

# ASHP Therapeutic Position Statement on the Prevention and Treatment of Osteoporosis in Adults

## Position

Osteoporosis is a devastating disease that may lead to significant morbidity and mortality from resultant fractures.<sup>1-3</sup> The efficacy of medications as one method to prevent and treat osteoporosis and avert future fractures, particularly vertebral fractures, is well documented in large clinical trials. However, despite this evidence, many patients at risk for osteoporosis are not screened or treated.<sup>4-8</sup> Screening for osteoporosis is considered a quality-of-care indicator by the Centers for Medicare and Medicaid Services and the National Committee for Quality Assurance.<sup>9,10</sup> The American Society of Health-System Pharmacists (ASHP) believes that all women age 65 years or older, postmenopausal women younger than age 65 years who have an increased risk of developing osteoporosis, all adult women with a history of nontraumatic fracture, and men with a significant risk of fracture should be screened for osteoporosis and treated, if indicated.

ASHP believes that there is a gap between the evidence and practice of prevention and treatment of osteoporosis in adults. In addition, ASHP believes that prevention and treatment of osteoporosis can decrease the morbidity and mortality associated with this condition, consistent with the *Healthy People 2010* objectives of reducing the percentage of adults with osteoporosis and those hospitalized with vertebral fractures.<sup>11</sup> Calcium and vitamin D,<sup>12-17</sup> bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid),<sup>18-25</sup> calcitonin,<sup>26</sup> estrogen (with or without a progestin),<sup>27,28</sup> raloxifene,<sup>29</sup> and teriparatide<sup>30</sup> have all been shown to decrease the risk of osteoporotic fractures, though differences exist in each drug's ability to reduce fractures at all sites. Therefore, each drug's place in therapy varies.

ASHP encourages health care professionals to educate patients about risk factors associated with osteoporosis. In addition, the Society encourages health care professionals to identify and triage at-risk patients for osteoporosis screening and diagnosis. ASHP believes that patients at risk for osteoporosis and medical complications related to osteoporosis should receive an assessment of bone mineral density (BMD) by central dual-energy x-ray absorptiometry (DEXA) and both nonpharmacologic and pharmacologic therapy to prevent further bone loss and promote increased bone quality. Pharmacists may be well suited to provide osteoporosis screenings us-

ing peripheral devices and offer patient education regarding osteoporosis prevention and treatment,<sup>31-35</sup> though central DEXA is required for diagnosis.<sup>36</sup>

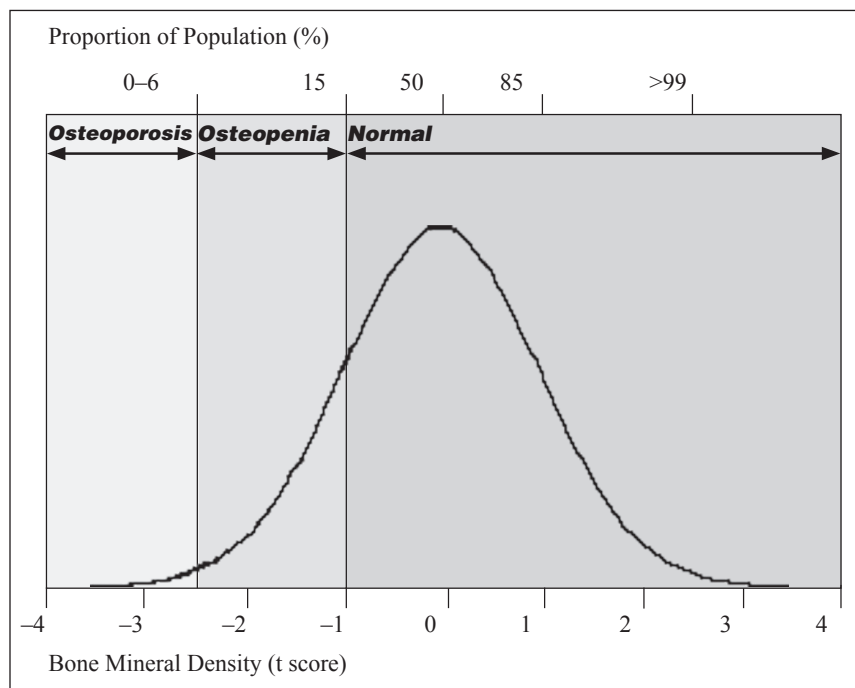
## Background

Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue. Low bone mass may be due to either increased loss of bone or failure to achieve sufficient peak bone mass.<sup>37</sup> A decline in bone mass due to advancing age, medications, or other risk factors increases bone fragility and susceptibility to fractures, especially at the hip, spine, forearm, and wrist.

The World Health Organization (WHO) defines osteoporosis as a BMD of 2.5 or more standard deviations below that of a normal young adult (t score of  $\leq -2.5$ ) for postmenopausal women and men over age 50 years as measured by central DEXA.<sup>3,38</sup> Osteopenia is defined as a BMD between  $-1$  and  $-2.5$  standard deviations below the young adult mean; a normal BMD value is defined as within 1 standard deviation of the mean BMD for a young adult. Patients who have a t score of  $\leq -2.5$  and have already had one or more fractures are classified as having severe or established osteoporosis. Figure 1 shows the distribution of BMD in healthy women age 30-40 years.<sup>36</sup>

Osteoporosis is a major public health problem in the United States. In 2002, over 10 million individuals had known osteoporosis, 80% of whom were women.<sup>39,40</sup> Approximately 44 million men and women over age 50 years have either os-

**Figure 1.** Distribution of bone mineral density in healthy women age 30-40 years. Reproduced from reference 36, with permission.



teoporosis or low BMD. If these trends continue, this figure may increase to over 61 million by 2020.<sup>39</sup>

Osteoporotic fractures are associated with significant morbidity and mortality. Patients who sustain a fracture are more likely to have lower health-related quality of life, depression, pain, disability, physical deconditioning due to inactivity, vertebral deformities with a resultant decrease in pulmonary function and increase in gastrointestinal complications (e.g., refractory reflux esophagitis), pressure ulcers, increased likelihood of nursing home placement, and changes in self-image.<sup>41–51</sup> Hip fractures, which are the most serious complication of osteoporosis, are associated with significant mortality.<sup>52–55</sup> Up to 38% of patients may die within one year after a hip fracture, and the risk of death is approximately double that of patients who do not sustain a hip fracture.<sup>52,53,55</sup>

The economic consequences of osteoporosis are enormous. In 1995, osteoporotic fractures were responsible for approximately 432,000 hospital admissions, 2.5 million physician's office visits, and 180,000 nursing home admissions.<sup>1</sup> Health care costs associated with osteoporotic fractures in 2001 were an estimated \$17 billion. As the population of the United States continues to age, these costs will likely increase, with the number of hip fractures and associated costs possibly tripling by 2040.<sup>1</sup>

Despite the significant morbidity, mortality, and economic consequences of osteoporosis and resultant fractures, many patients are not screened or treated. In a study of 3812 women with an average age of 71 years who sustained a new fragility (i.e., minimal-trauma) fracture, only 11.7% had a diagnosis of osteoporosis before the index fracture, and only 46.4% were managed as specified by clinical guidelines.<sup>5</sup> In another study of patients who sustained a fragility fracture, few patients received densitometry testing either before (13%) or after (22.2%) the index fracture.<sup>4</sup> Only 18.5% were diagnosed with osteoporosis, and only 32.4% received calcium supplementation. Thus, significant improvements must be made in the diagnosis and treatment of osteoporosis.

## Risk Assessment

Osteoporosis risk factor analysis is useful to identify patients at high risk of fractures, raise awareness of osteoporosis, promote strategies for prevention of fractures, and stimulate osteoporosis treatment (Table 1).<sup>1,3,56</sup> Prior fragility fracture as an adult and low BMD in patients with or without fractures are the two most important risk factors, both of which are clear indications for additional evaluation and possible therapeutic intervention.<sup>3</sup> Additional risk factors are listed in Table 1. ASHP encourages osteoporosis screening by all health care professionals, with specific attention to patients taking medications associated with decreased bone mass, including glucocorticosteroids, anticonvulsants (e.g., phenytoin, phenobarbital, carbamazepine), immunosuppressants, and excessive thyroid supplementation.<sup>1</sup>

ASHP believes health care professionals should conduct fall-risk assessment in conjunction with osteoporosis screening. All high-risk or elderly patients should be routinely asked about falls in the past year.<sup>57</sup> Older persons reporting a single fall should be assessed for balance and gait to detect balance problems.<sup>57,58</sup> Older persons who report recurrent falls or have gait or balance abnormalities will ben-

efit from a comprehensive fall evaluation.<sup>57</sup> Most patients demonstrate multiple risk factors for falls; common risk factors include muscle weakness, use of assistive devices, visual deficits, use of certain medications, arthritis, impaired activities of daily living, depression, cognitive impairment, and age greater than 80 years.<sup>57</sup> Three risk factors—hip weakness, unstable balance, and use of four or more medications—are highly predictive for one-year fall risk.<sup>59</sup> ASHP encourages a comprehensive drug regimen review to identify medications or drug-related problems that may increase fall risk. Medications commonly associated with increased falls include psychotropics, cardiovascular medications, and central nervous system agents.<sup>57,60,61</sup>

## Evaluation

Patients at risk for osteoporosis and related fractures should receive BMD testing by central DEXA. These patients include women age 65 years or older (regardless of risk factors), postmenopausal women under age 65 years with risk factors (Table 1), and postmenopausal women with a history of non-traumatic fracture. In addition, testing should be considered for men age 70 years or older, for patients with diseases that may result in decreased bone strength, for patients taking long-term medications known to decrease BMD, and to assess response in patients receiving medications for the treatment of osteoporosis. These recommendations are consistent

Table 1.

### Risk Factors for Osteoporosis and Related Fractures<sup>1,3,57</sup>

- Personal history of minimal-trauma fracture as an adult<sup>a</sup>
- History of fragility fracture in a first-degree relative<sup>a</sup>
- Low body weight (e.g., <127 lb)<sup>a</sup>
- Current smoking<sup>a</sup>
- Use of oral corticosteroid therapy for more than three months<sup>a</sup>
- Female sex
- Caucasian race
- Low physical activity
- Late menarche or early menopause
- Hypogonadism
- Low lifelong calcium intake
- Vitamin D deficiency
- Weight loss
- Impaired vision
- Dementia
- Poor health or frailty
- Recent falls
- Consumption of more than two alcoholic drinks per day
- Use of medications associated with falls (e.g., psychotropics, cardiovascular medications, central nervous system agents)
- Other medications with adverse bone effects (e.g., anticonvulsants, long-term heparin, immunosuppressants)
- Hyperthyroidism
- Hyperparathyroidism
- Renal hypercalciuria
- Chronic kidney or liver disease
- Gastrointestinal abnormalities (e.g., malnutrition, malabsorption, maldigestion)
- Rheumatoid arthritis
- Weightlessness

<sup>a</sup>Major risk factors in Caucasian postmenopausal women.<sup>1</sup>

**Prevention and Treatment**

with those of the National Osteoporosis Foundation (NOF), the American Association of Clinical Endocrinologists, and the U.S. Preventative Services Task Force.<sup>1,3,62</sup> While these recommendations may be considered broad, the use of validated risk assessments, such as SCORE (Simple Calculated Osteoporosis Risk Assessment) and ORAI (Osteoporosis Risk Assessment Instrument), may be useful in identifying women likely to have osteoporosis, thereby decreasing the number of women who undergo unnecessary central DEXA testing.<sup>63-65</sup> Further, a WHO working group in collaboration with the International Osteoporosis Foundation and NOF is developing and validating a new risk assessment tool.<sup>66</sup> This tool will use independent risk factors to calculate fracture probability, with or without the use of BMD, allowing treatment to be recommended for those with a fracture probability above the threshold for treatment.<sup>67</sup> A risk-assessment tool for use in men is discussed later in this document.

Currently, measurement of BMD by central DEXA is considered the gold standard for diagnosing osteoporosis, as it correlates significantly with the risk of fractures.<sup>62,68,69</sup> For each standard deviation decrease in femoral neck BMD, there is an approximate 2.5-fold increased risk of hip fracture.<sup>70,71</sup> Advantages of central DEXA include high sensitivity and specificity and the ability to measure BMD at numerous areas, including the hip, spine, and wrist. Disadvantages of central DEXA for mass screenings include equipment size and lack of portability, need for a dedicated room, expense, ionizing radiation, need for a radiation-certified and trained technician, lack of measurement of structure, and significant time required to screen and read the results.

Peripheral bone densitometers may be an ideal choice for mass screening and for assessing fracture risk.<sup>68</sup> These machines are generally much smaller and portable, require significantly less time to screen and read results, are available in models that use ultrasound rather than radiation, and have been shown to predict fracture risk.<sup>72</sup> Though useful in screening and identifying at-risk patients, peripheral bone densitometers should not be used as the primary tool for diagnosis or for monitoring treatment response due to their inability to measure BMD at all sites and the possibility of false-negative results.

**Nonpharmacologic Therapies.** Several nonpharmacologic interventions for the prevention of osteoporotic fractures should be considered for all patients. The attainment of high peak bone mass early in life is one of the most important protective factors against reduced BMD later in life.<sup>2</sup> In addition, strategies to maintain current bone mass for patients in later stages of life should be instituted. Thus, appropriate weight-bearing exercise, minimization or elimination of various modifiable risk factors (e.g., smoking, excessive alcohol intake, maintenance of euthyroid status), and maintenance of adequate calcium and vitamin D intake should be recommended for all patients.<sup>1-3,37</sup>

Adequate calcium and vitamin D intake is considered an essential component of osteoporosis prevention and treatment,<sup>1-3,37</sup> yet many men and women over age 65 years consume only 600 mg of calcium daily. However, there is controversy regarding calcium and vitamin D supplementation. There is no universal consensus for the most appropriate daily dose (Table 2), though all groups recommend at least 1000 mg, and data are lacking regarding the most effective calcium salt. In addition, questions have been raised about the efficacy of calcium and vitamin D for prevention of fractures.

Several randomized controlled trials found that supplemental calcium or vitamin D<sub>3</sub> or both were effective in decreasing the risk for fractures.<sup>12-16</sup> In a primary prevention study of 3270 healthy postmenopausal women (mean age, 84 years), 1200 mg of elemental calcium (as the tricalcium phosphate) plus 800 IU of vitamin D given daily for 18 months was associated with a 43% decrease in the risk of hip fractures (number needed to treat [NNT] = 56, *p* = 0.043) and a 32% decrease in nonvertebral fractures (NNT = 29, *p* = 0.015).<sup>12</sup> In a primary prevention study of 389 ambulatory men and women over age 65 years, 500 mg of calcium (as calcium citrate) plus 700 IU of vitamin D<sub>3</sub> given daily for three years decreased the risk of nonvertebral fractures by 50% (NNT = 14; 95% confidence interval [CI], 0.2-0.9; *p* = 0.02).<sup>13</sup>

However, two more recently published studies appear to contradict previous findings. In the Randomized

Table 2.

**Recommended Daily Dietary Reference Intakes of Elemental Calcium and Vitamin D<sup>a</sup>**

Supplement	National Academy of Sciences <sup>73-75</sup>	National Osteoporosis Foundation <sup>1</sup>	NIH Consensus Panel <sup>76</sup>
Elemental calcium	Age 31-50 yr: 1000 mg	Age <50 yr: 1000 mg	Age 25-65 yr and women >50 yr receiving estrogen: 1000 mg
	Age >50 yr: 1200 mg	Age ≥50 yr: 1200 mg	Age >65 yr and women >50 yr not receiving estrogen: 1500 mg
Vitamin D	Age 31-50 yr: 200 IU	Age <50 yr: 400-800 IU	. . . <sup>b</sup>
	Age 50-70 yr: 400 IU	Age ≥50 yr: 800-1000 IU	
	Age >70 yr: 600 IU		

<sup>a</sup>Recommendations are for both men and women unless otherwise stated. NIH = National Institutes of Health.  
<sup>b</sup>The NIH consensus panel does not provide recommendations for vitamin D supplementation.

Evaluation of Calcium or Vitamin D (RECORD) secondary prevention study, 5,292 elderly patients (mean age, 77 years) who had a low-trauma, osteoporotic fracture in the previous 10 years were randomized to receive 1000 mg calcium (as the carbonate), 800 IU of vitamin D<sub>3</sub>, the combination, or placebo.<sup>77</sup> After a median follow-up of 45 months, there was no significant difference in the rate of new low-trauma fractures ( $p > 0.05$  for all active treatments versus placebo). A significant limitation of this study was a low adherence rate at 24 months based on mailed questionnaires (60% adherence based on returned questionnaires, 47% adherence assuming nonresponders were nonadherent). Likewise, in the Women's Health Initiative (WHI) Calcium with Vitamin D Trial, which evaluated the effect of calcium and vitamin D supplementation on the frequency of hip and other bone fractures, 1000 mg calcium (as the carbonate) plus 400 IU of vitamin D given daily failed to reduce the risk of hip fracture, clinical spine fracture, or total fracture in 36,282 healthy postmenopausal women over seven years of use and increased the risk of renal calculi (number needed to harm [NNH] = 273).<sup>78</sup> There are several possible explanations for this lack of benefit, including the relatively low daily dose of vitamin D used, the fact that most patients did not have low BMD at baseline (mean hip t score,  $-0.65$  in subgroup for whom BMD was measured), and a possible lack of power attributable to a lower-than-expected hip fracture rate. In patients who adhered to therapy at least 80% of the time, fractures were reduced by 29%.

The results of a meta-analysis of double-blind, randomized controlled trials of patients over age 60 years suggest that vitamin D dosages of 700–800 IU daily with or without calcium reduced the risk for hip fracture and any nonvertebral fracture by 26% (NNT = 45) and 23% (NNT = 27), respectively, versus calcium alone or placebo.<sup>79</sup> However, no significant fracture reduction was seen with low daily doses (400 IU) of vitamin D.

In 2007, a large meta-analysis of more than 63,000 patients in 29 randomized trials found good evidence that the use of calcium, alone or in combination with vitamin D, prevented osteoporosis in women and men age 50 years and older.<sup>17</sup> This study also showed a 12% reduction in the risk of fractures, with treatment being more effective at higher doses of calcium ( $>1200$  mg) and vitamin D ( $>800$  IU).

Based on available evidence, NOF in July 2007 updated its recommendations for daily adequate calcium and vitamin D intake to provide 1000 mg of elemental calcium and 400–800 IU of vitamin D daily for adults under age 50 years and 1200 mg of elemental calcium and 800–1000 IU of vitamin D daily for adults age 50 years or older.<sup>73</sup> These recommended doses should be taken in two or three divided doses daily and used in addition to other nonpharmacologic modalities. Specific dosing recommendations provided by the National Academy of Sciences, NOF, and the National Institutes of Health Consensus Panel are outlined in Table 2. It is important to note that all studies assessing osteoporosis medications included calcium and vitamin D as background therapy. Thus, for patients with osteoporosis or who are at high risk of developing osteoporosis (e.g., patients with osteopenia; those with prior vertebral, nonvertebral, or hip fracture; patients with a history of long-term systemic corticosteroid use), use of an antiresorptive or anabolic agent in addition to nonpharmacologic modalities and calcium and vitamin D supplementation should be considered.

**Pharmacologic Therapies.** A wide range of medications are used in the prevention and treatment of osteoporosis (Table 3). In addition to bisphosphonates, which are the primary treatment approach, other therapies, such as calcitonin, estrogen-replacement therapies or estrogen-receptor modulators, and teriparatide, are approved by the Food and Drug Administration (FDA) for the prevention or treatment of osteoporosis. Several other therapies are currently under investigation (Table 4).

**Bisphosphonates.** The bisphosphonates alendronate, risedronate, ibandronate, and zoledronic acid are nitrogen-containing compounds that increase BMD by inhibiting osteoclast-mediated bone resorption.<sup>76</sup> They have been shown to increase BMD approximately 2–8%, depending upon the dose and site measured, and have demonstrated efficacy in primary and secondary prevention of osteoporotic fractures.<sup>18–25</sup>

In the Fracture Intervention Trials (FIT), the effects of alendronate in patients with and without vertebral fractures were evaluated. In the arm that included patients without vertebral fractures, 4432 women (mean age 68 years) who had low BMD (mean t score,  $-0.6$ ) with no history of vertebral fracture were randomized to receive either alendronate 5 mg for two years followed by 10 mg for two years or placebo.<sup>18</sup> After a mean follow-up of 4.2 years, women treated with alendronate demonstrated a 14% decrease in the rate of new clinical fractures, but this decrease was not statistically significant (hazard ratio [HR] = 0.86; 95% CI, 0.73–1.01). However, in patients with a femoral t score of  $<-2.5$ , the rate of clinical fractures was reduced by 36% (NNT = 15; 95% CI, 0.50–0.82) and clinical vertebral fractures decreased by 50% (NNT = 34; 95% CI, 0.31–0.82). Of the women who had at least one vertebral fracture ( $n = 2027$ ), alendronate decreased the rate of clinical fractures by 55% at the vertebrae (NNT = 37; 95% CI, 0.27–0.72), by 51% at the hip (NNT = 91; 95% CI, 0.23–0.99), and by 48% at the wrist (NNT = 53; 95% CI, 0.31–0.87).<sup>19</sup>

Risedronate has also been associated with a decreased risk of vertebral, nonvertebral, and hip fractures. In the Vertebral Efficacy with Risedronate Therapy in North America (VERT-NA) and Vertebral Efficacy with Risedronate Therapy—Multinational (VERT-MN) studies, risedronate sodium 2.5 and 5 mg daily were compared with placebo in ambulatory postmenopausal women with at least one vertebral fracture.<sup>20,21</sup> The 2.5-mg treatment option was discontinued after one year in the VERT-NA study and after two years in the VERT-MN study. After three years, the rate of new vertebral fractures decreased in risedronate-treated women by 41% in VERT-NA (NNT = 20; 95% CI, 0.18–0.58;  $p = 0.003$ ) and by 49% in VERT-MN (NNT = 10; 95% CI, 0.66–0.73;  $p < 0.001$ ); nonvertebral fractures decreased by 39% (NNT = 31; 95% CI, 0.06–0.61;  $p = 0.02$ ) and 33% (95% CI, 0.44–1.04;  $p = 0.063$ ) in the VERT-NA and VERT-MN studies, respectively. In another study specifically designed to assess hip-fracture prevention, women age 70–79 years with confirmed osteoporosis (mean femoral neck t score,  $-3.7$ ) or women age 80 years or older with at least one clinical risk factor were randomized to receive either risedronate sodium 2.5 or 5 mg daily or placebo. After three years, risedronate decreased the overall risk of hip fracture by 30% (NNT = 91; 95% CI, 0.6–0.9;  $p = 0.02$ ). However, this effect was limited only to women age 70–79 years who had confirmed osteoporosis (relative risk [RR] =

Table 3.  
**Medications Used in the Management of Postmenopausal Osteoporosis**

Agent	Labeled Indications	Typical Dosage	Fracture Reduction Data Available		
			Vertebral	Nonvertebral	Hip
Bisphosphonates <sup>a</sup>					
Alendronate	Prevention and treatment <sup>80</sup>	10 mg p.o. daily or 70 mg p.o. weekly <sup>b</sup>	Yes <sup>18,19</sup>	Yes <sup>19</sup>	Yes <sup>19</sup>
Ibandronate	Prevention and treatment <sup>81,82</sup>	2.5 mg p.o. daily or 150 mg p.o. monthly	Yes <sup>23</sup>	No	No
Risedronate	Prevention and treatment <sup>83</sup>	3 mg i.v. every 3 mo 5 mg p.o. daily, 35 mg p.o. weekly, or 75 mg p.o. given on two consecutive days monthly (2 tablets/mo)	No Yes <sup>20,21</sup>	No Yes <sup>20</sup>	No Yes <sup>20</sup>
Zoledronic acid	Treatment <sup>84</sup>	5 mg i.v. once yearly	Yes <sup>24,25</sup>	Yes <sup>24,25</sup>	Yes <sup>25</sup>
Calcitonin	Treatment <sup>85</sup>	1 spray (200 IU) intranasally, alternating nostrils daily	Yes <sup>26</sup>	No	No
Estrogen-replacement therapy	Prevention <sup>86</sup>	0.625 mg conjugated estrogens p.o. daily	Yes <sup>27,28</sup>	Yes <sup>27,28</sup>	Yes <sup>27,28</sup>
Raloxifene	Prevention and treatment <sup>87</sup>	60 mg p.o. daily	Yes <sup>29</sup>	No	No
Teriparatide	Treatment in patients at high risk for fracture <sup>88,c</sup>	20 µg s.c. daily	Yes <sup>30</sup>	Yes <sup>30</sup>	No

<sup>a</sup>Alendronate and risedronate are approved for the treatment of osteoporosis in men, glucocorticoid-induced osteoporosis, and Paget's disease. Ibandronate and zoledronic acid injections are approved only for treatment in postmenopausal women.

<sup>b</sup>Dosage for treatment. May use 5 mg p.o. daily or 35 mg p.o. weekly for the prevention of osteoporosis.<sup>80</sup>

<sup>c</sup>Approved for the treatment of osteoporosis in men at high risk for fracture.

Table 4.  
**Investigational Agents for the Treatment of Osteoporosis**

Agent	Typical Dosage	Fracture Reduction Data Available		
		Vertebral	Nonvertebral	Hip
Denosumab	30 mg s.c. every 3 mo or 60 mg s.c. every 6 mo <sup>89</sup>	No	No	No
Parathyroid hormone 1-84	100 µg s.c. daily	Yes <sup>90</sup>	No	No
Sodium fluoride, sustained release	25 mg p.o. b.i.d. for 12 mo, then 2-mo drug-free interval <sup>91,92</sup>	Yes <sup>91-93</sup>	No	No
Strontium ranelate	2 g p.o. daily <sup>94,95</sup>	Yes <sup>94,95</sup>	Yes <sup>95</sup>	Yes <sup>95,a</sup>

<sup>a</sup>Hip fracture reduction seen only in patients at high risk (age ≥74 years with femoral neck bone mineral density t score of ≤-3).

0.60; NNT = 77; 95% CI, 0.4–0.9; *p* = 0.009), not in women selected primarily on the basis of clinical risk factors (RR = 0.80; 95% CI, 0.6–1.2; *p* = 0.35).

Ibandronate is the newest oral bisphosphonate approved for the prevention and treatment of postmenopausal osteoporosis. In the Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) of 2946 postmenopausal women (mean age, 69 years) with a BMD t score of -2.0 to -5.0 in at least one vertebra (L1-4), ibandronate sodium 2.5 mg daily or 20 mg every other day for 12 doses every three months for three years decreased the risk of new vertebral fractures by 62% (NNT = 20; 95% CI, 0.41–0.75; *p* = 0.0001) and 50% (NNT = 21; 95% CI, 0.22–0.66; *p* = 0.0006), respectively, compared with placebo.<sup>23</sup> There was no significant difference in the frequency of nonvertebral fractures (8.2%, 9.1%, and 8.9% for daily ibandronate, intermittent ibandronate, and placebo, respectively). However, baseline BMD at the proximal femur and femoral

neck was relatively high (mean t scores, -1.73 and -2.03, respectively) compared with that found in other studies.

The use of intermittent i.v. bisphosphonate infusions for osteoporosis has been investigated. Ibandronate sodium injection given as a 3-mg i.v. infusion once every three months was recently approved by FDA for the treatment of postmenopausal osteoporosis.<sup>80</sup> In the Phase III, randomized, double-dummy, Dosing Intravenous Administration (DIVA) study, ibandronate sodium injection given as a 3-mg i.v. infusion once every three months for one year to 1395 postmenopausal women (mean age, 66–67 years) increased BMD at the lumbar spine and total hip to a greater extent than did 2.5 mg given orally (4.8% versus 3.8% and 2.1% versus 1.5%, respectively) (*p* < 0.05 for both comparisons).<sup>97</sup>

Zoledronic acid has also been found to increase BMD in a similar manner when given as an intermittent i.v. infusion.<sup>98</sup> In August 2007, zoledronic acid became the first bisphosphonate to receive FDA-approved labeling for once-

yearly administration in the treatment of osteoporosis in postmenopausal women.<sup>84</sup> Results of the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial (PFT) demonstrated that a 5-mg i.v. infusion given once yearly for three years was effective in reducing the risk of new vertebral fractures by 70% (NNT = 13,  $p < 0.001$ ), hip fractures by 41% (NNT = 91,  $p = 0.002$ ), and nonvertebral fractures by 25% (NNT = 37,  $p < 0.001$ ).<sup>25</sup> While most adverse effects were similar between groups, atrial fibrillation was more common in those receiving zoledronic acid (20 versus 50 patients) (NNH = 125,  $p < 0.001$ ).

The subsequent HORIZON Recurrent Fracture Study assessing the effect of once-yearly zoledronic acid i.v. within 90 days after surgical repair of a hip fracture reduced the risk of any new clinical fracture by 35% (NNT = 19,  $p = 0.001$ ), new clinical vertebral fractures by 46% (NNT = 48,  $p = 0.02$ ), and new nonvertebral fractures by 27% (NNT = 32,  $p = 0.03$ ) compared to placebo.<sup>24</sup> There was no statistically significant reduction in hip fractures (2.0% versus 3.5%,  $p = 0.18$ ). However, mortality was reduced by 28% (NNT = 27,  $p = 0.01$ ). The rate of atrial fibrillation in the zoledronic acid group (1.1%) was similar to the placebo group (1.3%).

While administration of bisphosphonates for postmenopausal osteoporosis allows for intermittent dosing (i.e., 70 mg orally once weekly for alendronate, 35 mg orally once weekly or 75 mg orally given on two consecutive days once a month for risedronate, 150 mg orally every month or 3 mg i.v. every three months for ibandronate, and 5 mg i.v. once yearly for zoledronic acid), it is important to note that, with the exception of zoledronic acid, studies specifically designed to assess fracture equivalency are lacking. Data demonstrating equivalency of BMD effects for oral intermittent and daily dosing are available.<sup>99–101</sup> Thus, intermittent regimens may be advocated, as they are likely to have similar efficacy regarding fracture reduction and have the potential to increase adherence and improve gastrointestinal tolerability,<sup>102,103</sup> though future studies are needed to confirm these benefits. In addition, while other bisphosphonates with a variety of indications are available (e.g., etidronate, pamidronate, tiludronate), these agents lack data demonstrating fracture reduction in postmenopausal osteoporosis and should not be used as a first-line treatment for this indication.

The long-term bone safety of bisphosphonates has recently been questioned. Unusual fractures and delayed healing, possibly due to oversuppression of bone turnover, have been reported.<sup>103,105</sup> In addition, there have been highly publicized cases of osteonecrosis of the jaw.<sup>106</sup> However, it is important to note that the majority of cases have occurred with i.v. bisphosphonates in patients with multiple myeloma and metastatic cancer of the skeleton, where the dosages used are considerably higher than those used for osteoporosis.<sup>106</sup> Thus, it is not known whether patients using bisphosphonates for the prevention or treatment of osteoporosis are at significant increased risk. In addition, long-term studies of alendronate and risedronate have not demonstrated these adverse effects.<sup>107,108</sup> Considering the increasing use of these agents, continued monitoring for potential adverse bone effects should be advocated.

**Calcitonin.** Calcitonin is a 32-amino-acid peptide that inhibits osteoclast-mediated bone resorption.<sup>109</sup> The salmon form is approximately 40-fold more potent than the human form, due to conformational flexibility.<sup>110</sup> Data are available

that support the use of salmon calcitonin for treatment of vertebral fractures in women with osteoporosis, though nonvertebral fracture data are generally lacking. In the Prevent Recurrence of Osteoporotic Fractures (PROOF) study, intranasal salmon calcitonin (100, 200, or 400 IU daily) was compared with placebo in 1255 postmenopausal women with preexisting vertebral compression fractures.<sup>26</sup> After five years of follow-up, 200 IU of salmon calcitonin daily was associated with a 33% decrease in the rate of new vertebral fractures (NNT = 13; RR = 0.67; 95% CI, 0.47–0.97;  $p = 0.03$ ). No significant differences in the rate of new vertebral fractures were demonstrated in patients taking 100 or 400 IU of salmon calcitonin. One factor that may have limited the findings of this study was the high dropout rate. Fifty-nine percent of patients withdrew from the study early, though rates of discontinuation were similar in all treatment groups. In addition to the ability to prevent future vertebral fractures, salmon calcitonin also appears to possess analgesic activity.<sup>111,112</sup> Thus, this agent may be useful in the treatment of acute vertebral fractures, in which back pain can be significant.

**Estrogen.** Although estrogen-replacement therapy (ERT) was used as an antiresorptive therapy for many years for the prevention or treatment of osteoporosis, there was a paucity of data from clinical trials demonstrating a reduction in the risk of fractures, particularly at the hip. Previous recommendations for routine use of estrogen were based on observational studies and meta-analyses that indicated an approximate 30–60% reduction in vertebral and nonvertebral fractures with five or more years of ERT use.<sup>113–116</sup>

With the publication of the results of the WHI study, guidelines for ERT have significantly changed, now recommending against the use of ERT solely to prevent osteoporosis and encouraging the use of alternative therapies first.<sup>1,3</sup> The WHI study was the largest randomized, prospective trial to evaluate the risks and benefits of estrogen with and without a progestin in healthy postmenopausal women. The estrogen plus progestin group included 16,608 women with an intact uterus who received either 0.625 mg of conjugated equine estrogen (CEE) plus 2.5 mg of medroxyprogesterone acetate or placebo.<sup>27</sup> The estrogen-only group included 10,739 women with a prior hysterectomy who received 0.625 mg of CEE daily or placebo.<sup>28</sup> After an average follow-up of 5.2 years, estrogen plus progestin was discontinued due to a slightly increased risk of breast cancer (NNH = 237). In addition, investigators found that these women had a small increase in the risk of coronary heart disease (CHD) (NNH = 237), pulmonary embolism (NNH = 227), stroke (NNH = 225), and deep venous thrombosis (NNH = 141). There was a slight decrease in the risk of hip fracture (NNT = 345), clinical vertebral fracture (NNT = 387), and lower arm or wrist fracture (NNT = 125).<sup>117</sup> Likewise, estrogen-only therapy was discontinued after a mean follow-up of 6.8 years due to lack of benefit for the primary outcome of CHD and an increased risk of stroke (NNH = 125). While the estrogen-only group did have an increased risk of deep venous thrombosis (NNH = 220), there was no increased risk of pulmonary embolism or breast cancer. CEE alone did decrease the risk of hip and vertebral fractures slightly (NNT = 216 and NNT = 225, respectively).

Based on the results of the WHI study, estrogen should not be used to prevent CHD or as first-line therapy for postmenopausal osteoporosis and should generally be used

at the lowest therapeutic dosage for the shortest time possible to control significant menopausal symptoms (e.g., hot flashes).<sup>27,28,118</sup> Strong consideration of other medications that have been shown to decrease the risk of fractures and weighing of the risks and benefits are recommended before using estrogen solely to prevent osteoporosis.

**Raloxifene.** Raloxifene is a selective estrogen receptor modulator that has estrogenic effects on some tissues (e.g., bone [ $\approx 2$ – $3\%$  increase in BMD depending on dosage and site measured], lipid metabolism, clotting cascade) while having antiestrogenic effects on others (e.g., uterine endometrium, breast tissue).<sup>29,119</sup> Data are available that support the use of raloxifene for the treatment of osteoporosis. In the Multiple Outcomes of Raloxifene Evaluation (MORE), 7705 postmenopausal women (mean age, 67 years) with osteoporosis were randomized to receive raloxifene 60 mg daily, raloxifene 120 mg daily, or placebo.<sup>29</sup> After 36 months, the use of raloxifene 60 and 120 mg daily was associated with a 30% and 50% decrease in the rate of new vertebral fractures, respectively (NNT = 29; 95% CI, 0.5–0.8 and NNT = 21; 95% CI, 0.4–0.7). There was no significant difference in the rate of nonvertebral fractures (RR = 0.9; 95% CI, 0.8–1.1). Importantly, raloxifene increased the rate of venous thromboembolism (NNH = 143; 95% CI, 1.5–6.2). Raloxifene was not associated with vaginal bleeding or breast pain, and patients who took the drug had a lower incidence of breast cancer than women who received placebo (RR = 0.3; 95% CI, 0.2–0.6). However, hot flashes were more common in the raloxifene group (9.7% and 11.7% for the 60- and 120-mg dosages, respectively, versus 6.5% for placebo).

The role of raloxifene in the management of osteoporosis may be further elucidated with the publication of two recent studies. The National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 study was a prospective, double-blind, randomized trial of 19,247 postmenopausal women (mean age, 58.5 years) with an increased risk of breast cancer (mean risk, 4.03%).<sup>120</sup> After a mean follow-up of 3.9 years, raloxifene 60 mg daily was shown to be as effective as tamoxifen in decreasing the risk of invasive breast cancer (168 cases with raloxifene versus 163 cases with tamoxifen) (RR = 1.02; 95% CI, 0.82–1.28). The Raloxifene for Use of the Heart (RUTH) study, a prospective, double-blind, randomized trial of 10,101 postmenopausal women (mean age, 67.5 years) with CHD or multiple risk factors for CHD, was designed to assess the effects of raloxifene 60 mg daily on cardiovascular disease.<sup>121</sup> After a median follow-up of 5.6 years, raloxifene did not decrease the risk of the primary outcome of death from coronary causes, myocardial infarction, or hospitalization for acute coronary syndrome (HR = 0.95; 95% CI, 0.84–1.07) or stroke (HR = 1.10; 95% CI, 0.92–1.32), though it did increase the risk of venous thromboembolism (NNH = 157) and fatal stroke (NNH = 251). Similar to other studies, raloxifene did decrease the risk of clinical vertebral fractures (NNT = 154), noninvasive breast cancer (NNT = 169), estrogen-receptor positive breast cancer (NNT = 169), and death from noncardiovascular and noncancer causes (NNT = 118 and NNT = 138, respectively).

The use of raloxifene for the management of osteoporosis should be based on a risk–benefit assessment. It may be an ideal choice for women who have contraindications to or do not tolerate a bisphosphonate, are not experiencing vasomotor symptoms, and do not have CHD or multiple risk

factors for CHD. In addition, it may be particularly appealing for patients at high risk for breast cancer.

**Teriparatide.** Teriparatide, a recombinant form of parathyroid hormone (PTH 1-34), may increase or decrease BMD, depending on the route of administration. Given as an exogenous, intermittent injection, teriparatide increases BMD by stimulating bone formation.<sup>122</sup> The effects of teriparatide in postmenopausal women with prior vertebral fractures have been evaluated. In a placebo-controlled study of 1637 postmenopausal women (mean age, 69 years) with at least one prior vertebral fracture 20 and 40  $\mu\text{g}$  of teriparatide given daily by subcutaneous injection decreased the rate of new vertebral fractures by 65% and 69%, respectively (NNT = 11 and NNT = 10).<sup>30</sup> In addition, new nonvertebral fragility fractures were decreased 53% and 54% for the 20- and 40- $\mu\text{g}$  groups, respectively (NNT = 33 for both treatment groups).

Data from rat carcinogenicity studies have suggested a possible increased risk of osteosarcomas associated with the use of PTH 1–34 analogues.<sup>122</sup> Thus, teriparatide should not be used in patients who have an increased risk of developing osteosarcomas (e.g., those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, or prior external beam or implant radiation therapy involving the skeleton), and administration should be limited to two years' use.<sup>88</sup> In addition, due to significant costs ( $\approx \$850$  per month<sup>123</sup>) and the need for daily injections, teriparatide should only be used in patients with established osteoporosis who have a high risk of future fractures or who are intolerant to or have contraindications to both bisphosphonates and raloxifene.

**Combination therapies.** There are limited data supporting the use of combination antiresorptive treatments for osteoporosis. While data are available demonstrating greater increases in BMD with the use of estrogen or raloxifene in combination with a bisphosphonate,<sup>124–127</sup> fracture data are lacking. In addition, the use of a bisphosphonate with PTH 1-84 or PTH 1-34 may result in attenuation of the anabolic effects of PTH,<sup>128,129</sup> though sequential treatment with a bisphosphonate after therapy with PTH 1-84 appears to maintain or increase BMD gains.<sup>130</sup> Thus, until fracture outcomes data are available, concurrent combination therapy should generally be avoided or used with caution by an osteoporosis specialist.

**Investigational treatments.** Denosumab is a monoclonal antibody to the receptor activator for nuclear factor-kappa B ligand (RANKL) that mimics osteoprotegerin and decreases bone resorption through inhibition of osteoclast differential, activation, and survival.<sup>131</sup> In a recent Phase II study, the safety and efficacy of denosumab were assessed in 412 postmenopausal women (mean age, 63 years) with low BMD (mean lumbar t score,  $-2.0$  to  $-2.3$ ; mean femoral neck t score,  $-1.7$  to  $-2.0$ ).<sup>89</sup> Patients were randomized to receive subcutaneous denosumab every 3 months (doses of 6, 14, or 30 mg), every 6 months (doses of 14, 16, or 30 mg), open-label alendronate sodium 70 mg p.o. weekly, or placebo. After 12 months of treatment, denosumab increased BMD at the lumbar spine by 3.0–6.7% (versus 4.8% with alendronate and  $-0.8\%$  with placebo [ $p < 0.001$  for comparison of denosumab with placebo]) and total hip by 1.9–3.6% (versus 2.1% with alendronate and  $-0.6\%$  with placebo [ $p < 0.001$  for comparison of denosumab with placebo]). Thus, denosumab holds promise as a future agent and may be particularly appealing from an adherence standpoint, though data regarding its ability to protect against fractures are needed.

PTH 1-84 is the full-length 84-amino acid PTH that was approved in April 2006 in the European Union for treatment of osteoporosis in postmenopausal women at high risk for fracture<sup>132</sup> and has received an approvable letter from FDA.<sup>133</sup> In the randomized, double-blind, placebo-controlled, Phase III Treatment of Osteoporosis with PTH (TOP) trial, 100 µg of PTH 1-84 was given subcutaneously once daily to 2532 postmenopausal women with osteoporosis (mean t score, -3.0), 19% of whom had experienced a prior vertebral fracture.<sup>90</sup> After a median of 18 months, PTH 1-84 decreased the risk of new vertebral fractures by 61% (NNT = 48,  $p = 0.001$ ). There was no difference in the incidence of any nonvertebral fracture (5.52% for PTH 1-84 versus 5.86% for placebo).<sup>134</sup> In a recent international, multicenter, double-blind, randomized, parallel group trial of 2532 postmenopausal women with osteoporosis with and without prior fractures, 100 µg of PTH 1-84 given subcutaneously daily was compared with placebo.<sup>135</sup> After 18 months, PTH 1-84 decreased the risk of new or worsened vertebral fractures by 60% (NNT = 50,  $p = 0.001$ ) in a modified intent-to-treat analysis, though this rate change was based on assumptions of fracture rates for those who withdrew early from the study. Adverse effects that were more common in the group treated with PTH 1-84 than in the placebo group included hypercalciuria (46.0% versus 22.3%, NNH = 4), hypercalcemia (27.8% versus 4.5%, NNH = 4), nausea (22.6% versus 9.2%, NNH = 7), and vomiting (7.7% versus 4.3%, NNH = 29). Thus, PTH 1-84 has potential as a future anabolic treatment for women at high risk for fracture, though comparative data with teriparatide (PTH 1-34) are needed to elucidate if any clinical differences in BMD or fracture efficacy exist between the full-length and shortened (i.e., PTH 1-34) versions.

Sodium fluoride is an anabolic agent that increases BMD by stimulating osteoblast activity.<sup>136,137</sup> While it has been available for many years and may be considered an alternative agent in Europe,<sup>56</sup> oral therapy has not been approved for use in the United States due to concerns regarding decreases in bone quality and strength, despite increases in BMD, and adverse effects such as gastrointestinal symptoms and lower-extremity pain.<sup>138</sup> These concerns may have been caused by higher doses and immediate-release formulations given on a continuous basis. While lower doses of a sustained-release formulation have been shown to increase BMD in vertebrae L2–L4 by 5.4% and decrease vertebral fractures by 68% (NNT = 8; 95% CI, 0.14–0.73;  $p = 0.007$ ), with no additional increases in gastrointestinal and musculoskeletal adverse effects,<sup>91</sup> it is doubtful this agent will be approved for use in the United States.

Strontium ranelate is an orally active distronium salt that has both anabolic and antiresorptive effects on bone.<sup>139</sup> It was approved in Europe in September 2004 for the treatment of postmenopausal osteoporosis<sup>140</sup> but is not yet approved for use in the United States. Strontium has been shown to decrease both vertebral and nonvertebral fractures. In a Phase III study of 1649 postmenopausal women with osteoporosis (mean age, 69 years) and at least one vertebral fracture, 2 g of strontium ranelate daily for three years decreased the rate of new vertebral fractures by 41% (NNT = 8; 95% CI, 0.48–0.73;  $p < 0.001$ ).<sup>94</sup> In the Treatment of Peripheral Osteoporosis Study (TROPOS), strontium ranelate 2 g daily for three years in 5091 postmenopausal women with osteoporosis (mean age, 77 years) decreased the rate for all

nonvertebral fractures by 16% and decreased the rate of major fragility fractures (i.e., hip, wrist, pelvis, sacrum, ribs and sternum, clavicle, and humerus) by 19% (NNT = 59 for both fracture types) versus placebo.<sup>95</sup> There was no significant difference in hip fractures in the intent-to-treat population, but, for those in the high-risk subgroup (age  $\geq 74$  years with femoral neck BMD t score of  $\leq -3$ ), there was a 36% reduction in fracture risk (NNT = 48; 95% CI, 0.412–0.997;  $p = 0.046$ ). Strontium ranelate has potential as a future treatment in the United States for osteoporosis, though it remains to be seen if this agent will be brought to market.

**Special Populations. Nursing-home patients.** Approximately 80–85% of U.S. nursing-home residents suffer from osteoporosis.<sup>141</sup> Because nursing-home residents are often afflicted with multiple diseases, disabilities, and fragility, their fracture rates are much higher than the community-dwelling elderly. Other factors associated with the higher fracture rate among nursing-home residents include immobility, low body mass, difficulty transferring (e.g., moving from a bed to a wheelchair), falls, and multiple medications.<sup>142</sup> In addition, many nursing-home residents have inadequate nutritional status, including low intake of calcium and vitamin D as well as inadequate sunlight exposure.<sup>142,143</sup> Osteoporosis treatment for nursing-home residents ideally involves a multifactorial approach emphasizing fall prevention, adequate nutrition, strength and balance training, medication review, and environmental modifications (e.g., redesigning home environments, removal of floor rugs). While devices such as hip protectors have been shown to prevent fractures in patients at high risk,<sup>144</sup> more recent data indicated that these are ineffective interventions.<sup>145</sup> Underuse of osteoporosis diagnostic procedures in nursing-home residents is well documented.<sup>146</sup> Even when osteoporosis is diagnosed and documented in the medical record, few patients receive optimal therapy despite data demonstrating that screening and treatment are highly cost-effective.<sup>147</sup>

Calcium and vitamin D supplements are prescribed for approximately 60% of nursing-home residents with osteoporosis and only 25% of residents with hip fractures.<sup>148</sup> Similarly, bisphosphonate use among nursing-home residents with documented hip fractures approaches 25%.<sup>149</sup> Because the majority of nursing-home residents with osteoporosis receive inadequate drug therapy, ASHP urges interdisciplinary team approaches to detect and manage osteoporosis in this setting. Osteoporosis guidelines are useful and may be cost-effective, with implementation dependent on cooperation from the facility medical director, attending physicians, the director of nursing, therapists, and the consultant pharmacist.<sup>150</sup>

**Men.** Two million American men have osteoporosis and another 12 million are at risk for developing osteoporosis.<sup>151</sup> Thirty percent of hip fractures occur in men, and one in eight men over age 50 years will have an osteoporosis-related fracture in his lifetime.<sup>152</sup> Hip fracture-related mortality and morbidity are significantly greater in men than in women, with one-year mortality after hip fracture approximately double that of women.<sup>153</sup> After sustaining a hip fracture, up to 50% of men require institutional care.

Despite the serious consequences of hip fracture for men, osteoporosis has only recently received attention as a major men's health issue. There remain significant barriers, particularly reimbursement for screening. Medicare

will only cover screening costs for “qualified individuals”: estrogen-deficient women, individuals with vertebral abnormalities, those with known primary hyperparathyroidism, individuals receiving steroid therapy, and those receiving FDA-approved osteoporosis medications.<sup>154</sup> Risk factors associated with osteoporosis in men include hypogonadism associated with low testosterone and low estradiol, chronic diseases, chronic obstructive pulmonary disease, prolonged exposure to osteoporosis-inducing medications, Caucasian race, heredity, and advanced age.<sup>151,155</sup> Lifestyle may increase the risk of osteoporosis in men, including current smoking, excessive alcohol use, low calcium intake, and low physical activity. The Male Osteoporosis Risk Estimation Score, or MORES, has been developed as one approach to identify men age 60 years or older at risk for osteoporosis.<sup>156</sup> Those men found to be at risk should be referred for a DEXA scan. Osteoporosis treatment in men comprises calcium and vitamin D supplements; bisphosphonates; testosterone replacement, if indicated (i.e., hypogonadism); and teriparatide for men at high risk of fracture.<sup>1,129,157</sup>

### Summary

ASHP believes that patients at risk for osteoporosis and related fractures (e.g., women age 65 years or older regardless of risk factors, postmenopausal women under age 65 years with risk factors, postmenopausal women with a history of nontraumatic fracture, men with a significant risk of fracture) should receive appropriate risk assessment and evaluation of BMD using central DEXA. Patients with confirmed low BMD who are at risk for fractures should receive treatment. ASHP believes that medications shown to reduce the risk of fractures should be used. These include calcium and vitamin D for all patients, bisphosphonates, raloxifene, calcitonin, estrogen, and teriparatide. ASHP acknowledges that the choice of agent will depend on its ability to increase BMD and decrease fractures, as well as various patient-specific criteria (e.g., medical history, contraindications, patient beliefs or preferences, finances). In general, agents that have been shown to decrease vertebral, nonvertebral, and hip fractures should be used preferentially.

ASHP believes that clinicians need to be actively involved in educating both patients and collaborative health care professionals regarding risk factors associated with osteoporosis and fractures. Efforts should include recommendations for appropriate weight-bearing exercise, identification of agents that may decrease BMD (e.g., corticosteroids) or increase the risk for falls (e.g., long-acting benzodiazepines), and appropriate calcium and vitamin D intake. Well-designed clinical trials are needed to better assess who should be screened, compare various medications’ effects on fracture rates, and better identify patients who should receive treatment with antiresorptives, anabolic agents, or combination therapy.

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