, and vitamin D-fortified milk (400 IU per quart) and cereals (40 to 50 IU per serving). Dietary intake contributes relatively little to total vitamin D levels. Some calcium supplements and most multivitamin tablets also contain vitamin D, but in highly variable amounts.

**Vitamin D and sunlight exposure**

Adequate sun exposure (without sunscreen and not through glass) on the face, hands and arms for approximately 10 minutes on most days of the week may be sufficient for vitamin D production in fair-skinned people, but many older patients living in northern latitudes do not achieve even this amount of exposure, especially in the winter months. This is especially true of elderly patients who are homebound or live in nursing facilities and whose skin is less efficient in the sun-related production of vitamin D. People with darker skin require more sun exposure, but not enough is known about how 25(OH)D levels vary with ethnicity, sunscreen use, or latitude. It is also not known if there is an amount of sunlight exposure that will maintain normal serum 25(OH)D levels without increasing the risk of skin cancer.

**Vitamin D level assessment and deficiency**

A normal serum 25(OH)D level is 30 ng/ml (75 nmol/L) or higher. Recommended daily intake of vitamin D is 800 to 1,000 IU of vitamin D per day for adults 50 and older. However, some elderly patients may need at least 2,000 IU per day to maintain an adequate 25(OH)D level. Several strategies have been proposed for treating vitamin D deficiency e.g. 50,000 IU weekly of oral ergocalciferol for 8 weeks, followed by a maintenance dose of 50,000 IU every 2-4 weeks or oral cholecalciferol 1,000 IU once daily. There is controversy about the optimal extent of increased exposure to sunlight in correcting vitamin D deficiency. Supplemental vitamin D should be given to bring the serum 25(OH)D level to 30 ng/ml (75 nmol/L) or higher.

Serum 25(OH)D will rise by about 1 ng/mL for every 100 IU/day of additional cholecalciferol. Re-test serum 25(OH)D levels after at least 12 weeks of supplementation because steady state of 25(OH)D is not achieved until that time.

**Vitamin D and fall risk**

In older adults, low serum 25(OH)D levels are associated with higher risk of falls, and vitamin D supplementation can reduce that risk through a mechanism that seems to be independent of its effects on bone. A meta-analysis of 5 randomized controlled trials found that vitamin D supplementation reduced the risk of falls in older (mean age 60 years) community-dwelling or institutionalized people by 22% (odds ratio, 0.78; 95%CI, 0.64-0.92; number needed to treat = 15) compared to calcium or placebo. A more recent study found that a dose of 800 IU per day (but not lower doses) of vitamin D for 5 months reduced the incidence of falls in elderly nursing home
residents by 72% compared to placebo (relative risk, 0.28; 95% CI, 0.11-0.75). A 2009 meta-analysis found that supplemental vitamin D of 700-1,000 IU/day reduced fall risk by 19% (relative risk, 0.81; 95% CI 0.71 to 0.92), and serum 25(OH)D concentrations of ≥ 60 nmol/L resulted in a 23% reduction (relative risk, 0.77; 95% CI 0.65 to 0.90). Falls were not reduced by lower doses of vitamin D (200-600 IU/day) or by serum 25(OH)D concentrations of < 60 nmol/L.

**Bottom line:** All patients over 50 should have a daily intake of 800-1,000 IU of vitamin D and at least 1,200 mg of elemental calcium, including supplements if necessary. Higher doses of vitamin D may be needed to correct deficiency and maintain adequate vitamin D levels in some patients. Vitamin D may also reduce the risk of falls, and may reduce the risk of fractures when given with calcitriol.

**Exercise**

Weight-bearing and muscle-strengthening exercise can improve agility, strength, posture, and balance, which can reduce the risk of falls. In addition, weight bearing and resistance exercise in adults can increase bone density by 1-3%. Lifelong physical activity is important for osteoporosis prevention, as benefits are lost when the person stops exercising. Weight-bearing exercise (in which bones and muscles work against gravity as the feet and legs bear the body’s weight) includes walking, running, stair climbing, dancing, and tennis. Muscle-strengthening exercise includes weight training and other resistance exercises. There is insufficient data on the effect of exercise compared to medications in reducing fracture risk.

**Other strategies to prevent falls**

In addition to maintaining adequate vitamin D levels and physical activity, other strategies to reduce falls include:

- reviewing prescription medications that can cause impaired balance/mobility, sedation, or confusion
- checking and correcting vision and hearing
- evaluating gait, mobility, and balance
- assessing and treating orthostatic hypotension
- improving safety at home

For a detailed discussion of falls prevention, see the iDiS evidence document for preventing falls and enhancing mobility at www.RxFacts.org. Also, the 2010 American Geriatrics Society guideline for falls prevention in older persons is available at: http://www.americangeriatrics.org/health_care_professionals/clinical_practice/clinical_guidelines_recommendations/2010/.

**Smoking and alcohol use**

Smoking increases the risk of osteoporosis and patients should be encouraged to quit smoking. For more information on smoking cessation strategies, see the iDiS monograph on the management of COPD, available at www.RxFacts.org. Excessive alcohol intake (3 or more standard drinks per day) also increases the risk of
However, moderate alcohol intake does not appear to have a negative effect on bone.3

When are osteoporosis medications needed?

Consider a prescription drug for osteoporosis in postmenopausal women and men aged 50 years and older who have one or more of the following:3,9

• An osteoporotic hip or vertebral fracture, or
• T-score \( \leq -2.5 \) at the femoral neck, total hip, or lumbar spine, or
• Low bone mass (T-score between -1.0 and -2.5) as well as:
  - a 10-year probability of a hip fracture \( \geq 3\% \) based on FRAX, or
  - a 10-year probability of a major osteoporosis-related fracture (spine, hip, shoulder, or wrist) \( \geq 20\% \) based on FRAX (available at [http://RxFacts.org/FRAX.php](http://RxFacts.org/FRAX.php) for Hispanic, Black, Caucasian, and Asian people).

FDA-approved indications for medications used to reduce fracture risk are shown in Table 4.
Table 4. FDA-approved drugs to reduce fracture risk

<table>
<thead>
<tr>
<th>Drug#</th>
<th>Method of administration</th>
<th>Management of postmenopausal women with T-score between -1.0 and -2.5 and high fracture risk</th>
<th>Management of postmenopausal women with osteoporosis (T-score ≤ -2.5 or previous fragility fracture)</th>
<th>Management of steroid-induced osteoporosis</th>
<th>Management of osteoporosis in men</th>
</tr>
</thead>
<tbody>
<tr>
<td>alendronate (generics, Fosamax, Fosamax plus D*)</td>
<td>oral daily or weekly, or liquid weekly</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>ibandronate (Boniva)</td>
<td>oral daily or monthly or intravenous every 3 months</td>
<td>Y</td>
<td></td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>risedronate (Actonel, Actonel with calcium**)</td>
<td>oral daily, weekly, twice monthly, or monthly</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>zoledronate (Reclast)</td>
<td>once yearly intravenously</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>teriparatide (Forteo)</td>
<td>subcutaneous injection daily</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>raloxifene (Evista)</td>
<td>oral daily</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>calcitonin (generic forms, Miacalcin, Fortical)</td>
<td>SC/IM injection or nasal daily</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>estrogens and/or HRT</td>
<td>oral daily</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>denosumab (Prolia)</td>
<td>SC 6 monthly</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

#drug therapy should be given with adequate calcium and vitamin D intake, by supplementation if necessary

*Fosamax plus D is alendronate/cholecalciferol, 70 mg/2,800 units and 70 mg/5,600 units for once-weekly dosing; equivalent to 400 units/day and 800 units/day of vitamin D respectively

**Actonel with calcium is risedronate 35mg once weekly/calcium carbonate 1,250 mg once daily
Pharmacotherapy: postmenopausal women

**Bisphosphonates**

Bisphosphonates slow bone resorption by inhibiting osteoclast activity. Their efficacy in increasing BMD in postmenopausal women is well established. However, increases in BMD do not necessarily predict the degree of fracture risk reduction. For example, an analysis of 3 clinical trials examining the efficacy of risedronate found that changes in BMD did not predict the degree of reduction in risk of non-vertebral fractures. Therefore, while BMD is often used as a surrogate marker of fracture risk, incidence of fractures is a more clinically relevant outcome.

**Fracture risk reduction**

A large number of clinical trials and several systematic reviews have found that bisphosphonates reduce the risk of fractures in postmenopausal women. Many of these studies included women at high risk of fracture (e.g. those with established osteoporosis and/or a previous vertebral fracture). Fewer studies have evaluated fracture risk reduction in lower-risk groups (e.g. women with osteopenia). Criteria for defining fracture risk levels are not identical across studies, and trials often have mixed populations of low BMD and established osteoporosis, with or without prior fracture. Definitions of primary and secondary prevention differ between systematic reviews, and primary prevention in these reviews is not defined simply as an absence of fracture at baseline. These issues make it difficult to determine the overall effectiveness of treatment by either fracture risk level or by primary vs. secondary prevention.

The table on the opposite page summarizes the clinical trial data for the efficacy of bisphosphonates (compared to placebo) at reducing fractures in postmenopausal women.
Table 5. Fracture risk reduction (compared to placebo) with bisphosphonates in the treatment of postmenopausal women

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative risk reduction* (number needed to treat)**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vertebral fractures</td>
</tr>
<tr>
<td>alendronate (generics, Fosamax)</td>
<td>44-55% (14-60)</td>
</tr>
<tr>
<td>ibandronate (Boniva)</td>
<td>50-62% (20-21)</td>
</tr>
<tr>
<td>risedronate (Actonel)</td>
<td>41-49% (10-20)</td>
</tr>
<tr>
<td>zoledronate (Reclast)</td>
<td>70-77% (13-48)</td>
</tr>
</tbody>
</table>

*P < 0.05 for all values  
**Number of patients needed to treat with 1-4 years of drug therapy (most trials were 3 years)

There are insufficient data to establish whether any particular bisphosphonate is superior to others. Several head-to-head trials have compared the effects of bisphosphonates on BMD and bone turnover markers, but these studies do not provide information about reductions in fracture risk.

Duration of treatment

The Fracture Intervention Trial Long-term Extension (FLEX) study compared the effect of discontinuing alendronate treatment after 5 years versus continuing for 10 years. In this study, over 1,000 postmenopausal women with low femoral neck BMD who had previously taken alendronate for an average of 5 years during and after the Fracture Intervention Trial (FIT), were randomized to continue to receive alendronate 5 mg or 10 mg daily, or placebo, for an additional 5 years. The incidence of fractures is shown in the table on page 19.
Table 6. Incidence of fractures in the FLEX trial

<table>
<thead>
<tr>
<th>Fracture type</th>
<th>Fracture incidence, placebo group</th>
<th>Fracture incidence, alendronate groups</th>
<th>RRR*</th>
<th>ARR*</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-vertebral fractures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>any non-vertebral</td>
<td>19.0%</td>
<td>18.9%</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>hip</td>
<td>3.0%</td>
<td>3.0%</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>forearm</td>
<td>4.3%</td>
<td>4.7%</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clinical</td>
<td>5.3%</td>
<td>2.4%</td>
<td>55%</td>
<td>2.9%</td>
<td>35</td>
</tr>
<tr>
<td>radiologically confirmed</td>
<td>11.3%</td>
<td>9.8%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05 unless otherwise stated
RRR = relative risk reduction; ARR = absolute risk reduction; NNT = number needed to treat with alendronate for 10 years compared to five years of treatment to prevent one vertebral fracture; NS = Not significant.

Patients who stopped taking alendronate after 5 years (placebo group) did not have a significantly higher risk of fractures (other than clinically diagnosed vertebral fractures) compared with patients who continued with the drug for another 5 years. A post hoc analysis of FLEX found that continuing alendronate for 10 years instead of stopping after 5 years reduced the risk of non-vertebral fractures in women without prevalent vertebral fracture whose T-score, after 5 years of alendronate, was ≤ -2.5 (relative risk, 0.50; 95% CI, 0.26-0.96).46

Therefore, continuation of bisphosphonate therapy after 5 years may not significantly decrease fracture risk in most women with low BMD, but it may be reasonable to continue therapy beyond 5 years in women with a T-score of ≤ 2.5 after 5 years of drug therapy.

**Bottom line:** Bisphosphonates are first-line drug therapy for postmenopausal women. They have been shown to reduce the risk of vertebral, non-vertebral, and hip fractures. Therapy beyond 5 years may not provide additional benefit for most women.

**Teriparatide**

Teriparatide [PTH(1-34)] is a recombinant form of the first 34 amino acids of human parathyroid hormone (PTH). Intact human PTH contains 84 amino acids and is called PTH(1-84). Teriparatide is FDA-approved for the treatment of osteoporosis in postmenopausal women, osteoporosis in men, and steroid-induced osteoporosis, and is delivered by subcutaneous injection.

Many clinical trials with teriparatide and PTH(1-84) have reported increases in BMD in postmenopausal osteoporosis.47-51 However, only a few trials (notably the Fracture Prevention Trial52) have examined the effect of teriparatide on fracture risk.
Fracture risk reduction

Fracture Prevention Trial

This trial randomly assigned 1,637 postmenopausal women with at least one prior vertebral fracture to treatment with placebo, teriparatide 20 µg/day, or teriparatide 40 µg/day for 18 months. All women received daily calcium (1000 mg) and vitamin D (400-1200 IU). The study’s primary outcome was incident vertebral and non-vertebral fractures. The trial results are summarized below.

Table 7. Fracture incidence in the Fracture Prevention Trial.

<table>
<thead>
<tr>
<th></th>
<th>Incidence of fractures</th>
<th>RRR compared to placebo*</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>placebo</td>
<td>teriparatide 20µg/day</td>
<td>teriparatide 40µg/day</td>
</tr>
<tr>
<td>Vertebral fracture</td>
<td>14%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Non-vertebral fracture</td>
<td>6%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

*P < 0.05 for all values

RRR = relative risk reduction; NNT = number needed to treat with teriparatide for 18 months compared to placebo to prevent one fracture of type shown

European Forteo Observational Study

This open-label, non-placebo controlled study examined the effectiveness of teriparatide in 1,648 postmenopausal women with severe osteoporosis (mean T-score -3.3) who were treated for up to 18 months in community clinical practice. There was a 47% reduction in the risk of any fracture in the last 6 month period compared to the first 6 months (P < 0.005).

Contraindications

Teriparatide increases the incidence of osteosarcoma in rats, so it is contraindicated in patients with an increased risk of osteosarcoma (e.g., those with Paget’s disease). It is also contraindicated in patients with a history of radiation therapy, bone metastases, skeletal malignancy, hypercalcemia, or hyperparathyroidism.

Bottom line: Teriparatide (Forteo) can reduce the risk of vertebral and non-vertebral fractures in postmenopausal women with a prior vertebral fracture. Duration of therapy (up to 2 years only) and its high cost may limit its usefulness. Bisphosphonates remain first line-treatment for those who tolerate that therapy.

Raloxifene

As with the bisphosphonates, changes in BMD with raloxifene correlate poorly with vertebral fracture risk reduction.
The Multiple Outcomes of Raloxifene Evaluation (MORE) study examined the effect of raloxifene on fracture risk in postmenopausal women with a femoral neck or lumbar spine T-score $<-2.5$, or low bone mineral density and $\geq 1$ vertebral fractures, or who had $\geq 2$ moderate vertebral fractures regardless of bone mineral density. The trial randomly assigned 7,705 women to receive 60 mg or 120 mg daily, or placebo for 36 months. The primary outcome measure was the incidence of vertebral and non-vertebral fractures. The risk of vertebral fracture was significantly reduced (by 30-50%) in women with or without a previous fracture as shown in Figure 2.

**Figure 2. Reductions in new vertebral fractures in the MORE study**

Women did or did not have vertebral fracture at the beginning of the study. RR indicates relative risk; CI, confidence interval.


The risk of non-vertebral fracture was not significantly different between the groups (relative risk 0.9; 95% CI, 0.8-1.1 for combined raloxifene groups).

Women given raloxifene in the MORE study had an increased risk of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism, compared to placebo (relative risk 3.1; 95% CI, 1.5-6.2). Hot flashes can also limit the tolerability of raloxifene in postmenopausal women.

In the Continuing Outcomes Relevant to Evista (CORE) breast cancer trial of 4,011 women continuing the MORE study for 4 additional years, the incidence of non-vertebral fractures was still not significantly different between placebo (22.9%) and raloxifene (22.8%) after a total of 8 years of raloxifene therapy.
A 2006 meta-analysis of 7 clinical studies examined the efficacy of raloxifene in reducing the risk of vertebral fractures in postmenopausal women. Relative risk reductions were 40% for raloxifene 60 mg daily (95% CI, 26% to 51%) and 49% for raloxifene 120 or 150 mg daily (95% CI, 36% to 59%).

Raloxifene is a treatment option for women who have contraindications to bisphosphonates or are intolerant of them, who have had an unsatisfactory response to bisphosphonates (reduction in BMD or osteoporotic fracture during treatment), or who are at high risk of breast cancer.

**Bottom line:** Raloxifene (Evista) can reduce the risk of vertebral fractures (but not the risk of non-vertebral fractures) in postmenopausal women with osteoporosis, and is recommended for patients unable to take bisphosphonates. It should also be considered for women at high risk of breast cancer.

**Calcitonin**

Calcitonin is a hormone that inhibits osteoclasts and bone resorption. Salmon calcitonin is more potent than human calcitonin, and most studies have used this preparation, which is FDA-approved for the treatment of osteoporosis in women who are at least 5 years postmenopausal.

The Prevent Recurrence of Osteoporotic Fractures study (PROOF) study examined the efficacy of salmon calcitonin nasal spray for reducing the risk of vertebral fractures in postmenopausal women with osteoporosis. Approximately 1/3 of women had no previous vertebral fracture. The trial randomly assigned 1,255 women to receive it (100, 200, or 400 IU) or placebo daily for 5 years; the primary outcome measure was incident vertebral fractures. The 200-IU dose reduced the risk of new vertebral fractures by 33% compared with placebo (relative risk, 0.67, 95% CI 0.47-0.97). In the 817 women with prior vertebral fractures, the risk was reduced by 36% (relative risk, 0.64, 95% CI, 0.43 to 0.96). The reductions in vertebral fractures in the 100-IU and the 400-IU groups were not significantly different from placebo.

A meta-analysis of 4 clinical trials (including PROOF) examining the effect of calcitonin on BMD and fracture risk in postmenopausal women found that calcitonin reduced the incidence of vertebral fractures by 54% (relative risk, 0.46; 95% CI, 0.25-0.87; p = 0.02), with a non-significant reduction in non-vertebral fracture risk.

**Bottom line:** Calcitonin can reduce the risk of vertebral fractures, but not the risk of non-vertebral fractures, in postmenopausal women with osteoporosis, and is an option for patients unable to take bisphosphonates or raloxifene.

**Estrogen-based Hormone Therapy (HT)**

Hormone therapy (estrogens with or without progestogens) is FDA-approved for use in postmenopausal women. However, in patients where the sole aim is the treatment of low bone mass, the FDA recommends that other pharmacotherapy be
considered before HT, because of the capacity of HT to cause cancer and cardiovascular side effects. A recent Cochrane review concluded that long-term HT use is not indicated for the treatment of osteoporosis. The benefits of HT on bone mass are lost soon after discontinuation of treatment.

The Woman's Health Initiative Randomized Controlled Trial examined the effect of 5 years of conjugated equine estrogen and medroxyprogesterone (combined HT) therapy in postmenopausal women, with or without low BMD and with or without prior fracture. HT reduced the risk of clinical vertebral fractures and hip fractures by 34% (relative risk, 0.66; 95% CI, 0.44-0.98 for both), and other osteoporotic fractures by 23% (relative risk, 0.77; 95% CI 0.69-0.86; absolute risk reduction, 0.39%; NNT 256). Absolute risk reduction of hip fractures was 5 per 10,000 person-years of treatment.

The Women's Health Initiative (WHI) documented increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis in women taking HT. Due to these risks, other therapies are recommended for the treatment or prevention of osteoporotic fractures.

**Denosumab (Prolia)**

Denosumab is a recently approved human monoclonal antibody that decreases bone resorption and increases bone density by inhibiting the development and activity of osteoclasts.

The Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial examined the ability of denosumab to reduce the risk of fractures in postmenopausal women with osteoporosis. It randomly assigned 7,808 women (mean age 72) to receive either 60 mg of denosumab or placebo subcutaneously every 6 months for 36 months. The primary outcome was the incidence of new vertebral fracture. Secondary outcomes were the incidence of new non-vertebral and hip fractures. The trial results are presented below.

**Table 8. Incidence of fractures in the FREEDOM trial**

<table>
<thead>
<tr>
<th>Fracture type</th>
<th>Fracture incidence placebo group</th>
<th>Fracture incidence denosumab group</th>
<th>RRR*</th>
<th>ARR*</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral</td>
<td>7.2%</td>
<td>2.3%</td>
<td>68%</td>
<td>4.9%</td>
<td>21</td>
</tr>
<tr>
<td>Non-vertebral</td>
<td>8.0%</td>
<td>6.5%</td>
<td>20%</td>
<td>1.5%</td>
<td>67</td>
</tr>
<tr>
<td>Hip</td>
<td>1.2%</td>
<td>0.7%</td>
<td>40%</td>
<td>0.5%</td>
<td>200</td>
</tr>
</tbody>
</table>

*P < 0.05

RRR = relative risk reduction; ARR = absolute risk reduction; NNT = number needed to treat with denosumab for 3 years compared to placebo to prevent one fracture of type shown.

In June 2010, the FDA approved the use of denosumab for the prevention of fracture in postmenopausal women with osteoporosis and high fracture risk. Patients at
high risk include those who have a history of osteoporotic fracture, have several risk factors, or have failed other treatments. Injection with denosumab is recommended twice a year.

Further information is available at:
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm214150.htm

**Other issues for postmenopausal women**

**Osteopenia**

Although “osteopenia” (T-score between −1 and −2.5) is a common finding on bone mineral density testing in postmenopausal women, it is a less serious problem than actual osteoporosis (T-score lower than −2.5). Despite the high frequency of BMD reports of osteopenia, there is little clinical trial data documenting the usefulness of medications in such patients if they do not have major risk factors or prior fracture.26

An analysis of four large clinical trials 28, 29, 63, 64 examined the effect of risendronate on fracture risk in postmenopausal women with osteopenia at the femoral neck without a prior vertebral fracture.65 The drug reduced the risk of vertebral and non-vertebral fractures by 73% over 3 years compared to placebo (relative risk, 0.27; 95% CI, 0.09-0.83). However, this benefit was primarily seen among patients who had frank osteoporosis in their lumbar vertebrae. When the analysis of these patients excluded those who had a T-score lower than −2.5 at the lumbar spine, the reduction in fracture risk was not statistically significant.

Another analysis from the Fracture Intervention Trial examined the effect of alendronate on vertebral fracture risk in postmenopausal women with osteopenia (defined in this study as BMD T scores of -1.6 to -2.5 at the femoral neck).66 It found a reduction in vertebral fractures, but the benefit was significant only in women who had already had a vertebral fracture.

A cost-effectiveness analysis found that in light of this limited clinical benefit, prescribing alendronate to postmenopausal women who only have osteopenia but do not have a history of fractures or risk factors for fracture would not be cost-effective.67

National guidelines recommend drug therapy (particularly a bisphosphonate) for postmenopausal women with osteopenia only if they also have:3, 9
- a 10-year risk of a hip fracture ≥ 3%, based on FRAX, or
- a 10-year risk of any major osteoporosis-related fracture (spine, hip, shoulder, or wrist) ≥ 20%, based on FRAX

**Bottom line:** A BMD diagnosis of “osteopenia” does not automatically warrant treatment with bisphosphonates. However, these drugs can be useful for patients who also have a high fracture risk.
Comparative effectiveness of osteoporosis medications

Many agents reduce the risk of fracture in postmenopausal women at high risk of fracture. No studies have prospectively compared these therapies for anti-fracture efficacy, so there are insufficient data to definitively determine whether:

- bisphosphonates are more effective than other medications for reducing fracture risk
- one bisphosphonate is more effective than another for reducing fracture risk

A recent retrospective cohort study of more than 43,000 patients in a state-wide database examined the relative effectiveness of oral bisphosphonates, nasal calcitonin, and raloxifene to reduce non-vertebral fracture risk among patients aged ≥ 65 years (96% were women). The primary outcome was non-vertebral fracture (hip, humerus, or radius or ulna) within 12 months of treatment initiation. Main results were as follows:

- No significant differences in fracture risk were found between risedronate (hazard ratio, 1.01; 95% CI, 0.85 to 1.21) or raloxifene (hazard ratio, 1.18; 95% CI, 0.96 to 1.46) compared to alendronate.
- Patients with a previous fracture who received raloxifene had a significantly increased risk of non-vertebral fractures compared with those who received alendronate (hazard ratio, 1.78; 95% CI, 1.20 to 2.63)
- Patients who received nasal calcitonin had a significantly increased risk of non-vertebral fractures compared with those who received alendronate (hazard ratio, 1.40; 95% CI, 1.20 to 1.63).

Table 9 on the opposite page summarizes the efficacy of medications for reducing the risk of fractures in postmenopausal women.
Table 9. Fracture risk reduction of medications approved for the treatment of postmenopausal women, compared to placebo

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vertbral fractures</th>
<th>Non-vertebral fractures</th>
<th>Hip fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alendronate (generics, Fosamax)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>ibandronate (Boniva)</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>risedronate (Actonel)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>zoledronate (Reclast)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Anabolics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>teriparatide (Forteo)</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Selective estrogen receptor modulators*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>raloxifene (Evista)</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Hormones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>calcitonin (generics, Miacalcin, Fortical)*</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>estrogen-based hormone therapy (HT)#</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Denosumab (Prolia)*</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>*antiresorptive agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#not recommended because of increased risk of cancer and cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y  = significant reduction in fracture risk; N = no reduction, or non-significant reduction, or insufficient data.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Steroid-induced osteoporosis

Although corticosteroids are widely used in inflammatory conditions such as asthma, inflammatory bowel disease, and connective tissue diseases, reduction in BMD is a serious adverse effect. Bisphosphonates and teriparatide can be helpful in these patients; other medications have not been studied or have not demonstrated efficacy.69

Bisphosphonates

A Cochrane review70 of the prevention or treatment of corticosteroid-induced osteoporosis with bisphosphonates analyzed 13 trials with a total of 842 patients. Participants were adults taking a mean steroid dose of 7.5 mg/day or more. The review found that bisphosphonates are effective at preventing and treating corticosteroid-induced bone loss at the lumbar spine and femoral neck (weighted mean difference in BMD between treatment and placebo groups was 4.3% (lumbar) and 2.1% (femoral...
There was a 24% reduction in the risk of vertebral fractures (HR 0.76, 95% CI 0.37 to 1.53), but the result was not statistically significant.

A number of subsequent studies have examined the efficacy of bisphosphonates for reducing fracture risk in patients treated with corticosteroids. Results of several studies are summarized below.

### Table 10. Fracture risk reduction with bisphosphonates in patients receiving steroid therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients, duration</th>
<th>Incidence of vertebral fractures</th>
<th>RRR*</th>
<th>ARR*</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wallach^200071</td>
<td>518, 1 year</td>
<td>16.0% (placebo)</td>
<td>70%</td>
<td>11.0%</td>
<td>9</td>
</tr>
<tr>
<td>Adachi#200172</td>
<td>208, 2 years</td>
<td>6.8% (placebo)</td>
<td>90%</td>
<td>6.1%</td>
<td>16</td>
</tr>
<tr>
<td>Reid†200173</td>
<td>184, 1 year</td>
<td>24% (placebo)</td>
<td>82%</td>
<td>19%</td>
<td>5</td>
</tr>
<tr>
<td>Ringe**200374</td>
<td>115, 3 years</td>
<td>22.8% (alfacalcidol)</td>
<td>62%</td>
<td>14.2%</td>
<td>7</td>
</tr>
</tbody>
</table>

*P < 0.05 for all values

RRR = relative risk reduction; ARR = absolute risk reduction; NNT = number needed to treat for duration of therapy compared to control to prevent one vertebral fracture

^trial enrolled men and women receiving ≥ 7.5 mg of oral prednisone or equivalent daily

#trial enrolled men and women receiving ≥ 7.5 mg of oral prednisone or equivalent daily

† trial enrolled men beginning corticosteroid treatment at a dose of ≥ 7.5 mg/day of prednisone or equivalent (prevention arm) or continuing long-term treatment of corticosteroid at that dose (treatment arm).

**trial enrolled men and women with established osteoporosis induced by the long-term administration of high-dose corticosteroids

### Teriparatide

Several studies have found that teriparatide significantly reduces the risk of fractures in patients with steroid-induced osteoporosis.75 One recent trial assigned 428 patients with osteoporosis who had received ≥ 5 mg/day of prednisone equivalent for ≥ 3 months to treatment with teriparatide (20 µg/day) or alendronate (10 mg/day) for 3 years.76 Outcome measures included changes in lumbar spine and hip BMD and fracture incidence. Results are shown in Table 11:
Table 11. BMD and incidence of new fractures

<table>
<thead>
<tr>
<th>Outcome</th>
<th>alendronate group</th>
<th>teriparatide group</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in BMD from baseline:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>5.3%</td>
<td>11.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral neck</td>
<td>3.4%</td>
<td>6.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fracture incidence:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertebral</td>
<td>7.7%</td>
<td>1.7%</td>
<td>78%*</td>
<td>6.0%*</td>
<td>17</td>
</tr>
<tr>
<td>Non-vertebral</td>
<td>7.0%</td>
<td>7.5%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05

RRR = relative risk reduction; ARR = absolute risk reduction; NNT = number needed to treat with teriparatide for 3 years compared to alendronate to prevent one vertebral fracture; NS = not significant; ... = not applicable

Bottom line: Bisphosphonates and teriparatide reduce the risk of vertebral fractures in steroid-induced osteoporosis. Consider testing BMD in adults of any age using oral steroids (at a daily dose ≥ 5mg prednisone or equivalent for > 3 months), and initiating drug therapy in those with low BMD.

Osteoporosis in men

Bisphosphonates

Fracture risk reduction with bisphosphonates in men is less well studied than in postmenopausal women. A 2005 meta-analysis examined the anti-fracture efficacy of alendronate compared to placebo, calcium, vitamin D, or any combination of these in men with osteoporosis. The analysis found that alendronate decreased the risk of vertebral fractures in men by 56% (relative risk, 0.44; 95% CI, 0.23-0.83). There was a non-statistically significant 40% reduction of non-vertebral fracture risk (relative risk, 0.60; 95% CI 0.29-1.44), but the small number of trials limited the ability to detect a significant difference. The results of several randomized controlled trials published since the 2005 meta-analysis are shown in Table 12.
Table 12. Vertebral fracture risk reduction with bisphosphonates in men with osteoporosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients (duration)</th>
<th>Incidence of vertebral fractures (control group)</th>
<th>Incidence of vertebral fractures (treatment) group</th>
<th>RRR*</th>
<th>ARR*</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ringe 200678</td>
<td>316 (1 year)</td>
<td>12.7% (placebo)</td>
<td>5.1% (alendronate)</td>
<td>60%</td>
<td>7.6%</td>
<td>13</td>
</tr>
<tr>
<td>Ringe 200479</td>
<td>134 (3 years)</td>
<td>24.2% (alfacalcidol)</td>
<td>10.3% (alendronate)</td>
<td>57%</td>
<td>13.9%</td>
<td>7</td>
</tr>
<tr>
<td>Ringe 200980</td>
<td>316 (2 years)</td>
<td>23.6% (alfacalcidol or vitamin D)</td>
<td>9.2% (risedronate)</td>
<td>61%</td>
<td>14.4%</td>
<td>7</td>
</tr>
</tbody>
</table>

*P < 0.05 for all values

RRR = relative risk reduction; ARR = absolute risk reduction; NNT = number needed to treat for duration of therapy compared to control to prevent one vertebral fracture

Teriparatide

A randomized, placebo-controlled study of 437 men with low vertebral or hip BMD (with or without prior fractures) examined the effect of teriparatide 20 µg/day or 40 µg/day. The study was stopped after 12 months because of data from routine toxicology studies in rats that teriparatide may increase the risk of osteosarcoma. At 12 months, vertebral BMD increased by 5.9% (20 µg/day) and 9.0% (40 µg/day) above baseline (p < 0.001 vs. placebo for both comparisons). Femoral neck BMD increased by 1.5% (20 µg/day; p = 0.029) and 2.9% (40 µg/day; p < 0.001).81

BMD and vertebral fracture incidence in 355 of the men from the trial was assessed at 30 months post-treatment.82 Participants may have received follow-up antiresorptive therapy after discontinuing teriparatide. BMD gradually decreased following discontinuation of teriparatide therapy, but remained significantly higher than at baseline. There was a non-significant 51% relative risk reduction of new vertebral fractures in the combined teriparatide groups compared to placebo (p = 0.07). In men with a prior vertebral fracture at baseline, there was a 13% absolute risk reduction of new vertebral fractures in the combined teriparatide groups compared to placebo (p < 0.05). There were no significant differences between groups in the risk of non-vertebral fractures.82

Another study examined the effect of bisphosphonate therapy immediately after discontinuing teriparatide therapy in 21 men. After 12 months, lumbar spine BMD increased by 5.1% in the bisphosphonate group, while it declined by 3.7% in those without bisphosphonate therapy (p < 0.002). The findings suggest that the use of bisphosphonates following teriparatide may help to optimize gains in BMD.83
**Bottom line:** Medications for the treatment of osteoporosis in men are less well studied than in women; bisphosphonates and teriparatide reduce the risk of vertebral fractures in men.

**Intravenous bisphosphonates after hip fracture**

The HORIZON Recurrent Fracture Trial (HORIZON-RFT) examined the efficacy of IV zoledronate for reducing fractures in men and women who had undergone surgical repair of a hip fracture within 90 days. The trial randomly assigned 2,127 patients (76% women) to receive yearly IV zoledronate or placebo for 1.9 years. At baseline, only 42% of patients had a T score < -2.5 SD at the femoral neck. The primary outcome measure was a new fracture. Results are shown below.

**Table 13. Fracture risk reduction in HORIZON-RFT**

<table>
<thead>
<tr>
<th>Type of fracture</th>
<th>Fracture Rate (placebo)</th>
<th>Fracture Rate (zoledronate)</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any new fracture</td>
<td>13.9%</td>
<td>8.6%</td>
<td>35%</td>
<td>5.3%</td>
<td>19</td>
<td>0.001</td>
</tr>
<tr>
<td>Vertebral fracture</td>
<td>3.8%</td>
<td>1.7%</td>
<td>46%</td>
<td>2.1%</td>
<td>48</td>
<td>0.02</td>
</tr>
<tr>
<td>Non-vertebral fracture</td>
<td>10.7%</td>
<td>7.6%</td>
<td>27%</td>
<td>3.1%</td>
<td>32</td>
<td>0.03</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>3.5%</td>
<td>2.0%</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>0.18</td>
</tr>
</tbody>
</table>

RRR = relative risk reduction; ARR = absolute risk reduction; NNT = number needed to treat with zoledronate for 1.9 years compared to placebo to prevent one fracture of type shown; NS = not significant;

Zoledronate (Reclast) is given once yearly and incurs a significant up-front cost of approximately $1,100. However, once-yearly dosing may benefit patients at high risk of non-adherence with other osteoporosis medications.

**Adherence and persistence**

Adherence with dosing schedules and persistence with long-term use of treatments for osteoporosis (including calcium and vitamin D) is quite low, even though the need for therapy is usually lifelong. Part of the prescribing process must be assessment of how well the patient will be able to take the medication as prescribed and the possible barriers to long-term therapy. Factors that affect adherence and persistence include adverse effects, absence of disease-related symptoms, comorbidities, ethnicity, socioeconomic status, complex dosing regimens, and polypharmacy.
A recent study examined the effect of compliance with osteoporosis medications on fracture risk. Over 11,000 women aged > 45 years (mean 68 years) prescribed one or more medications (including alendronate, risedronate, etidronate, calcitonin, or estrogen) were followed-up for a mean of 2 years. The compliance definition was how often a prescription was refilled in relation to the quantity dispensed. Patients were considered to be highly compliant if they had medication available during 80% or more of the time. Women with high compliance had a 16% lower fracture rate than those with low compliance (see figure below).

**Figure 3. Compliance and fracture risk**

<table>
<thead>
<tr>
<th>Compliance with osteoporosis medications and risk of fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image.png" alt="Compliance and fracture risk" /></td>
</tr>
</tbody>
</table>

Strategies to improve adherence and persistence include:

- educate patients about the importance of the medication and the need to take it consistently
- choose the most affordable effective option
- consider weekly dosing of oral bisphosphonates to improve adherence and persistence, compared with daily dosing in some patients
- provide written instructions on dosing and duration of therapy
- encourage a reminder system or use of a compliance aid such as a pill box
- ask the patient about cessation of medication use or missing doses
- talk about adverse effects (such as gastrointestinal side effects with bisphosphonates, or hot flashes with raloxifene) at the start of treatment and at each subsequent visit
- consider an alternative medication if side effects hamper adherence
Monitoring response to therapy

The following strategies should be used to monitor response to therapy:

1. Review modifiable risk factors and encourage appropriate calcium and vitamin D intake, exercise, fall prevention, and other lifestyle measures.

2. Ask patients about adverse effects and compliance.

3. Perform DXA BMD testing of the hip and spine 2 years after initiating pharmacotherapy, and every 2 years thereafter. More frequent testing may be warranted in certain clinical situations e.g. patients on high-dose corticosteroids. Changes in BMD of greater than 5% are considered significant. Changes in BMD of less than 5% from test to test may be due to the precision error of the test.

4. Consider discontinuing a bisphosphonate after 5 years unless the patient has a T-score of ≤ -2.5 after 5 years of drug therapy.

5. The routine use of biochemical markers of bone turnover in clinical practice is not generally recommended.9

Adverse effects of bisphosphonates

Bone and muscle pain

In January 2008, the FDA issued an alert warning of severe and sometimes incapacitating joint, muscle, and/or bone pain in patients taking bisphosphonates.

- The pain may occur within days, months, or years after starting a bisphosphonate.
- Some patients have reported complete relief of symptoms after discontinuing the bisphosphonate, whereas others have reported slow or incomplete resolution.
- The risk factors for and incidence of severe musculoskeletal pain associated with bisphosphonates are unknown.
- This severe musculoskeletal pain is in contrast to the acute phase response characterized by fever, chills, bone pain, myalgia, and arthralgia that sometimes accompanies initial administration of intravenous bisphosphonates and may occur with initial exposure to once-weekly or once-monthly doses of oral bisphosphonates. The symptoms related to the acute phase response tend to resolve within several days with continued drug use.
- Consider whether bisphosphonate use might be responsible for new onset of severe musculoskeletal pain in patients who present with these symptoms, and consider temporary or permanent discontinuation of the drug.
Further information is available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124165.htm

**Atrial fibrillation**

In October 2007, the FDA issued a safety review regarding a potential increased risk for atrial fibrillation in patients treated with bisphosphonates. The HORIZON-PFT study had reported a significantly increased incidence of serious atrial fibrillation events (1.3% with zoledronate vs. 0.5% with placebo; p < 0.001), in postmenopausal women with osteoporosis treated with intravenous zoledronate. Serious atrial fibrillation was defined as events resulting in hospitalization or disability or judged to be life-threatening. An analysis of the Fracture Intervention Trial (FIT), a study of oral alendronate for postmenopausal osteoporosis, reported a trend toward an increased incidence of serious atrial fibrillation events in patients treated with alendronate compared to placebo during an average of 4 years of treatment (1.5% vs. 1.0% relative risk, 1.51; 95% CI, 0.97 to 2.40; p = 0.07), but there was no increased risk of all atrial fibrillation events.

In November 2008, the FDA issued an update to the 2007 review after analyzing data on 19,687 bisphosphonate-treated patients and 18,358 placebo-treated patients who were followed between 6 months and 3 years. The occurrence of atrial fibrillation was rare, with most studies containing 2 or fewer events. The absolute difference in event rates between bisphosphonate and placebo groups varied from 0-3 per 1,000. There was no clear association between overall bisphosphonate exposure and the rate of serious or non-serious atrial fibrillation, and increasing dose or duration of bisphosphonate therapy was not associated with an increased rate of atrial fibrillation.

The FDA acknowledged discordant results from studies about the incidence and clinical course of atrial fibrillation in patients taking bisphosphonates, and continues to monitor post-market reports of atrial fibrillation in patients who have taken bisphosphonates.


A recent meta-analysis examined the risk of atrial fibrillation associated with bisphosphonates. Bisphosphonate use was not found to be associated with an increased risk of atrial fibrillation (adjusted odds ratio, 1.04, 95% CI, 0.92-1.16).

**“Atypical” femoral fractures**

In March 2010, the FDA raised the possibility of a possible increased risk of atypical subtrochanteric femur fractures (below the femoral neck) caused by oral bisphosphonates. However, the agency’s review of available data from case reports and clinical trial data did not show a clear connection between bisphosphonate use and risk of such atypical fractures.
The FDA also reviewed a study that analyzed data from two large observational studies in patients with osteoporosis. The study found that subtrochanteric femur fractures labeled as “atypical” had many similar features in common with classical osteoporotic hip fractures. Patients taking bisphosphonates and those not taking bisphosphonates had similar numbers of atypical subtrochanteric femur fractures.


**Further to the FDA alert:** A 2010 study found atypical femoral shaft fractures (subtrochanteric and diaphyseal) are rare compared to typical fractures of the hip (that are prevented by bisphosphonates), even with bisphosphonate use for up to 10 years. Atypical fractures account for 2-4% of all hip fractures, and those associated with bisphosphonates account for only about one-third of that 2-4%.

The study involved secondary analysis of data from 3 large trials of bisphosphonates: FIT, FLEX, and HORIZON-PFT. As compared with placebo, the combined rate of subtrochanteric or diaphyseal femur fracture was 2.3 per 10,000 patient-years. The relative risks of atypical hip fractures with bisphosphonates compared to placebo were as follows:

- **FIT** (alendronate): relative risk, 1.03; 95% CI, 0.06 to 16.46
- **HORIZON-PFT** (zoledronate): relative risk, 1.50; 95% CI, 0.25 to 9.00
- **FLEX** (alendronate): relative risk, 1.33; 95% CI, 0.12 to 14.67

**Bisphosphonates and fracture healing**

Fracture repair is a complex process that includes an extended period of resorption and new bone formation, resulting in restoration of bone strength. It has been suggested that inhibition of osteoclasts by bisphosphonates may affect bone remodeling and delay fracture healing. However, there is an absence of clinical data in humans regarding the effect of these agents on fracture healing. It is not known whether initiation of bisphosphonate therapy should be delayed until after fracture healing has occurred.

**Osteonecrosis of the jaw**

Bisphosphonate-related osteonecrosis of the jaw (ONJ) was first reported in 2003, and hundreds of cases have been reported worldwide. The majority have occurred with intravenous zoledronate and pamidronate, but ONJ has also been reported with oral alendronate and oral risedronate.

Studies have established a strong association between monthly IV bisphosphonate use in cancer patients and ONJ. However, a causal association between ONJ and oral or IV bisphosphonates used to treat osteoporosis is less well established. A small risk of developing ONJ from oral bisphosphonate therapy must be weighed against the significant health benefits of using these drugs if they are indicated.
Although the incidence of ONJ with oral bisphosphonates is low, the large number of patients receiving these agents for the treatment of osteoporosis/osteopenia means that clinicians are likely to encounter patients with ONJ. U.S. prescriptions for oral bisphosphonates exceeded 30 million in 2006.

The table below provides the incidence of ONJ in various patient groups. Dental extraction increases the incidence of ONJ by approximately eight-fold in all patient groups. Patients treated with oral bisphosphonate therapy are at a considerably lower risk for ONJ than cancer patients treated with monthly IV bisphosphonates.

**Table 14. Incidence of ONJ with bisphosphonate therapy**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Incidence</th>
<th>Incidence with dental extraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>0.05% to 0.10%</td>
<td>0.4% to 0.8%</td>
</tr>
<tr>
<td>Patients with osteoporosis</td>
<td>0.01% to 0.04%</td>
<td>0.1% to 0.3%</td>
</tr>
<tr>
<td>Patients with Paget’s disease</td>
<td>0.3% to 1.8%</td>
<td>2.1% to 13.5%</td>
</tr>
<tr>
<td>Patients with malignancy</td>
<td>0.9% to 1.2%</td>
<td>6.7% to 9.1%</td>
</tr>
</tbody>
</table>

Pathophysiology

The jawbones are in constant use and undergo a high degree of active remodeling and very high loads due to chewing. Bisphosphonates might accumulate there preferentially, resulting in concentrations that exceed those found elsewhere in the skeleton. The potent anti-angiogenic properties of bisphosphonates are well established. The combination of inhibition of bone remodeling from reduced osteoclast activity and decreased intraosseous vascular supply may predispose to ONJ. Onset can be months to years after commencing bisphosphonate therapy. The median time to onset of ONJ with oral alendronate has been reported as 24 months.

Diagnosis

Signs and symptoms of ONJ include loose teeth, dental abscesses, toothache, non-healing extraction sockets, bone exposure, and severe pain. ONJ is associated with significant morbidity such as osteomyelitis and chronic exposure of necrotic bone. Patients may be considered to have drug-related ONJ if all of the following three characteristics are present:

1. current or previous treatment with a bisphosphonate;
2. exposed bone in the maxillofacial region persisting for more than 8 weeks; and
3. no history of radiation therapy to the jaw.
Strategies for prevention

Assess risk factors\textsuperscript{95-97, 101, 103}

The major risk factors for ONJ are IV bisphosphonate use and invasive dental procedures (extractions, dental implants, periodontal surgery). More than 90\% of ONJ have followed the use of IV pamidronate or zoledronate in patients with cancer.

Assess for symptoms and signs

Check for severe jaw pain, exposed bone, numbness, loose teeth, soft tissue infection, impaired healing, denture sore points; refer for specialist management if any of the above occur.

Dental procedures

- Consider full dental assessment and, if possible, complete any dental procedures before starting bisphosphonate treatment.\textsuperscript{98}
- Routine dental treatment need not be modified because of the use of oral bisphosphonates.\textsuperscript{98}
- All patients taking an oral bisphosphonate should be informed that:\textsuperscript{98}
  - this places them at very low risk of developing ONJ;
  - they should tell their doctor if they require any dental work and tell their dentist that they are taking this medication (or have taken it in the past);
  - good oral hygiene and regular dental care may be the best way to lower the risk of developing ONJ; and
  - if any problems occur in their mouth, contact a dentist.

Table 15. Recommendations for bisphosphonates and oral surgery\textsuperscript{97}

<table>
<thead>
<tr>
<th>Duration of oral bisphosphonate therapy</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 years and no clinical risk factors</td>
<td>No alteration or delay in planned oral surgery is necessary.</td>
</tr>
<tr>
<td>&lt;3 years with concomitant corticosteroids or &gt;3 years with or without corticosteroids</td>
<td>Consider discontinuation of the oral bisphosphonate for at least 3 months prior to oral surgery if systemic conditions permit. The bisphosphonate should not be restarted until bone has fully healed.</td>
</tr>
</tbody>
</table>

Treatment

Management of ONJ is not well established, so emphasis should be on prevention.\textsuperscript{93, 101} Treatment usually involves antibiotics, antiseptic mouth rinses, analgesia, withdrawal of bisphosphonates, hyperbaric oxygen therapy, and sequential removal of loose bony sequestra.\textsuperscript{101} Extensive surgical excision/debridement of the
necrotic tissue are often ineffective and may worsen the condition. For many patients, complete healing may never occur.\textsuperscript{101}

**Antibiotic prophylaxis for bisphosphonate-induced osteonecrosis of the jaw**

There is no evidence that the use of antibiotics is effective in preventing ONJ, and the use of prophylactic antibiotics after dental surgery should be based on the risk of infection and not on bisphosphonate therapy.\textsuperscript{98} American Dental Association guidelines for the management of patients receiving oral bisphosphonates report that prophylactic antibiotics are neither mandatory nor routinely recommended for procedures such as extractions.\textsuperscript{104}

**Bottom line:** The risk of bisphosphonate-related osteonecrosis of the jaw is very low with oral agents used for the treatment of osteoporosis, but dental surgery increases the risk. Consider discontinuing an oral bisphosphonate for at least 3 months prior to oral surgery in patients who have taken the drug for <3 years with concomitant corticosteroids, and in all patients who have taken the drug for >3 years.

**FDA safety alert with proton pump inhibitors**

In May 2010, the U.S. Food and Drug Administration (FDA) revised the prescription and over-the-counter (OTC) labels for proton pump inhibitors (PPIs) to include new safety information about a possible increased risk of fractures of the hip, wrist, and spine with the use of these medications.

To date, randomized clinical trials have not found an increased risk of fractures with PPIs. The new safety information is based on FDA's review of 7 epidemiological studies that reported on the risk of fractures of the hip, wrist, and spine with PPI use. In summary:

- Six of the seven studies reported an increased risk of fractures associated with PPI use. The seventh study was limited to individuals without major risk factors for fracture.
- This increased risk of fracture was primarily observed in people ≥ age 50.
- Two studies reported an increase in fractures with higher doses of PPIs, and two studies reported an increase in fractures with longer duration of use.

Based on the available data, it has not been definitively established that PPIs cause the increased risk of fractures seen in these studies. The FDA plans to analyze data from several large, long-term, placebo-controlled clinical trials of bisphosphonates to assess the risk of fractures in women who used or did not use PPIs. Despite this uncertainty, clinicians should consider using the lowest dose and shortest duration of PPI therapy that will adequately treat the patient's condition.
Further information is available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm

Other medications

Neither tamoxifen nor testosterone is FDA-approved for the prevention or treatment of osteoporosis. There is little or no evidence that these agents reduce the risk for fractures, and one trial found that tamoxifen is not associated with fracture risk reduction.26

Costs

Cost may be a barrier to patient adherence and persistence. Generic alendronate is now available, making bisphosphonate therapy more affordable. Injectable drugs may incur a high upfront expense.5 The costs of a 30-day supply of the defined daily dose for medications are provided in the figure below. The price of calcium and vitamin D varies, but these medications are widely available and inexpensive (under $10 per month).5

Figure 4. Cost of medications used in the treatment of osteoporosis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate 10 mg oral</td>
<td>$95</td>
</tr>
<tr>
<td>Ibandronate (Boniva) 5 mg oral</td>
<td>$111</td>
</tr>
<tr>
<td>Risedronate (Actonel) 5 mg oral</td>
<td>$119</td>
</tr>
<tr>
<td>Zoledronate (Reclast) 5 mg IV</td>
<td>$93</td>
</tr>
<tr>
<td>Raloxifene (Evista) 60 mg oral</td>
<td>$123</td>
</tr>
<tr>
<td>Teriparatide (Forteo) 20 micrograms SC</td>
<td>$948</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>$75</td>
</tr>
<tr>
<td>Fortical 200 units nasal</td>
<td>$75</td>
</tr>
<tr>
<td>Miacalcin 100 units SC/IM</td>
<td>$477</td>
</tr>
<tr>
<td>Miacalcin 200 units nasal</td>
<td>$131</td>
</tr>
<tr>
<td>Generics 200 units nasal</td>
<td>$110</td>
</tr>
<tr>
<td>Denosumab (Prolia) 60 mg SC</td>
<td>$135</td>
</tr>
</tbody>
</table>

Prices from www.epocrates.com, March 2010
Figure 5. Comparative efficacy, safety, cost and overall value of osteoporosis medications

<table>
<thead>
<tr>
<th>Drug^</th>
<th>Efficacy (fracture risk reduction)*</th>
<th>Adverse effects</th>
<th>Cost</th>
<th>Overall value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post-menopausal women</td>
<td>Steroid-induced osteoporosis</td>
<td>Osteoporosis in men</td>
<td>GI#</td>
</tr>
<tr>
<td>bisphosphonates**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>calcitonin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>raloxifene (Evista)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>teriparatide (Forteo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>denosumab (Prolia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Unknown or no effect</th>
<th>Best outcome</th>
<th>Intermediate</th>
<th>Problem</th>
</tr>
</thead>
</table>

*with adequate calcium and Vitamin D intake by diet, sun exposure, or supplementation
^estrogen-based hormone therapy excluded because FDA recommends that other pharmacotherapy be considered ahead of HT for patients where the sole aim is the prevention of osteoporosis.
#gastrointestinal effects including one or more of: abdominal pain, acid regurgitation, nausea, dyspepsia, constipation, diarrhea, and flatulence
##deep vein thrombosis/pulmonary embolism
**alendronate (generics, Fosamax); ibandronate (Boniva); risedronate (Actonel); zoledronate (Reclast)
^^in animal studies
Putting it all together

Figure 6. Management algorithm for fracture risk reduction

Document bone density using DXA

**Estimate 10-year probability** of fracture using the WHO FRAX tool

If treatment warranted

**All patients**
- at least 1,200 mg of elemental calcium daily
- measure serum 25(OH)D in patients at risk of deficiency and correct if present.
- maintenance dose of 800-1000 units of vitamin D daily
- weight bearing and muscle strengthening exercise
- assess falls risk and use risk-reduction strategies
- stop smoking
- avoid excessive alcohol

Consider pharmacotherapy in postmenopausal women and men aged 50 years and older with:
- an osteoporotic hip or vertebral fracture;
- T-score ≤ -2.5 at the femoral neck, total hip, or lumbar spine; or
- T-score between -1.0 and -2.5 at the femoral neck or spine) **AND** a FRAX 10-year probability of hip fracture ≥ 3% or a 10-year probability of major osteoporosis-related fracture (spine, hip, shoulder, or wrist) ≥ 20%

**Postmenopausal women**
- a bisphosphonate
- 2nd line therapies: raloxifene, teriparatide, calcitonin, denosumab

**Steroid-induced osteoporosis**
- a bisphosphonate
- 2nd line therapy: teriparatide

**Men**
- a bisphosphonate
- 2nd line therapy: teriparatide

**Bisphosphonates** include alendronate (generics, Fosamax, Fosamax plus D), ibandronate (Boniva), risedronate (Actonel, Actonel with calcium), and zoledronate (Reclast).

**Monitor response to therapy**
- Check for adverse effects and compliance.
- Review risk factors and encourage appropriate calcium and vitamin D intake, exercise, fall prevention, and other lifestyle measures.
- Perform DXA BMD testing of hip and spine 2 years after initiating pharmacotherapy and every 2 years thereafter. More frequent testing may be warranted in certain clinical situations e.g. patients on high-dose corticosteroids.
- Consider discontinuing a bisphosphonate after 5 years unless the T-score is ≤ 2.5 after 5 years of treatment.
Appendix 1. The FRAX algorithm

The following charts provide the 10-year risk of a major osteoporotic fracture (vertebral, hip, forearm or proximal humerus) in Caucasian and Black women aged 60 and 80 years. The full suite of FRAX charts for women and men are available at http://RxFacts.org/FRAX_charts.php

US (Caucasian) - probabilities of a major osteoporotic fracture in Caucasian women

The following tables give the 10-year probability (%) of a major osteoporotic fracture (hip, spine, forearm or proximal humerus fracture) according to the T-score for femoral neck BMD, the number of clinical risk factors (CRFs) and age. Each table provides a mean estimate and a range, based on the epidemiology of the US (Caucasian). The range is not a confidence interval, but because the weight of different risk factors varies, is a true range.

Note that the BMI is set at 24 kg/m^2. CRFs are: previous fracture, family history of hip fracture, use of oral glucocorticoids (in a daily dose ≥ 5 mg prednisone or equivalent for ≥ 3 months), smoking, excessive alcohol use (3 or more drinks per day), and rheumatoid arthritis.

![Table for Age 60 years]

![Table for Age 80 years]
Appendix 1. The FRAX algorithm (cont’d)

US (Black) - probabilities of a major osteoporotic fracture in Black women

The following tables give the 10-year probability (%) of a major osteoporotic fracture (hip, clinical spine, forearm or proximal humerus fracture) according to the T-score for femoral neck BMD, the number of clinical risk factors (CRF) and age. Each table provides a mean estimate and a range, based on the epidemiology of the US (Black). The range is not a confidence interval, but because the weight of different risk factors varies, is a true range.

Note that the BMI is set at $24 \text{ kg/m}^2$. CRFs are: previous fracture, family history of hip fracture, use of oral glucocorticoids (in a daily dose $\geq 5$ mg prednisone or equivalent for $\geq 3$ months), smoking, excessive alcohol use (3 or more drinks per day), and rheumatoid arthritis.

### Age = 60 years

<table>
<thead>
<tr>
<th>Number of CRFs</th>
<th>BMD T-score (femoral neck)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-4.0</td>
</tr>
<tr>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
</tr>
</tbody>
</table>

### Age = 80 years

<table>
<thead>
<tr>
<th>Number of CRFs</th>
<th>BMD T-score (femoral neck)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-4.0</td>
</tr>
<tr>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
</tr>
</tbody>
</table>
Appendix 2. Estimating dietary calcium intake - the calcium calculator

A reproduction of the input screen, instructions for use, and an example calculation from a calcium calculator (available at [http://www.myoptumhealth.com/portal/ManageMyHealth/CalciumCalculator](http://www.myoptumhealth.com/portal/ManageMyHealth/CalciumCalculator)) is shown below.

Enter your gender and age. Below those boxes, you'll find your daily calcium requirement. Then, under the tabs - Dairy, Vegetables, Grains/Nuts and Other Foods - find the specific foods you want to check. Enter the serving amount in the box on the right. As you add foods, the calculator adds up the total milligrams of calcium. The box labeled "Your Intake" tells you the percent of daily required calcium you have reached. Figures shown in black are input by the patient; figures shown in red are calculated by the program.

<table>
<thead>
<tr>
<th>Gender: Male ○ Female ●</th>
<th>Age: 56</th>
<th>Calcium requirement: 1200 mgs/day</th>
<th>Your intake: 54%</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAIRY</td>
<td>VEGETABLES</td>
<td>GRAINS/ NUTS</td>
<td>OTHER FOODS</td>
</tr>
<tr>
<td>Plain yogurt, fat free – 1 cup</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>American cheese (2 oz)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ricotta cheese, part skim (1/2 cup)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Yogurt w/fruit, low fat or fat free (1 cup)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Milk, fat free, low fat, or whole (8 oz)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cheese pizza (1 slice)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cheddar cheese (1 oz)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Macaroni and cheese (1/2 cup)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cottage cheese (1 cup)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ice cream, soft serve (1/2 cup)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Total: 650 mgs

Servings
References


18. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. May 12;303(18):1815-1822.


31. Watts NB, Geusens P, Barton IP, Felsenberg D. Relationship between changes in BMD and nonvertebral fracture incidence associated with risedronate: reduction


51. Roe EB, Sanchez SD, Del-Puerto GA. Parathyroid hormone 1-34 (hPTH 1-34) and estrogen produce dramatic bone density increases in postmenopausal osteoporosis: results from a placebo controlled, randomized trial. J Bone Miner Res 1999;14(Suppl 1):S137.


The Diagnosis, Treatment, and Prevention of Osteoporosis

The Diagnosis, Treatment, and Prevention of Osteoporosis


