Pharmacotherapeutics for Osteoporosis Prevention and Treatment

Michele R. Davidson, CNM, PhD

Osteoporosis is a silent disease that affects 10 million Americans; 80% of those affected are women. Although the disease is more common in postmenopausal Caucasian women, all ages and races are at risk. Osteoporosis can be a debilitating disease that can cause pain, fractures, depression, and social withdrawal. Signs of osteoporosis include kyphosis, loss of height, and protrusion of the abdomen. Because symptoms generally do not occur until after the disease has progressed, clinicians should include osteoporosis screening and preventative education as part of the regular gynecologic care. Diagnosis is typically made by a dual energy x-ray absorpitometry (DEXA) scan. Treatment consists of dietary and lifestyle changes, along with pharmacologic intervention. Although hormone therapy has been shown to be effective in preventing osteoporosis, the risks of long-term treatment with HRT are discussed. The following effective treatment options for women who have been diagnosed with the disease are discussed: bisphosphonates, calcitonin, and selective estrogen receptor modulators (SERMs). Because midwives regularly care for women of all ages, they are ideal candidates to provide women with preventative education, screening, counseling, and treatment. J Midwifery Womens Health 2003;48:39–52 © 2003 by the American College of Nurse-Midwives.

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INTRODUCTION

Osteoporosis, which comes from Greek meaning porous bone, is a condition or disease process that is marked by structural deterioration of bone tissue and low bone mass. Low bone mass can lead to bone fragility and increase a woman's risk of fractures. Although 80% of Americans who suffer from osteoporosis are women, osteoporosis also affects men. The disease can occur at any age and in any racial or ethnic group, although it is more common in the in postmenopausal women, especially those who are Asian or Caucasian.[1] Osteoporosis affects 10 million Americans with another 18 million at risk due to low bone mass. Each year, 1.5 million fractures occur as a direct result of osteoporosis.[1] The cost directly related to these fractures exceeds 13.8 billion dollars annually. Fifty percent of women over the age of 50 will experience an osteoporosis-related fracture at sometime during their lifetime.[1] Osteoporosis can be a debilitating disease that can result in chronic pain, fractures, an inability to participate in normal daily activities, depression, social withdrawal, loss of independence, and deformities.[2] Of the women who do experience hip fractures as a result of osteoporosis, 50% will spend a portion of their recovery in a long-term care facility. Long-term sequelae even can include death. It is estimated that 20% of women who suffer a hip fracture will die within a year from indirect cause.[3,4]

Clinicians should assess for risk factors of osteoporosis in all women at each office visit. Adolescents should be evaluated for risk factors that can lead to osteoporosis. Because adolescents are both building bone and establishing lifelong health habits, intervention during this time period can be critical. Other high-risk groups, such as smokers, chronic alcohol users, or individuals on certain medications, should be offered appropriate screening. Lifestyle risks, such as smoking, alcohol use, and lack of exercise, should be reviewed and eliminated when possible. Non-pharmacologic treatments can be discussed and pharmacologic regimens can be ordered when appropriate. A diet analysis should be performed on all women regardless of their age to assess for adequate calcium intake. Counseling aimed at decreasing the risk of osteoporosis should be part of a woman's annual examination.

The role of the midwife in osteoporosis screening, diagnosis, and management varies. Certainly, all midwives should provide risk assessment and education regarding osteoporosis. Midwives can also order diagnostic testing for all women at risk for osteoporosis. For women without other medical complications, such as malabsorption problems or persistent glucocorticoid steroid use, it is reasonable for midwives to initiate pharmacologic management. Women who have difficulty tolerating medications or who have had a fracture should be referred to a physician for management.

PATHOPHYSIOLOGY OF OSTEOPOROSIS

The physiology of bone formation is a complex process interdependent on multiple factors. On the conclusion of linear growth, bone is constantly being remodeled (built and reabsorbed and rebuilt again). This process is critical to the formation of healthy bone tissue and allows the body to repair microfractures within the bone that are caused from the daily stress that is exerted on the bones.[3] Bones also serve as the storage compartment for the body's supply of calcium. Dietary calcium deficiency and calcium, absorp-

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tion problems, lack of physical activity, and certain drugs such as prednisone can lead to a low bone mass.[5] In bone remodeling, bone is absorbed from the remodeled site by osteoclasts. The vacant cavity is then occupied by osteoblasts, which fill the space with new, stronger bone.[6] This is a continuous, on-going process. Multiple factors cause the net loss of bone mass seen in persons with osteoporosis including too many bone remodeling units (osteoclasts), which results in an imbalance of osteoclasts and osteoblasts at the resorption site. Depletion or too few osteoblasts can also lead to osteoporosis because the remodeled site is not properly filled with osteoblast cells during the bone remodeling process. Extracellular levels of calcium and phosphorus maintain the systemic regulation of bone remodeling. Parathyroid hormone and vitamin D are also key regulators. Parathyroid hormone stimulates bone resorption and formation.[7] Estrogen enhances bone formation by stimulating the estrogen receptors, located on the osteoblasts.

RISK FACTORS FOR OSTEOPOROSIS

Postmenopausal women represent the most common risk group for osteoporosis. Decreased levels of estrogen, which occur from either natural or surgically induced menopause, lead to acceleration in bone loss. It is estimated that 21% to 30% of Caucasian, postmenopausal women have osteoporosis, and an additional 54% have low bone mass, causing susceptibility to both osteoporosis and risk of fractures later in life.[4] Previously, it was believed that estrogen replacement therapy (ERT) and hormone replacement therapy (HRT) both prevented and treated osteoporosis. New findings indicate that although ERT/HRT may prevent osteoporosis by decreasing the rate of bone loss, there is no evidence that it is effective for treatment of osteoporosis.[8] The Food and Drug Administration (FDA) recently required that the indication labeling on HRT products be changed from a treatment and preventative therapy to a preventative therapy only.[7] In May 2002, the authors of the Women's Health Initiative, a randomized controlled primary prevention trial of 16,608 women, recommended that the study be stopped 3 years early and that HRT not be prescribed for long-term prevention of chronic diseases.[9] Although the study demonstrated a reduction in observed hip and clinical vertebral fracture rates by one third compared to placebo, the Women's Health Initiative authors recommend the use of alternative preventive and treatment strategies for osteoporosis to avoid the increased significant risk of breast cancer for which the Women's Health Initiative was stopped at 5.2 years (planned duration, 8.5 years).[9]

Combined oral contraceptive pills appear to have protective bone benefits to users.[10,11] Oral contraceptives used for perimenopausal symptoms in the fourth decade of life offer relief from vasomotor symptoms in addition to estrogen supplementation to decrease bone loss that can occur when estrogen levels begin to fall.

Table 1. Risk Factors Associated with Osteoporosis

Potentially Modifiable	Nonmodifiable
Current cigarette smoking	Personal history of fracture
Diet low in calcium/vitamin D	First-degree relative with fracture
Use of glucocorticoids, anticonvulsants	Race (Caucasian or Asian)
Excessive alcohol intake	Elderly age
Sedentary lifestyle	Poor health
Body weight less than 127 lb	Dementia
Lack of estrogen	Hormonal disorders
Environmental risks (loose rugs, dark stairs, etc.)	Neoplastic disorders
Poor eyesight	Metabolic abnormalities
	Connective tissue disorders
	History of organ transplants

Personal Medical History and Family History

Personal and family histories are key components that may alert a woman and her clinician to an increased risk for osteoporosis. Women with a history of previous fractures should undergo bone mineral density testing to evaluate the status of their bone mass. Certain medical conditions can also predispose an individual to a loss in bone mass, which can lead to osteoporosis. Hormonal abnormalities, such as hyperthyroidism, and hyperparathyroidism can impair the bone-making process. Individuals with a history of neoplastic disorders, such as multiple myeloma, are also at risk. Individuals with metabolic disorders, such as osteomalacia, or connective tissue diseases (osteogenesis imperfecta) should also be screened.[2,3] Most individuals with these conditions will already be receiving care from a specialist; however, it is important to ensure that the woman is receiving proper medical screening and treatment. Women with these disorders who have not been screened for osteoporosis should be referred to a specialist for follow-up care. Nutritional deficiencies, such as inadequate calcium or vitamin D intake, are additional risk factors that should be assessed.[5] In addition, women with a family history of osteoporosis or of fractures that have occurred in first-degree relatives are also at an increased risk for the disease.[2] Both modifiable and non-modifiable risk factors for osteoporosis are listed in Table 1.

Factors that are protective and associated with a decreased risk of osteoporosis include high parity (because pregnancy is a high-estrogen state), large body habitus, and history of moderate exercise.[10] During breastfeeding there is a depletion of estrogen; however, the bone loss that

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occurs is regained after nursing is discontinued.[11–13] Even multiparous women who have breastfed for an extended period of time do not appear to have a significant decrease in bone mineral density when compared with women who breastfed for shorter times.[14] Karlsson and colleagues[12] compared average bone mineral density measurements of 73 lactating postpartum women with the bone mineral density measurements of 55 age-matched women who served as controls. A subgroup of 39 multiparous women with greater than four births was compared with a control group that consisted of 58 premenopausal women who had a maximum of two births. The results were controlled for differences in total fat mass and total lean mass. Lumbar bone mineral density was 7.6% $\pm$ 0.1% and total bone mineral density was 3.9 $\pm$ 0.1% lower in women postpartum than in the control group ($P < .001$). Mothers who were breastfeeding for a duration of 1 to 5 months decreased femoral neck bone mineral density by 2.0% $\pm$ 1.0% during the first 5 months postpartum; however, no additional bone mineral density loss was seen during 6 to 12 months in lactating women ($P = .05$). Women in the subgroup with at least four deliveries did not show a significant difference in bone mineral density compared with the women with only two deliveries. Total duration of lactation was not correlated with present bone mineral density. Extended lactation and multiple pregnancies did not increase a woman's risk of osteoporosis.[12] Although bone mineral density and calcium levels decline during lactation, transient bone loss normalizes after weaning.[12] The risk for older women who become pregnant, breastfeed, and then quickly enter menopause are less clear. Some studies have revealed that parity in itself is protective against osteoporosis. Bone mineral densities in postmenopausal multiparous women increased with the number of births until age 69.[13] Fractures occurred more commonly in nulliparous women and in women over the age of 70. These findings may impact clinical decisions in recommending hormone replacement as well as counseling women on the protective benefit of pregnancy.[14]

Age and Risk of Osteoporosis

Age is the most important risk factor for osteoporotic fractures. Women, especially elderly women, in poor health, those with dementia, or those with poor uncorrected eyesight have a higher risk for falls or fractures.[2,15] Although osteoporosis occurs most commonly in postmenopausal women, it is occurring more frequently in adolescent girls, especially young female athletes who participate in endurance activities such as gymnastics, ice-skating, and dance. These girls are prone to fractures due to low bone mineral density, overtraining, and vigorous dieting practices.[2] Some young athletes experience multiple health problems including eating disorders, amenorrhea, and low bone mass. Young women who experience this cluster of symptoms known as the "female athletic triad" (eating disorders, amenorrhea, and low bone mass) may permanently lose their opportunity to establish a healthy bone mass, thus increasing their risk for osteoporosis and fractures in later life.[2,4,16] The peak bone mass for all persons is achieved during the adolescent years, a crucial time for bone growth. Ninety-eight percent of the skeletal mass is acquired by age 20.[1] Gradual loss of bone starts to occur sometime between the ages of 30 and 40. For women, rapid bone loss accelerates at the time of menopause with a loss of 2% to 5% over the next 10 years.[7] The need for a well-balanced diet and physical activity are essential to tissue and bone growth. Adolescence is also a time when lifelong health promotion habits are forming. Counseling should focus on healthy eating patterns, promotion of physical activity, and reaching or maintaining an appropriate weight range for young women.

Role of Lifestyle Factors in Risk for Osteoporosis

A sedentary lifestyle, cigarette smoking, and excessive alcohol intakes are lifestyle factors associated with an increased risk for osteoporosis. Clinicians can identify these risks and provide educational teaching to decrease both risk factors and environmental hazards.

Pharmacologic Risk Factors

Certain medications may put individuals at risk for a reduction in bone mass.[17,18] Phenytoin sodium (Dilantin) is an example of an anticonvulsant that can predispose an individual to osteoporosis when used for long-term management. Glucocorticoids have a negative impact on the bone formation process. They reduce bone formation by decreasing the osteoid thickness, the mineral apposition rate, the rate of bone mineralization, and the osteoblast activity. High doses may also lead to trabecular thinning and a loss of trabecular connectivity.[18] This can result in fractures of the pelvis, vertebrae, and ribs. These drugs also decrease uptake of vitamin D in the intestinal tract, which leads to an increase in renal calcium secretion.[7] Sachs reviewed the effects of glucocorticoid administration in asthmatic children and found that 46% suffered from osteopenia.[17] Glucocorticoid medications are commonly used to treat asthma, inflammatory disorders, cystic fibrosis, chronic obstructive pulmonary diseases, as well as patients who have received transplants.[7,18,19] The use of these drugs accounts for 25% of the cases of osteoporosis. Individuals taking these drugs often have other risk factors, such as elderly age, postmenopausal status, smoking, sedentary lifestyle, and malnutrition.[7,19]

Medroxyprogesterone acetate (Depo-Provera) also may increase bone resorption because it induces a hypoestrogenic state. Studies have yielded mixed findings on the effects this drug has on bone mineral density. Bahamondes and colleagues[20] compared bone mineral density in 50 premenopausal women who had never used hormonal contraception with 50 premenopausal women who had used

Depo-Provera for at least 1 year. Bone mineral density was significantly lower in the group who were currently receiving Depo-Provera. Although bone mineral density was lower, the authors stated they could not conclude that Depo-Provera users were at risk for osteoporosis. Another study compared the bone mineral density in women aged 30 to 34 years of age; Depo-Provera users, oral contraceptive users, and women who had never used hormonal contraceptives. Study results did not find a difference in the three groups when bone mineral density was measured.[21] The practice of prescribing Depo-Provera (depo-medroxyprogesterone acetate) to young adolescents (<16 years of age) for prolonged periods of time (e.g., >5 years) may warrant caution because these young women have not yet reached peak bone mass.[22]

PHYSICAL EXAMINATION FOR OSTEOPOROSIS: SIGNS AND SYMPTOMS

Typically, osteoporosis is a "silent disease" (i.e., there are frequently no symptoms) until a fracture has occurred. As the disease progresses, symptoms may include back pain, fractures, loss of height, skeletal deformity (kyphosis or kyphoscoliosis), neck strain (due to an exaggerated cervical lordosis), midabdominal pain (caused from the ribs resting on the iliac crest), alterations in bowel function, such as constipation (caused by compression of the abdominal contents), and rarely, restrictive lung disease (which occurs as a result of limited respiratory capacity caused by advanced kyphosis.[2,10] Women may report that they have difficulty finding clothes that fit appropriately. This is caused by a combination of physical factors, including the thoracic hump, foreshortened waist, and protruding abdomen.[10] Some practitioners advocate measuring a woman from crown to pubis, noting that this measurement should be within 1 in of the pubis to floor measurement. If the former is less, further evaluation for spinal compression should be done because this can be indicative of early spinal changes. Symptoms related to endocrine dysfunction can also be an indication of possible osteoporosis.[23] Laboratory values, thyroid-stimulating hormone and dihydroepiandrosterone sulfate (DHEAS), may be obtained if thyroid disease or adrenal insufficiency is suspected because these conditions may raise calcium levels, which can lead to a decline in bone mass.

PHYSICAL EXAMINATION

The physical examination may reveal tenderness or pain with palpation over the site of a fracture. A thorough assessment of recent falls or injuries is imperative. Women may present with spinal deformities. The exaggerated thoracic kyphosis, known as dowager hump, is a classic sign. Loss of height can be as great as 2 in.[8] In addition, women may experience a change in balance due to the shift in gravity to a more forward position.[10] An abdominal examination may reveal a protrusion of the abdomen ("pouchy stomach") with lax muscle tone, which could be mistaken for obesity. Often, difficulty with walking and inability or difficulty performing previous activities of daily living can be a common complaint. Women with risk factors, physical symptoms, or suggestive findings on the physical examination should be referred for diagnostic testing.

WHO SHOULD BE OFFERED DIAGNOSTIC TESTS?

The National Osteoporosis Foundation Guidelines suggest that the following groups be tested: all postmenopausal women under the age of 65 with one or more risk factors (in addition to postmenopausal status), all women over the age of 65, postmenopausal women who present with fractures, women considering treatment for osteoporosis (if findings would impact their decision-making efforts), and women who have been on HRT for extended periods of time. Recommendations to screen women who are currently on HRT are warranted to evaluate the effectiveness of HRT therapy. If bone mineral density has continued to decrease despite HRT, additional pharmacologic agents may be added to increase bone mineral density and decrease the risk of osteoporosis. Other risk factors that may warrant screening include women with a weight of less than 127 pounds (57.6 kg), family history of a fracture, and current cigarette smoking.[4] In addition, women with other risk factors, including those on glucocorticoids or anticonvulsant drugs or those with medical conditions that may affect bone mass, should also be screened.[1,3,4,7,24]

Practitioners should be aware there are a number of scales that can be used to determine candidates for screening, including the National Osteoporosis Foundation Guidelines, the Simple Calculated Osteoporosis Risk Estimation, the Osteoporosis Risk Assessment Instrument, and the Age, Body Size, No Estrogen Scale.[7] All scales assign a numerical value to various risk factors to determine a risk score. Individuals who have a certain number of points (or a certain score as outlined by that scale) are then referred for diagnostic testing to determine their bone mineral density. Table 2 provides screening guidelines to assist clinicians in clinical decision making.

Bone Density Measurements

Measuring an individual's bone density is the standard diagnostic test used to diagnose osteoporosis. Bone density indicates the strength of an individual's bone and correlates to the load-bearing capacity of the bone itself.[4,24] There are primarily two ways to measure bone density. Bone density can be measured at either central or peripheral sites. Dual-energy x-ray absorptiometry and quantitative computed tomography are measures of bone density at central sites. Dual-energy x-ray absorptiometry is the gold standard for measuring bone density. Sites that can be used include the spine and the hip.[7,24] Quantitative computed tomogra-

Table 2. Guidelines for Osteoporosis Screening

Guideline	Scoring	Cutoff Point for Recommended Screening
National Osteoporosis Foundation	One point each: Age ≥65 y Weight less than 57.6 kg Family history of fracture Current cigarette smoking	≥1
Osteoporosis Risk Assessment Instrument (ORAI)	15 points, age ≥75 y 9 points, age ≥65–74 y 5 points, age ≥55–64 y 9 points, weight less than 60 kg 3 points, weight 60–69.99 kg 2 points if not currently taking estrogen	≥9
Simple Calculated Osteoporosis Risk Estimation (SCORE)	5 points if not black race 4 points for rheumatoid arthritis 4 points for each fracture of wrist, hip, or rib since age 45 (maximum 12) 3 points times first digit of age in years 1 point no history of estrogen therapy −1 point times weight in pounds divided by 10	≥6

Adapted with permission from Davidson and DeSimone, 2002.[7]

phy directly calculates three-dimensional bone density, although it is not widely used as a bone mineral density screening tool. Dual-energy x-ray absorptiometry can distinguish between different types of bone tissues. The drawbacks of this technique include the high cost, limited availability, and the higher levels of radiation exposure.

Peripheral site-screening techniques include single-energy x-ray absorptiometry, peripheral dual-energy x-ray absorptiometry or quantitative computed tomography, radiographic absorptiometry, ultrasonometry, and single-photon absorptiometry. The single-energy x-ray absorptiometry and single-photon absorptiometry both use a single-energy source in the screening process.[24] Because these scans cannot distinguish between soft tissue and bone, they can only be used in the wrist and heel. They have been widely replaced by dual-energy x-ray absorptiometry in most settings, but they are still occasionally used as a screening tool, especially for mass screenings. Although these techniques are not as accurate as a hip dual-energy x-ray absorptiometry in predicting the risk of hip fractures, they do predict the overall risk of fractures in all sites fairly well. Radiographic absorptiometry is one of the oldest techniques and is no longer widely used.[24] Ultrasound densitometry is the newest technique that assesses bone mineral density. This technique is also not widely used, although the research regarding its use in BMD testing is promising.[25]

Although bone mineral density testing can be used by health care professionals to determine the risk of fracture,[1–4,7,8,10,24–26] it cannot provide definitive data (e.g., if a fracture will definitely occur). Bone mineral density testing provides information that details the relative risk based on the number of standard deviations the bone mineral density falls below the average (mean) for young healthy adults. The number of standard deviations below the mean of the young healthy adult-age population is referred to as the T score. Z scores, which compare the bone mineral density of the individual being screened with the standard bone mineral density of individuals of the same age and gender, also are calculated. Z scores should not be used to diagnose osteoporosis because a reduction in bone mass commonly occurs with age. Clinicians need to evaluate a woman's T score when interpreting test results. Criteria on interpreting results have been identified by the World Health Organization (WHO).[26] A normal test is a T score value within 1 SD of a young, healthy adult mean value. Low bone mass, or osteopenia, is diagnosed when the findings indicate the bone mineral density is more than 1 SD below the young adult mean value but not less than 2.5 SDs. Osteoporosis is diagnosed when the value is 2.5 SDs or more below the young adult mean.[4,17,19] Osteopenia is essentially the condition that develops before the loss of bone mass falls to a level where it fits the diagnostic criteria of osteoporosis.

RESEARCH SHORTCOMINGS

Before turning to treatment of osteoporosis, it is important to note that several limitations exist in the current research published on use of bone mineral density tests for diagnosis of osteoporosis. Many studies use small sample sizes with inadequate research time. Other studies may not consistently measure bone mineral density at the same site. Because the site used to measure bone mineral density can dramatically change the mean bone mineral density values obtained, these studies may be yielding inconclusive find-

Table 3. Non-Dairy Sources of Calcium

Food Source	Calcium (mg)	Food Source	Calcium (mg)
Mackerel, Canned (5 oz)	400	Turnip greens (frozen, cooked) (1/2 cup)	100
Sardines (in oil) (4 oz)	400	Almonds (1.5 oz)	100
Collard Greens (frozen, cooked) (1 cup)	300	Orange juice (6 oz)	50
Salmon (baked, broiled) (6 oz)	300	Broccoli, kale, mustard greens (1/2 cup)	50
Dried figs [10]	200	Baked beans (1/2 cup)	50
Instant oatmeal (1 packet)	150	English muffin, oatmeal muffin	50
Bok choy (1 cup)	150	Orange (1 medium)	50
Rhubarb (cooked with sugar) (1/2 cup)	150	Pita (1 small)	50
Soybeans (cooked) (1 cup)	100	Refried beans (1/2 cup)	25

ings. Some studies measure bone mineral density with a variety of techniques in much the same way as measuring the sites, which may result in entry into study via one method and determination of results by another. Because there is a margin of error between differing bone mineral density tests, results of these studies are questionable. In addition, researchers who fail to control for extraneous variables, such as parity, prior contraceptive use, supplementation with vitamins C, D, or other medications, may not have accurate findings. Although studies on bone mineral density results can provide valuable predictors of bone health, fracture rates are a better indicator of morbidity and mortality.

NONPHARMACOLOGIC INTERVENTIONS

Lifestyle modification should be the foremost aim of prevention for all women. Clinicians should counsel women about interventions that decrease the risk of fractures and bone loss. Lifestyle habits, such as cigarette smoking and excessive use of alcohol, can have a negative impact on bone health. Smoking results in a more rapid rate of bone loss by interfering with calcium absorption and lowering estrogen levels.[27] Smoking cessation programs or pharmacologic intervention should be discussed to aid women to discontinue smoking. Heavy alcohol consumption (defined as more than seven drinks per week) has been associated with an increased risk of falls and a decrease in bone mineral density, although the underlying for this finding is still not fully understood.[27] Women should be counseled to decrease or eliminate alcohol consumption to reduce the risk of osteoporosis. Clinicians can work with women to develop strategies to discontinue these behaviors. Women with alcoholism may be referred to Alcohol Anonymous or other support groups or counseling when deemed appropriate.

Weight-bearing exercises (e.g., low-impact aerobics, jogging, tennis, strength training with weights, dancing, and gardening) and walking programs can help build stronger bones and muscles and can be used to increase strength, flexibility, and balance.[4] High-impact exercises (e.g., running, gymnastics, or high-impact aerobics) appear to provide the most osteogenic stimulation.[27] Exercise can also improve balance, gait, coordination, proprioception, muscle strength, and reaction time in elderly individuals.[28] Exercise has also been associated with higher bone mineral density.[29] Good posture along with supportive shoes should also be encouraged.

Although exercise has been associated with a reduction in falls and fractures,[1,7] clinicians should encourage clients to examine living environments and eliminate environmental risks. Patient handouts that focus on injury prevention and home safety can be given. Loose rugs, poorly lit areas, such as stairways, and excessive clutter should all be corrected to minimize the risks of falls and fractures.

Nutrition should be evaluated, and a healthy, well-balanced diet high in calcium and vitamin D should be encouraged.[27] Women over the age of 65 have a 50% reduction in intestinal calcium absorption compared with adolescents. In addition, the renal enzymatic activity that produces vitamin D metabolites (which also controls calcium) is also decreased in postmenopausal women, making the need for adequate calcium and vitamin D intake or supplementation imperative for women in this age group.[27] Calcium can be obtained in a variety of nutritional sources, including milk, yogurt, cheese, ice cream, ice milk, fish, shellfish, and green vegetables.[5] A diet analysis can be done to assess the woman's calcium intake. In women who do not eat dairy products, the clinician can assume the woman is getting approximately 500 mg of calcium a day from non-dairy sources.[5] Examples of non-dairy sources of calcium are listed in Table 3, and these can be reviewed with women to ensure adequate intake of calcium.

PHARMACOLOGIC INTERVENTIONS

Pharmacologic interventions for the prevention and treatment of osteoporosis include vitamin and mineral supplementation, hormone replacement therapy, bisphosphonates, calcitonin, and selective estrogen receptor modulators, and fluoride supplementation. Other treatment modalities are also being explored but have not been approved by the FDA.

Diet and Vitamin or Mineral Supplementation

Vitamin D

Vitamin D plays a major role in calcium absorption and bone health. Vitamin D is the cofactor that facilitates the intestinal absorption of calcium and facilitates reabsorption of filtered calcium from the glomerular tubules back into plasma within the kidney.[4] Vitamin D, a fat-soluble vitamin, is derived from ergocalciferol (obtained from food sources) or cholecalciferol (formed from exposure to sunlight) sources.[5,30] The amount of vitamin D produced depends on the time of day, season, latitude, and an individuals' skin pigmentation. However, usually 10 to 15 minutes' exposure of hands, arms, and face two to three times a week (depending on one's skin sensitivity) is enough to satisfy the body's vitamin D requirement. Use of sunscreen agents dramatically decreases the body's absorption of vitamin D.[4]

Vitamin D deficiencies in adults will manifest as osteomalacia, a disorder marked by weakened bones. It is estimated that 30% of women with hip fractures have vitamin D deficiencies.[31] Few food sources contain naturally occurring vitamin D. Sources of ergocalciferol vitamin D include eggs, fish oil, vitamin D-fortified milk, fortified cereals, butter, salmon, herring, and liver. Because plant foods are poor sources of vitamin D, vegetarians will need to get their vitamin D through sunlight exposure.[5] Individuals at risk for osteoporosis, such as the elderly, vegetarians, or postmenopausal women who have low levels of blood cholecalciferol will benefit from vitamin D supplementation at 400 IU/d.[5]

Homik and colleagues[32] evaluated 274 subjects in a randomized control trial and found that those supplemented with calcium and vitamin D versus those given vitamin D alone had a statistically significant increase in their lumbar spine bone mineral density compared to the control group. Whether calcium supplementation alone is enough protection against osteoporosis is still under investigation; however, it is clear that calcium is a vital building block for healthy new bone.

Role of Dietary Protein

Recent studies examined the consumption of protein with calcium as a means to increase bone mineral density. Promislow and colleagues[33] examined animal protein intake in 572 women and 388 men aged 55 to 92. After a 4-year study period, the researchers found that for every 15 g of protein consumption per day, bone mineral density increased by 0.016 g/cm^2 at the hip ($P = .005$), 0.012 g/cm^2 ($P = .005$) at the femoral neck, and 0.015 g/cm^2 at the spine ($P = .04$). There was a negative association between vegetable protein intake and bone mineral density. The association between animal protein intake and an increase in bone mineral density was statistically significant for women in the study. Dawson-Hughes and Harris[34] also found an association between protein intake and calcium/vitamin D supplementation and increases in bone mineral density. In this 3-year, randomized controlled study of 342 healthy men and women, higher protein intake was also found to increase bone mineral density. These findings can help provide additional educational information for women at risk. These findings have significant counseling implications for women who consume a vegan diet. It is imperative that these women be counseled on the importance of sufficient calcium in their diet.

Table 4. Daily Dietary Calcium Requirements for Women

Premenopausal women	1,000 mg/d
Postmenopausal women on HRT	1,000 mg/d
Postmenopausal women not on HRT	1,500 mg/d
Adolescent girls, aged 9–17 years old	1,300 mg/d
Pregnancy, ≤18 years of age	1,300 mg/d
Pregnancy, 19–50 years of age	1,000 mg/d
Lactation, ≤18 years of age	1,300 mg/d
Lactation, 19–50 years of age	1,000 mg/d

From: Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutrition Board, Institute of Medicine.[35]

Calcium Supplementation

Supplementation with oral calcium salts can help increase calcium levels. Dietary recommendations of calcium are listed by age group in Table 4.[35] Calcium salts vary in the percentage of elemental calcium found within each supplement. Because different supplements contain different values of elemental calcium, patients should be advised to read label directions specific for each formulation to determine the appropriate dosage. Studies indicate that calcium supplementation decreases bone loss in postmenopausal women and results in a decrease in fracture rates.[16] Vitamin D supplementation has been shown to decrease the rate of fractures as well.[16] Supplementation with calcium and vitamin D should also be initiated in individuals receiving corticosteroids for greater than 1 month to retard bone loss and decrease fracture risk.[32] Although midwives would not initiate therapy for individuals with more complex medical diagnoses, such as malabsorption problems, it is likely they will encounter women interested in or in need of vitamin and mineral supplementation and can provide appropriate counseling regarding calcium needs.

Many women will ask their clinician, "What supplement is the best?" Supplement selection should be determined by a number of factors, including availability, purity, absorbability, and tolerance (Table 5). Calcium supplements that list ingredients, such as unrefined oyster shells, bone meal, or dolomite, have the most additives and should not be the first choice.[5] These supplements are usually the least expensive, however, so women who can only afford this type of supplement are better off taking a bone meal

Table 5. Oral Calcium Salts

Generic name	Trade Names	Calcium Content (per tablet) (%)	Strength of Each Tablet (mg)	No. of Tablets Needed for 500-mg Dose of Calcium
Calcium carbonate	Os-Cal, Tums*	40	1500	1
			1250	1
			835	3
			650	2
Calcium citrate	Citracal	21	950	2.5
Calcium glubionate	Neo-Calglucon	6.6	1800	5
Calcium gluconate	Kalcinate*	9	1000	5.5
			650	9
Calcium lactate*	none	13	650	6
			325	12
Dicalcium phosphate	none	23	500	4.5
Tricalcium phosphate	Posture	39	800	2

*Available in different strengths.

supplement than no supplement at all unless their diet is adequate without supplementation.

Although many women will tolerate a calcium pill supplement, others may prefer chewable or liquid calcium supplements. Some women may want to take their supplements with meals, in which case calcium carbonate can be recommended. The most commonly occurring side effect of calcium is gastrointestinal disturbances. Calcium can interfere with tetracycline absorption. Certain foods, such as rhubarb, spinach, and bran, as well as corticosteroids, can decrease calcium absorption. Adverse reactions include hypercalcemia and hypercalciuria.[31] Calcium supplements are not recommended for children and should be used cautiously in women with hypoparathyroidism.[31] Women who report gastrointestinal symptoms, such as bloating, constipation, or flatus, should try one of the other forms of calcium as a means to eliminate these side effects.[31] Table 5 summarizes the different types of calcium available.

Microcrystalline hydroxyapatite, available over the counter, is the best-absorbed calcium source. Although the cost of this form of calcium varies, in general, it is more expensive than some other calcium supplements. It contains 25% elemental calcium and can be administered to individuals with malabsorption problems. It is the only supplement that is a complete bone food and can increase bone mass. Other calcium sources are not complete bone foods, meaning they do not contain all of the minerals that are needed to build healthy bone.[31]

Citrate calcium (Citracal) contains 22% elemental calcium and is well absorbed. It has less risk of kidney stones than other agents. It is also absorbed well in individuals with digestive problems. It can be taken with food or on an empty stomach. Citrate calcium (Citracal) is absorbed more effectively in the presence of vitamin C.[31] Lactate calcium contains 18% elemental calcium but can cause flatus and other gastrointestinal symptoms because it is made from fermented molasses, whey, starch, or sugar. It also sometimes contains milk products or yeast by-products.[31] Calcium carbonate (Os-cal, Tums) is 40% elemental calcium but is the poorest absorbed of all calcium supplements.[31] Because calcium carbonate can cause gastrointestinal upset, it should be taken with food. Calcium carbonate is effective as an antacid; however, in women who do not have problems with excessive stomach acid, other sources should be recommended.[31] Although calcium carbonate is the least expensive, it is often not tolerated well by middle-aged or older adults. Bone meal calcium, which contains 30% elemental calcium, is not routinely recommended because its minerals are substantially destroyed in processing. In addition, it can contain lead, cadmium, and even arsenic.[31]

Sodium Fluoride

Slow release sodium fluoride directly promotes bone growth, although it is not FDA approved for this purpose. Fluoride directly stimulates the proliferation of osteoblasts as a means of promoting bone growth. Use of fluoride has been found to increase bone mineral density by 4% to 6% and reduce the incidence of new fractures.[3] Fluoride levels must be monitored closely and should remain between 95 and 195 ng/mL. The usual dosage is 25 mg twice daily for 12 months followed by a cessation of therapy for 2 months. Calcium supplementation is given simultaneously with treatment. High levels of fluoride can cause adverse effects, including the formation of abnormal bone that fractures more easily. Currently, fluoride treatment is not a common therapy used in osteoporosis management.

A metanalysis of 11 studies examined the efficacy of fluoride therapy on bone loss and vertebral and nonvertebral fractures in postmenopausal women.[36] Relative risks (RR) were calculated for continuous outcomes and weighted mean differences were used to determine the change in percentage from baseline. There was an increase in lumbar spine bone mineral density with a weighted mean difference of 8.1% (95% CI 7.15% to 9.09%) after 2 years

and 16.1% (95% CI 14.65% to 17.5%) after 4 years. The RR for new vertebral fractures was not significant at 2 or 4 years. The RR for new non-vertebral fractures was not significant at 2 years but was significant at 4 years (RR 1.85; 95% CI 1.36% to 2.5%) when used at high doses in the slow release form. The RR for gastrointestinal side effects was not significant at 2 years but was at 4 years in the treated group (RR 2.18; 95% CI 1.69% to 4.57%). Although fluoride did increase bone mineral density at the lumbar spine, it did not result in a reduction of vertebral fractures. At high doses, fluoride actually increases the risk of non-vertebral fractures and gastrointestinal side effects.[36]

Estrogen Replacement Therapy/Hormone Replacement Therapy

Until recently, the use of ERT or HRT had been widely accepted as a first-line treatment for both prevention and treatment of osteoporosis. However, new studies have indicated that although ERT/HRT may prevent low bone mass and bone loss, there is no concrete evidence to support its use as a *treatment* modality.[8]

Until recently, many perimenopausal women without contraindications to estrogen were advised to continue on oral contraceptive pills until menopause and then switch to HRT and continue use indefinitely. Research showed that early HRT/ERT administration reduced the incidence of fractures for menopausal women. Cauley et al.[8] conducted a 6-year prospective cohort study to evaluate the use of ERT/HRT and the incidence of fractures in 9,000 women over the age of 65. Women on ERT/HRT had significant decreases in wrist fractures (RR 0.39; 95% CI 0.24% to 0.64%) and non-vertebral fractures (RR 0.66; 95% CI 0.54% to 0.80%) compared with women who had never been on ERT/HRT. Early current users who initiated ERT/HRT 2 years before or up to 5 years after menopause had significant reductions in wrist fractures (RR 0.29; 95% CI 0.13% to 0.68%), hip fractures (RR 0.29; 95% CI 0.09% to 0.92%) and non-vertebral fractures (RR 0.50; 95% CI 0.36% to 0.70%) when compared with women who had never been on ERT/HRT. Women who initiated ERT/HRT after being in menopause for more than 5 years had non-significant differences in fracture risks, although there was a trend toward significance in non-vertebral fractures when compared with women who had never been on ERT/HRT.[8]

In May 2002, the Women's Health Initiative, a randomized controlled primary prevention trial of 16,608 postmenopausal women aged 50 to 79 years, demonstrated reduced hip and clinical vertebral fracture risk by one third compared with placebo. However, the HRT study arm (not ERT) was stopped after 5.2 years (expected duration was 8 years) primarily because of unacceptable increased incidence of breast cancer noted in the women who used HRT.[9]

Participants in the Women's Health Initiative study received conjugated equine estrogens, 0.625 mg/d and medroxyprogesterone acetate 2.5 mg/d (n = 8,506) or a placebo (n = 8,102). Although HRT proved protective for hip fractures (HR 0.66; 95% CI 0.45% to 0.98%) and all fractures combined (HR 0.98; 95% CI 0.82% to 1.18%), estimated risk ratios and nominal 95% CIs for adverse outcomes were as follows: coronary heart disease (RR 1.29; 95% CI 1.02% to 1.63%) with 286 cases; breast cancer (RR 1.26; 95% CI 1.00% to 1.59%) with 290 cases; stroke (RR 1.41; 95% CI 1.07% to 1.85%) with 212 cases; pulmonary embolism (RR 2.13; 95% CI 1.39% to 3.25%) with 101 cases.[9] The authors of the study recommended that despite protection from fracture by the use of combined HRT, the risks incurred made long-term use of HRT for bone protection unacceptable and recommended that providers no longer prescribe the combined hormone regimen for osteoporosis prevention or treatment. Until further data are evaluated, clinicians should consider these findings and individualize treatment regimens. Although the American College of Obstetricians and Gynecologists has supported the on-going use of HRT/ERT for short-term use of menopausal symptoms, the organization advises caution when prescribing these hormones for long-term prevention of chronic diseases until further research is available.[37]

For women attempting to prevent osteoporosis, calcium and vitamin D supplementation with lifestyle modifications is recommended. For women with osteoporosis, other pharmacologic interventions may be preferred. Table 6 summarizes available pharmacologic agents used to prevent and treat osteoporosis.

Bisphosphonates

Bisphosphonates are a class of drugs that reduce bone loss, increase bone density in both the spine and hip, and reduce the risk of spine and hip fractures by directly inhibiting resorption and hindering recruitment and activity of the osteoclasts at the surface of the bone.[7,10,38] Previously, HRT was widely recommended as a means of prevention for osteoporosis; however, many women are now opting for bisphosphonates because these medications are not associated with the same increased risks noted with use of HRT and they appear more effective than HRT. Alendronate (Fosamax) and risedronate (Actonel) are examples of drugs in this category. Etidronate (Didronel) (used to treat Paget's disease and hip fractures) are also in this category. Pamidronate (Aredia) and tiludronate (Skelid), although not available in the United States, are also members of this group. These drugs are contraindicated in individuals with esophageal abnormalities, which delay esophageal emptying times (stricture, achalasia), hypocalcemia, or in individuals who cannot remain standing or sitting upright for at least 30 minutes after administration. The drug should be used with caution in individuals with renal insufficiency and should be discontinued if esophageal reactions occur.

Table 6. Pharmacologic Agents Commonly Used to Prevent or Treat Osteoporosis

Drug Class/Drug Name	Dosage	Route	Mechanism on Disease
Estrogens	Conjugated estrogen 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg, 2.5 mg Ethinyl estradiol 0.02 mg, 0.05 mg Estradiol 0.5 mg, 1 mg, 2 mg Esterified estrogens 0.3 mg, 0.625 mg, 1.25 mg, 2.5 mg Estrone sodium sulfate 0.625 mg, 1.25 mg, 2.5 mg Estropipate 0.75 mg, 1.5 mg	Oral	Prevention
Progestins	Norethindrone acetate 5 mg Micronized progesterone 100 mg, 200 mg Medroxyprogesterone 2.5 mg, 5 mg, 10 mg 2.5–10 mg for 12–14 days during second half of menstrual cycle if on estrogen therapy	Oral	Prevention; (used in combination with estrogen when intact uterus)
Combination estrogens/progestins	Estradiol 1 mg/norethindrone 0.5 mg PO Ethinyl estradiol 5 mcg/norethindrone 1 mg (PO) Estradiol 1 mg/estradiol 1 mg/norgestimate 0.09 mg PO Conjugated estrogens .625 mg/medroxyprogesterone 2.5–5 mg Estradiol 0.5 mg/norethindrone 0.14 mg/patch	Oral, transdermal patch	Prevention
Bisphosphonates	Risedronate sodium 5 mg Alendronate sodium 5–10 mg/d or 70 mg/wk (single dose) Zoledronic acid 4 g IV single dose	Oral, intravenous	Prevention Treatment
Calcitonin	Calcitonin salmon 200 units nasally or 100 units SC/IM	Intranasally, SC/IM injection	Treatment
Slow release sodium fluoride	25 mg BID for 12 mon	Oral	Treatment
Selective estrogen receptor modulators	Raloxifene HCL 60 mg Alendronate 5 mg/d	Oral	Prevention Treatment
Selective estrogen receptor modulators	Raloxifene 60 mg/d	Oral	Prevention Treatment
Calcitonin	Calcitonin-salmon spray (200 units/1 spray per day) or 200 units SC or IM	Nasal spray, subcutaneous/intramuscular injection	Treatment

Clinicians should advise women that these drugs interact with calcium, aluminum, and magnesium-containing antacids, therefore, calcium supplements and should be taken at least 2 hours before or after bisphosphonates to improve the effectiveness of both drugs. The most significant problematic side effects concern the administration of the drug. Bisphosphonates must be taken on an empty stomach at least 30, but preferably 60 minutes, prior to meals or other medications.[30] The medication must be taken with at least 6 to 8 oz of water. Women must remain in an upright position for at least 30 minutes after taking the medication.[38,39] Many individuals find these parameters too stringent and may discontinue the drug for this reason. Side effects from these medications also include abdominal or musculoskeletal pain, nausea, heartburn, or irritation of the esophagus.[38,39]

Alendronate (Fosamax) comes in both a 10-mg daily dose, which is indicated for women with osteopenia, and a 20-mg daily dose, which is used for women who have been diagnosed with osteoporosis.[38,39] In addition, alendronate (Fosamax) now is available in a 70-mg once-weekly dosage regimen. Less frequent dosing can increase patient adherence and ultimately result in fewer side effects. The weekly dosing appears to have the same beneficial effects on bone mineral density as the daily dosing regimen. The less frequent dosing also yields fewer gastrointestinal side

effects, thus increasing gastrointestinal tolerability. Alendronate can improve bone mass by 7% to 8%.[40]

Risedronate (Actonel) can be used in postmenopausal women for the prevention and treatment of osteoporosis as well as for glucocorticoid-induced osteoporosis.[38,39] Like other medications in this class, it can be used in women who have contraindications to HRT or in addition to HRT. Lobo et al.[39] found that risedronate sodium (Actonel) taken with calcium (at different dosages) reduced fractures by 65%. Other studies have also noted a decrease in vertebral fractures and an increase in bone mineral density when subjects took risedronate sodium (Actonel) along with calcium supplements.[41,42] This third-generation bisphosphonate reportedly has fewer gastrointestinal side effects than alendronate sodium (Fosamax) (a second-generation bisphosphonate). The dosage is 5 mg/d for osteoporosis treatment. Bisphosphates are generally categorized by generations. Bisphosphonates are analogues of pyrophosphates with specific pharmacologic activity for bone. The multigenerational differences in the drugs are related to the different side chains of hydrogen. It is the differences in the side chains that alter the in vitro potency of the drugs and alters the side effects of each generation. The antiresorptive properties increase by approximately 10-fold between each generation.[3]

Although bisphosphonates have been shown to reduce bone resorption and inhibit osteoclasts, their effectiveness seems to be best for treatment in women with osteoporosis and they do not appear to work as well as estrogens in prevention of osteoporosis.[42] Multiple studies have examined the effectiveness of alendronate sodium (Fosamax). The Fracture Intervention Trial[43] followed 2,027 women and found that alendronate decreased the risk of vertebral and hip fractures compared with the control group who were given a placebo drug. But another study that included 1,174 postmenopausal women compared the effectiveness of HRT and alendronate sodium (Fosamax) and found that HRT was more effective in preventing fractures and bone mineral density loss, although alendronate also was effective in preventing bone loss.[44] Although long-term effects of these drugs have not yielded any adverse effects, long-term safety and efficiency have not been established. For patients with financial limitations, the bisphosphonates are more costly, up to twice as expensive as estrogen therapies.

Calcitonin

Calcitonin (Miacalcin) inhibits bone resorption by blocking osteoclastic activity.[38,39] There is evidence that markers of bone turnover decrease and that bone mineral density stabilizes (or even increases) with use of Calcitonin.[10] Calcitonin is indicated for the treatment of postmenopausal osteoporosis, Paget's disease, and hypercalcemia. Calcitonin is not recommended for women who are breastfeeding.[38] Although calcitonin has shown some improvement in bone mineral density, it does not appear to be a widely used pharmaceutical option for osteoporosis treatment.

Cranney and colleagues[44] recently performed a metanalysis using bone mineral density measurements in randomized, controlled studies where subjects took either calcitonin or a placebo. Participants were not given calcium supplementation. This study found a statistically significant weighted mean difference in bone mineral density measurements for the active treatment group of 3.2 (95% CI 0.3% to 6.1%) at the lumbar spine by 12 months. The weighted mean difference in bone mineral density at 24 months was 4.5, which was no longer statistically significant (95% CI −0.6% to 9.5%). Furthermore, no significance was found in bone mineral density measurements of the radius or femoral neck at 12 or 24 months. The RR of vertebral fractures in the treatment group was reduced (RR 0.71; 95% CI 0.26% to 1.89%) as was the risk for nonvertebral fractures (RR 0.52; 95% CI 0.14% to 1.96%), although neither reduction in risk was statistically significant. Calcitonin can be given by nasal inhalation or subcutaneous or intramuscular injection. Patients generally tolerate the nasal spray more easily than an every other day injection. The nasal spray should be administered as a single spray (200 units) alternated in different nostrils daily. The injection (100 units) can be given every other day. Side effects of the nasal spray include rhinitis, nasal and respiratory symptoms, back pain, and gastrointestinal upset. The injectable form can also cause gastrointestinal symptoms in addition to local inflammation, flushing, rash, and antibody formation.[44] Women should be counseled to ensure they have an adequate calcium and vitamin D intake while taking this medication. Advise a minimum calcium intake of at least 1,000 mg/d. There is some evidence that the injectable form of calcitonin may be effective as an analgesic secondary to the release of endogenous opioids; therefore, it may be a desirable treatment for women who have recently had painful fractures.[10] Although calcitonin has shown some improvement in bone mineral density, it does not appear to be the best pharmaceutical option for osteoporosis treatment. Other drugs, including selective estrogen receptor modulators, have been examined as an additional treatment measures.

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators are the newest class of drugs for the treatment of osteoporosis. Drugs in this class include tamoxifen (Nolvadex, Tamofen) and raloxifene (Evista) Observation of the effects of tamoxifen, which is used as a treatment for breast cancer, alerted researchers to the positive effects on bone mineral density. Selective estrogen receptor modulators, which are sometimes referred to as partial estrogen agonist/antagonists, function as either antagonists or agonists at specific estrogen receptors.

Johnell and colleagues[45] conducted a randomized, dou-

ble-blind 1-year study to assess the effects of raloxifene (Evista) and Alendronate (Fosamax) on 331 postmenopausal women who had been diagnosed with osteoporosis. Subjects received either a placebo, raloxifene, alendronate, or a raloxifene/alendronate combination. Bone mineral density was assessed at baseline and at 6 and 12 months. All treatment groups showed statistically significant improvement in bone mineral density at 12 months compared with their initial bone mineral density measurements. The combination group demonstrated the greatest increase in femoral neck bone mineral density with a 3.7% increase followed by the Alendronate group with a 2.7% increase and then the raloxifene group increasing by 1.7%. Although raloxifene has a lower bone mineral density score than either alendronate or the combination therapy, it is not known how this would correlate to fracture rates. Subjects were not taking calcium or vitamin D supplementation during the study period. Raloxifene (Evista) stimulates bone while blocking the effects of estrogen in the breast and uterus. Although it is a good choice of therapy for women with a history of breast or uterine cancer or for women with concerns about taking estrogen, it tends to induce vasomotor symptoms. Other side effects of leg cramps and venous thrombohemolytic events have been reported.[45] It may also be a better choice of therapy for women with severe gastrointestinal symptoms and for those who have difficulty tolerating the bisphosphonates. This class of drugs should be used with extreme caution for women who are perimenopausal because the drug is contraindicated in pregnancy. The drug manufacturer lists perimenopause as a contraindication because of the danger of pregnancy. The drug is pregnancy category X. All women prescribed these drugs should be using an effective method of birth control. Selective estrogen receptor modulators are contraindicated in persons who have a history of venous thromboembolic events. Women on warfarin (Coumadin) should be monitored more closely because selective estrogen receptor modulators can antagonize warfarin.[38,39] It also should be used in caution in women taking diazepam (Valium), diazoxide (Hyperstat), lidocaine (Xylocaine), or other protein-bound drugs because raloxifene HCl (Evista) can antagonize these drugs.[38,39] Raloxifene HCl (Evista) cannot be given concurrently with ERT/HRT because of the additive risk of thromboembolic events associated with both drugs; therefore, women with menopausal symptoms may need other pharmacologic intervention. The recommended dosage of raloxifene HCl (Evista) is 60 mg/d. Women taking raloxifene who are experiencing vasomotor symptoms can be given bellephren (Bellergal), gabapentin (Neurontin), clonidine (Catapres), megestrol acetate (Megace), methyldopa (Android), or venlafaxine (Effexor) to control hot flashes.[38,39]

FUTURE TRENDS IN OSTEOPOROSIS MANAGEMENT

Promising new drugs are currently under investigation by the FDA for the treatment of osteoporosis. Recombinant human parathyroid hormone shows promise as the first anabolic drug to positively affect bone mineral density and bone markers. In a clinical trial of 1,637 subjects, there was a 50% reduction in fracture rate in patients who received recombinant human parathyroid hormone versus a placebo.[46] The drug is administered by injection on a daily basis, therefore making patient compliance a potential problem. This treatment is currently under review by the FDA.

In February 2002, the FDA approved zoledronic acid (Zometa), a new member of the bisphosphonate family of drugs, for the treatment of bone metastases in cancer patients. This powerful bisphosphonate is effective in preventing and treating osteoporosis.[47] Zoledronic acid is administered by intravenous injection over a 15-minute period once every 12 months. Reid and colleagues[47] recently conducted a 1-year, double-blind, placebo-controlled trial of 331 postmenopausal women with low bone mineral density in which zoledronic acid was administered in varying doses with varying frequencies, which yielded the same effectiveness rates. Postmenopausal women in the least frequently administered drug group received a 4-mg dose of zoledronic acid one time. Other women received the drug at 3-month intervals. All groups demonstrated suppressed bone resorption throughout the study. Increases in bone mineral density for the spine were 4.3% to 5.1% higher in the group of women taking zoledronic acid than in the control group. Bone mineral density values for the femoral neck were 3.1% to 3.5% higher than in the control group. When these statistically significant results were compared with the bone mineral density results and fracture rates seen in women on a daily dosing regimen of other bisphosphonates, fracture rates were the same.[47] An annual dose of intravenous zoledronic acid may be an attractive alternative for patients who cannot tolerate oral bisphosphonates or who have compliance issues. Although it is unlikely that midwives will prescribe this once a year regimen, midwives can educate their clients about the availability of this treatment and provide referrals for women interested in this regimen.

One of the newest scientific advances is the identification of osteoprotegerin. Osteoprotegerin is a glycoprotein member of the tumor necrosis factor receptor family. This protein acts as a decoy receptor and binds to one of the enzymes responsible for osteoclast differentiation, thereby preventing osteoclast formation and then bone reabsorption.[47] Early studies have indicated that osteoprotegerin levels rise in the presence of 17 beta-estradiol. More recent research indicates that dietary sources of phytoestrogens may increase osteoprotegerin production and help prevent bone loss and bone resorption; however, rigorous data are needed before clinical recommendations can be made.[48,49]

CONCLUSION

Osteoporosis is a silent disease that can have devastating consequences for women. Although it primarily affects postmenopausal women, women of all ages should receive extensive education and counseling regarding prevention and treatment. Multiple lifestyle factors can increase a woman's risk for acquiring the disease. Women should be encouraged to make lifestyle modifications to decrease these risk factors. Midwives should include dietary analysis for calcium intake and personal and family history questions as a component of routine gynecologic care. Symptoms should be evaluated at every examination to determine the presence of osteoporosis-related symptoms and physical findings. Screening should be provided to all women with symptoms as well as women with risk factors. Although multiple screening tools exist, a dual-energy x-ray absorptiometry scan is the gold standard for determining bone mineral density status. Women with osteopenia or osteoporosis usually benefit from pharmacologic intervention.

Calcium supplementation, although imperative as an adjunct treatment, may not be a satisfactory treatment regimen alone. ERT/HRT has been shown to prevent osteoporosis by decreasing the bone loss that is common after menopause, although the recent findings of risks associated with HRT/ERT make this option one that deserves careful consideration of overall risks versus benefits. Other pharmacotherapeutic agents are needed both for treatment for women who have osteoporosis and for prevention for women who do not use ERT/HRT. Treatment options include bisphosphonates, calcitonin, and selective estrogen receptor modulators. Although slow release sodium fluoride treatment has been successful, it is not a mainstream treatment because of its adverse effects. Promising new drug therapies, including recombinant human parathyroid hormone, may expand treatment options in the future. Zoledronic acid (Zometa) is the newest drug to gain FDA approval. This treatment may be given as infrequently as once a year and still yield positive effects on bone mineral density. Osteoprotegerin may prove to play a pivotal role in future osteoporosis management. Midwives can play an active role in the prevention, detection, and treatment of osteoporosis by including simple educational strategies into their clinical management.

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